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Macrogol 6 Glycerol Caprylocaprate

General Notices

(Ph. Eur. monograph 1443)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of mainly mono- and diesters of polyoxyethylene glycerol ethers mainly with caprylic (octanoic) and capric (decanoic) acids. The average number of moles of ethylene oxide reacted per mole of substance is 6.

Macrogol 6 glycerol caprylocaprate may be obtained by ethoxylation of glycerol and esterification with distilled coconut or palm kernel fatty acids, or by ethoxylation of mono- and diglycerides of caprylic and capric acids.

CHARACTERS

Appearance

Pale yellow liquid.

Solubility

Partly soluble in water, freely soluble in castor oil, in glycerol, in isopropanol and in propylene glycol.

Viscosity

About 145 mPa·s.

IDENTIFICATION

A. Dissolve 1.0 g in 99 g of a mixture of 10 volumes of *2-propanol R* and 90 volumes of *water R*. Heat the solution obtained to about 40 °C. A turbidity is produced. Allow to cool until the turbidity disappears. The cloud point is between 15 °C and 35 °C.

B. Saponification value (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

Appearance

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The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution Y_2 (*2.2.2, Method I*).

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of *ethanol (96 per cent) R* and 10 mL of *water R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (*2.5.1*)

Maximum 5.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

165 to 225.

Saponification value (*2.5.6*)

85 to 105, determined on 2.0 g.

Composition of fatty acids

Gas chromatography (*2.4.22, Method A*).

Composition of the fatty-acid fraction of the substance:

— *caproic acid*: maximum 2.0 per cent;

— *caprylic acid*: 50.0 per cent to 80.0 per cent;

— *capric acid*: 20.0 per cent to 50.0 per cent;

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 1.0 per cent.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

Maximum 0.3 per cent.

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Macrogol 15 Hydroxystearate

General Notices

(Ph. Eur. monograph 2052)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of mainly monoesters and diesters of 12-hydroxystearic ((12Ξ)-hydroxyoctadecanoic) acid and macrogols obtained by ethoxylation of 12-hydroxystearic acid. The number of moles of ethylene oxide reacted per mole of 12-hydroxystearic acid is 15 (nominal value). It contains free macrogols.

CHARACTERS

Appearance

Yellowish, waxy mass.

Solubility

Very soluble in water, soluble in ethanol (96 per cent), insoluble in liquid paraffin.

It solidifies at about 25 °C.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution To 1.0 g add 100 mL of a 100 g/L solution of *potassium hydroxide R* and boil under a reflux condenser for 30 min. Acidify the warm solution with 20 mL of *hydrochloric acid R* and cool to room temperature. Shake the mixture with 50 mL of *ether R* and allow to stand until a separation of the layers is visible. Separate the clear upper layer, add 5 g of *anhydrous sodium sulfate R*, wait for 30 min, filter and evaporate to dryness on a water-bath. Dissolve 50 mg of the residue in 25 mL of *ether R*.

Reference solution Dissolve 50 mg of *12-hydroxystearic acid R* in 25 mL of *methylene chloride R*.

Plate *TLC octadecylsilyl silica gel plate R*.

Mobile phase *methylene chloride R*, *glacial acetic acid R*, *acetone R* (10:40:50 *V/V/V*).

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Application 2 µL.

Development Over 2/3 of the plate.

Drying In a current of cold air.

Detection Spray with a 80 g/L solution of *phosphomolybdic acid R* in *2-propanol R* and heat at 120 °C for 1-2 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and colour to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve 15.0 g in 50 mL of *water R*. The viscosity (*2.2.9*) has a maximum of 20 mPa·s.

C. Free macrogols (see Tests).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution B_6 or BY_6 (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent.

Acid value (*2.5.1*)

Maximum 1.0, determined on 2.0 g.

Hydroxyl value (*2.5.3, Method A*)

90 to 110.

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Peroxide value (*2.5.5, Method A*)

Maximum 5.0.

Saponification value (*2.5.6*)

53 to 63.

Free macrogols

Size-exclusion chromatography (*2.2.30*).

Test solution Dissolve 1.20 g of the substance to be examined in the mobile phase and dilute to 250.0 mL with the mobile phase.

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Reference solution (a) Dissolve about 0.4 g of *macrogol 1000 R* in the mobile phase and dilute to 250.0 mL with the mobile phase.

Reference solution (b) Dilute 50.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Precolumns (2):

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydroxylated polymethacrylate gel R* (6 µm) with a pore size of 12 nm.

Connect both precolumns to the column using a 3-way valve and switch the mobile phase flow according to the following programme:

— 0-114 s: precolumn 1 and column;

— 115 s to the end: precolumn 2 and column;

— 115 s to 7 min: flow back of precolumn 1.

Mobile phase *water for chromatography R*, *methanol R* (20:80 *V/V*).

Flow rate 1.1 mL/min.

Detection Refractometer.

Injection 50 µL.

Calculate the percentage content of free macrogols using the following expression:

$$\frac{A_1 \times m_2 \times 200}{m_1 \times \left(A_2 + 2A_3\right)}$$

m_1 = mass of the substance to be examined in the test solution, in grams;

m_2 = mass of *macrogol 1000 R* in reference solution (a), in grams;

A_1 = area of the peak due to free macrogols in the substance to be examined in the chromatogram obtained with the test solution;

A_2 = area of the peak due to macrogol 1000 in the chromatogram obtained with reference solution (a);

A_3 = area of the peak due to macrogol 1000 in the chromatogram obtained with reference solution (b).

Limit:

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— *free macrogols*: 27.0 per cent to 39.0 per cent.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 50 ppm of dioxan.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 2.00 g.

Total ash (*2.4.16*)

Maximum 0.3 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

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Macrogol 20 Glycerol Monostearate

General Notices

(Ph. Eur. monograph 2044)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Macrogol 20 glycerol monostearate is obtained by ethoxylation with ethylene oxide of different types of glycerol stearates, mainly *Glycerol monostearate 40-55 (0495)*. The number of moles of ethylene oxide reacted per mole of glycerol stearate is 20 (nominal value).

CHARACTERS

Appearance

Pale yellow, oily liquid or gel.

Solubility

Soluble in water at 40 °C and above and in ethanol (96 per cent), practically insoluble in light liquid paraffin and in fatty oils.

Relative density

About 1.07.

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Saponification value (see Tests).

C. Composition of fatty acids (see Tests).

D. Place 1 g in a test tube and add 0.1 mL of *sulfuric acid R*. Heat the tube until white fumes appear. The fumes turn filter paper impregnated with *alkaline potassium tetraiodomercurate solution R* black.

TESTS

Acid value (*2.5.1*)

Maximum 2.0, determined on 5.0 g.

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Hydroxyl value (*2.5.3, Method A*)

65 to 85, determined on 0.350 g.

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Peroxide value (*2.5.5, Method A*)

Maximum 6.0.

Saponification value (*2.5.6*)

40 to 60.

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*).

Composition of the fatty-acid fraction of the substance:

Type of macrogol 20 glycerol monostearate	Type of glycerol stearate used	Composition of fatty acids
Type I	Type I (obtained using stearic acid 50)	*Stearic acid*: 40.0 per cent to 60.0 per cent, *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent.
Type II	Type II (obtained using stearic acid 70)	*Stearic acid*: 60.0 per cent to 80.0 per cent, *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent.
Type III	Type III (obtained using stearic acid 95)	*Stearic acid*: 90.0 per cent to 99.0 per cent, *Sum of the contents of palmitic and stearic acids*: minimum 96.0 per cent.

Ethylene oxide and dioxan (*2.4.25, Method A*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

Maximum 0.2 per cent.

STORAGE

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Protected from light.

LABELLING

The label states the type of macrogol 20 glycerol monostearate.

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Macrogol 30 Dipolyhydroxystearate

General Notices

(Ph. Eur. monograph 2584)

Ph Eur

DEFINITION

Mixture of mainly diesters of polymerised 12-hydroxystearic ((12Ξ)-hydroxyoctadecanoic) acid and *Macrogols (1444)* obtained by esterification of macrogol with 12-hydroxystearic acid. The average number of moles of ethylene oxide reacted per mole of substance is 30.

CHARACTERS

Appearance

Brownish-red, waxy mass.

Solubility

Practically insoluble in water, very soluble in methylene chloride and soluble in most aliphatic and aromatic hydrocarbons.

mp

30 °C to 40 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *macrogol 30 dipolyhydroxystearate CRS*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 10.0.

Hydroxyl value (*2.5.3, Method A*)

12 to 30.

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Iodine value (*2.5.4, Method A*)

Maximum 10.0.

Peroxide value (*2.5.5*)

Maximum 5.0.

Saponification value (*2.5.6*)

125 to 145, determined on 2.0 g.

Use 30.0 mL of *0.5 M alcoholic potassium hydroxide*, heat under reflux for 60 min and add 50 mL of *anhydrous ethanol R* before carrying out the titration.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.50 g.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent.

Heat a silica crucible to redness for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.0 g in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C, until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting from “Moisten the substance to be examined...”.

STORAGE

In an airtight container.

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Macrogol 40 Sorbitol Heptaoleate

General Notices

(Ph. Eur. monograph 2396)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of esters of fatty acids, mainly *Oleic acid (0799)*, and sorbitol ethoxylated with approximately 40 moles of ethylene oxide for each mole of sorbitol. 7 moles of oleic acid are used for each mole of sorbitol. It also contains macrogol fatty acid esters.

CHARACTERS

Appearance

Clear or slightly opalescent, yellowish, viscous, hygroscopic liquid.

Solubility

Dispersible in water, soluble in isopropyl myristate, in isopropyl palmitate, in mineral oils and in vegetable fatty oils.

Relative density

About 1.0.

Viscosity (*2.2.9*): about 175 mPa·s at 25 °C.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *macrogol 40 sorbitol heptaoleate CRS*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

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D. Composition of fatty acids (see Tests).

TESTS

Acid value (2.5.1)

Maximum 12.0, determined on 3.0 g.

Hydroxyl value (2.5.3, Method A)

22 to 55.

Peroxide value

Maximum 10.0.

Introduce 10.0 g into a 100 mL beaker and dissolve with 20 mL of *glacial acetic acid R*. Add 1 mL of *saturated potassium iodide solution R*, mix and allow to stand for 1 min. Add 50 mL of *carbon dioxide-free water R* and a magnetic stirring bar. Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

Determine the peroxide value using the following expression:

$$\frac{\left(n_1 - n_2\right) \times M \times 1000}{m}$$

n_1 = volume of *0.01 M sodium thiosulfate* required for the titration of the substance to be examined, in millilitres;

n_2 = volume of *0.01 M sodium thiosulfate* required for the blank titration, in millilitres;

M = molarity of the sodium thiosulfate solution;

m = mass of the substance to be examined, in grams.

Saponification value (2.5.6)

90 to 110, determined on 4.0 g.

Use 30.0 mL of 0.5 M alcoholic potassium hydroxide, heat under reflux for 60 min and add 50 mL of *anhydrous ethanol R* before carrying out the titration.

Composition of fatty acids (2.4.22, Method C)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the substance:

— *myristic acid*: maximum 5.0 per cent;

— *palmitic acid*: maximum 16.0 per cent;

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— *palmitoleic acid*: maximum 8.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: minimum 58.0 per cent;

— *linoleic acid*: maximum 18.0 per cent;

— *linolenic acid*: maximum 4.0 per cent.

Ethylene oxide and dioxan (*2.4.25, Method A*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.50 g.

Sulfated ash

Maximum 0.25 per cent.

Heat a silica crucible to redness for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.0 g of the substance to be examined in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C, until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting from “Moisten the substance to be examined...”.

STORAGE

In an airtight container, protected from light.

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Macrogol Cetostearyl Ether

General Notices

(Ph. Eur. monograph 1123)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of ethers of mixed macrogols with linear fatty alcohols, mainly cetostearyl alcohol. It may contain some free macrogols and it contains various amounts of free cetostearyl alcohol. The number of moles of ethylene oxide reacted per mole of cetostearyl alcohol is 2 to 33 (nominal value).

CHARACTERS

Appearance

White or yellowish-white, waxy, unctuous mass, pellets, microbeads or flakes.

Solubility

— macrogol cetostearyl ether with low numbers of moles of ethylene oxide reacted per mole: practically insoluble in water, soluble in ethanol (96 per cent) and in methylene chloride;

— macrogol cetostearyl ether with higher numbers of moles of ethylene oxide reacted per mole: dispersible or soluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

It solidifies at 32 °C to 52 °C.

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Iodine value (see Tests).

C. Saponification value (see Tests).

D. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve the prescribed amount of substance to be examined (see table below) in a mixture of 1 volume of *water R* and 9 volumes of *methanol R* and dilute to 75 mL with the same mixture of solvents.

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Number of moles of ethylene oxide reacted per mole	Amount to be dissolved (g)
2 - 6	5.0
10 - 22	10.0
25 - 33	15.0

Add 60 mL of *hexane R* and shake for 3 min. The formation of foam can be reduced by the addition of some drops of *ethanol (96 per cent) R*. Filter the upper layer through *anhydrous sodium sulfate R*, wash the filter with 3 quantities, each of 10 mL, of *hexane R* and evaporate the combined filtrates to dryness. Dissolve 0.05 g of the residue in 10 mL of *methanol R* (the solution may be opalescent).

Reference solution Dissolve 25 mg of *stearyl alcohol CRS* in *methanol R* and dilute to 25 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *ethyl acetate R*.

Application 20 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with vanillin-sulfuric acid reagent prepared as follows: dissolve 0.5 g of *vanillin R* in 50 mL of *ethanol (96 per cent) R* and dilute to 100 mL with *sulfuric acid R*; allow to dry in air; heat at about 130 °C for 15 min and allow to cool in air.

Results The chromatogram obtained with the test solution shows several spots; one of these spots corresponds to the principal spot in the chromatogram obtained with the reference solution.

E. Dissolve or disperse 0.1 g in 5 mL of *ethanol (96 per cent) R*, add 2 mL of *water R*, 10 mL of *dilute hydrochloric acid R*, 10 mL of *barium chloride solution R1* and 10 mL of a 100 g/L solution of *phosphomolybdic acid R*. A precipitate is formed.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 5.0 g in *ethanol (96 per cent) R* and dilute to 50 mL with the same solvent.

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of *ethanol (96 per cent) R* and 10 mL of *water R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (*2.5.1*)

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Maximum 1.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

Number of moles of ethylene oxide reacted per mole (nominal value)	Hydroxyl value
2	150 - 180
3	135 - 155
5 - 6	100 - 134
10	75 - 90
12	67 - 77
15	58 - 67
20 - 22	40 - 55
25	36 - 46
30 - 33	32 - 40

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Saponification value (*2.5.6*)

Maximum 3.0, determined on 10.0 g.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 2.00 g.

Total ash (*2.4.16*)

Maximum 0.2 per cent, determined on 2.0 g.

STORAGE

In an airtight container.

LABELLING

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The label states the number of moles of ethylene oxide reacted per mole of cetostearyl alcohol (nominal value).

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Macrogol Glycerol Cocoates

General Notices

(Macrogoglycerol Cocoates, Ph. Eur. monograph 1122)

Action and use

Pharmaceutical aids.

Ph Eur

DEFINITION

Mixtures of mono-, di- and triesters of ethoxylated glycerol with fatty acids of vegetable origin having a composition corresponding to the fatty acid composition of the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. The average number of moles of ethylene oxide reacted per mole of substance (nominal value) is either 7 (macrogol 7 glycerol cocoate) or 23 (macrogol 23 glycerol cocoate).

CHARACTERS

Appearance

Clear, yellowish, oily liquid.

Solubility

Soluble in water and in ethanol (96 per cent) and practically insoluble in light petroleum (bp: 50-70 °C) for macrogol 7 glycerol cocoate and macrogol 23 glycerol cocoate.

Relative density

About 1.05 for macrogol 7 glycerol cocoate; about 1.09 for macrogol 23 glycerol cocoate.

IDENTIFICATION

A. Dissolve 1.0 g of macrogol 7 glycerol cocoate in 99 g of a mixture of 10 volumes of *2-propanol R* and 90 volumes of *water R*. Heat the solution to about 65 °C. A turbidity is produced. Allow to cool until the turbidity disappears. The cloud point is between 35 °C and 54 °C. Heat a 10 g/L solution of macrogol 23 glycerol cocoate in a 100 g/L solution of *sodium chloride R* to about 90 °C. A turbidity is produced. Allow to cool until the turbidity disappears. The cloud point is between 65 °C and 85 °C.

B. Iodine value (see Tests).

C. Saponification value (see Tests).

TESTS

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TESTS

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution Y_2 (2.2.2, Method I).

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of *ethanol (96 per cent) R* and 10 mL of *water R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (2.5.1)

Maximum 5.0, determined on 5.0 g.

Hydroxyl value (2.5.3, Method A)

See Table 1122.-1.

Saponification value (2.5.6)

See Table 1122.-1.

Table 1122.-1

Number of moles of ethylene oxide reacted per mole (nominal value)	Hydroxyl value	Saponification value (determined on 2.0 g)
7	170 - 210	85 - 105
23	80 - 100	40 - 50

Iodine value (2.5.4, Method A)

Maximum 5.0.

Composition of fatty acids

Gas chromatography (2.4.22, Method A).

Composition of the fatty-acid fraction of the substance:

— *caproic acid*: maximum 1.0 per cent;

— *caprylic acid*: 5.0 per cent to 10.0 per cent;

— *capric acid*: 4.0 per cent to 10.0 per cent;

— *lauric acid*: 40.0 per cent to 55.0 per cent;

— *myristic acid*: 14.0 per cent to 23.0 per cent;

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— *palmitic acid*: 8.0 per cent to 12.0 per cent;

— *stearic acid*: 1.0 per cent to 5.0 per cent;

— *oleic acid*: 5.0 per cent to 10.0 per cent;

— *linoleic acid*: maximum 3.0 per cent.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.0 g.

Total ash (*2.4.16*)

Maximum 0.3 per cent.

LABELLING

The label states the number of moles of ethylene oxide reacted per mole of substance (nominal value).

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Macrogol Isotridecyl Ether

General Notices

(Ph. Eur. monograph 2730)

Ph Eur

DEFINITION

Mixture of ethers of mixed macrogols with linear and branched fatty alcohols, mainly $C_{13}H_{28}O$. It contains a variable quantity of free $C_{13}H_{28}O$ and it may contain free macrogols. The number of moles of ethylene oxide reacted per mole of branched $C_{13}H_{28}O$ is 3 or 4 (nominal value).

CHARACTERS

Appearance

Colourless liquid.

Solubility

Practically insoluble in water, soluble or dispersible in ethanol (96 per cent), practically insoluble in light petroleum.

IDENTIFICATION

A. Gas chromatography (*2.2.28*).

Test solution Dissolve 0.200 g of the substance to be examined in *acetone R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 0.35 g of *lauryl alcohol R*, 0.35 g of *tridecyl alcohol R*, 0.15 g of *myristyl alcohol R* and 0.15 g of *ethylene glycol monododecyl ether R* in *acetone R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *acetone R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas: *hydrogen for chromatography R* or *helium for chromatography R*.

Flow rate: 1 mL/min.

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Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	120
	1 - 24	120 → 350
	24 - 34	350
Injection port		300
Detector		350

Detection Flame ionisation.

Injection 1 µL.

Retention time Lauryl alcohol = about 6.7 min; tridecyl alcohol = about 7.8 min; myristyl alcohol = about 9 min; ethylene glycol monododecyl ether = about 9.3 min.

System suitability Reference solution:

— *resolution*: minimum 5 between the peaks due to myristyl alcohol and ethylene glycol monododecyl ether.

Results The sum of the areas of the peaks eluting between the peak due to lauryl alcohol and the peak due to tridecyl alcohol is greater than the area of the peak due to tridecyl alcohol and the area of the peak due to lauryl alcohol.

B. Hydroxyl value (see Tests).

C. Iodine value (see Tests).

D. Saponification value (see Tests).

E. Dissolve or disperse 0.1 g in 5 mL of *ethanol (96 per cent) R*. Add 10 mL of *dilute hydrochloric acid R*, 10 mL of *barium chloride solution R1* and 10 mL of a 100 g/L solution of *phosphomolybdic acid R*. A precipitate is formed.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 5.0 g in *ethanol (96 per cent) R* and dilute to 50 mL with the same solvent.

Alkalinity

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Dissolve 2.0 g in a hot mixture of 10 mL of *ethanol (96 per cent) R* and 10 mL of *water R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (*2.5.1*)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

See Table 2730.-1.

Table 2730.-1

Ethylene oxide units per molecule (nominal value)	Hydroxyl value
3	165 - 185
4	145 - 160

Iodine value (*2.5.4*)

Maximum 2.0.

Saponification value (*2.5.6*)

Maximum 3.0, determined on 10.0 g.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent.

Ignite a silica crucible at 600 ± 50 °C for 30 min, allow to cool in a desiccator over a suitable desiccant and weigh. Evenly distribute 1.0 g in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting from “Moisten the substance to be examined...”.

STORAGE

In an airtight container.

LABELLING

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The label states the number of moles of ethylene oxide reacted per mole of $C_{13}H_{28}O$ (nominal value).

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Macrogol Lauryl Ether

General Notices

(Ph. Eur. monograph 1124)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of ethers of mixed macrogols with linear fatty alcohols, mainly $C_{12}H_{26}O$. It contains a variable quantity of free $C_{12}H_{26}O$ and may contain free macrogols. The number of moles of ethylene oxide reacted per mole of $C_{12}H_{26}O$ is 3 to 23 (nominal value).

CHARACTERS

— Macrogol lauryl ethers with 3 to 5 units of ethylene oxide per molecule.

Appearance

Colourless liquid.

Solubility

Practically insoluble in water, soluble or dispersible in ethanol (96 per cent), practically insoluble in light petroleum.

— Macrogol lauryl ethers with 9 units of ethylene oxide per molecule.

Appearance

White or almost white, unctuous, hygroscopic mass, melting at 24 °C into a colourless or yellowish, viscous liquid.

Solubility

Freely soluble in water, soluble or dispersible in ethanol (96 per cent), practically insoluble in light petroleum.

— Macrogol lauryl ethers with 10 to 23 units of ethylene oxide per molecule.

Appearance

White or almost white, waxy mass.

Solubility

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Soluble or dispersible in water, soluble in ethanol (96 per cent), practically insoluble in light petroleum.

IDENTIFICATION

Carry out tests A, B, C, D, E for macrogol lauryl ethers with 3 to 5 units of ethylene oxide per molecule.

Carry out tests A, B, C, D, F for macrogol lauryl ethers with 9 to 23 units of ethylene oxide per molecule.

A. Hydroxyl value (see Tests).

B. Iodine value (see Tests).

C. Saponification value (see Tests).

D. Dissolve or disperse 0.1 g in 5 mL of *ethanol (96 per cent) R*, add 10 mL of *dilute hydrochloric acid R*, 10 mL of *barium chloride solution R1* and 10 mL of a 100 g/L solution of *phosphomolybdic acid R*. A precipitate is formed.

E. Gas chromatography (*2.2.28*).

Test solution Dissolve 0.200 g of the substance to be examined in *acetone R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 0.15 g of *ethylene glycol monododecyl ether R*, 0.15 g of *lauryl alcohol R* and 0.15 g of *myristyl alcohol R* in *acetone R* and dilute to 100.0 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R* or *hydrogen for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	120
	1 - 24	120 → 350
	24 - 34	350
Injection port		300
Detector		350

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Detection Flame ionisation.

Injection 1.0 µL.

Identification of peaks Use the chromatogram obtained with the reference solution to identify the peaks due to ethylene glycol monododecyl ether, lauryl alcohol and myristyl alcohol.

Retention time Lauryl alcohol = about 6.7 min; myristyl alcohol = about 8.9 min; ethylene glycol monododecyl ether = about 9.3 min.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to myristyl alcohol and ethylene glycol monododecyl ether.

Results The sum of the areas of the peaks eluted before the peak due to lauryl alcohol is less than 10 per cent of the area of the peak due to lauryl alcohol; disregard the peak due to the solvent.

F. Gas chromatography (*2.2.28*).

Test solution Into a 50 mL round-bottomed flask fitted with a reflux condenser introduce 0.300 g of the substance to be examined, 15 mL of *hydriodic acid R*, 2.5 mL of a 603 g/L solution of *phosphorous acid R* and 2 or 3 anti-bumping granules. Heat to 140 °C using an oil bath or an electric heating mantle, then boil for 2 h. Allow to cool to room temperature and rinse the condenser with 5 mL of *ethanol (96 per cent) R*. Add the rinsings to the flask and transfer to a separating funnel, rinsing the flask with 2 quantities, each of 5 mL, of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*.

Extract with 15 mL of *heptane R* and wash the upper layer with 5 mL portions of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R* until the pH of the lower layer is greater than 3 using a *pH indicator strip R*.

Transfer the upper layer into a 20 mL glass vial with a screw cap and shake with 5 g of *anhydrous sodium sulfate R*. Allow to settle and transfer about 1 mL of the clear supernatant to an autosampler vial.

Reference solution Prepare as described for the test solution using 0.150 g of *2-butyloctanol R*, 0.150 g of *lauryl alcohol R* and 0.150 g of *myristyl alcohol R* instead of the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 1.0 µm).

Carrier gas *helium for chromatography R* or *hydrogen for chromatography R*.

Flow rate 3 mL/min.

Split ratio 1:30.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 5	100
	5 - 55	100 → 300
	55 - 70	300
Injection port		250
Detector		310

Detection Flame ionisation.

Injection 1.0 µL.

Identification of peaks Use the chromatogram obtained with the reference solution to identify the peaks due to 2-butyloctyl iodide, lauryl iodide and myristyl iodide.

Retention time 2-butyloctyl iodide = about 22.7 min; lauryl iodide = about 25.6 min; myristyl iodide = about 31.1 min.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to 2-butyloctyl iodide and lauryl iodide.

Results The sum of the areas of the peaks eluted before the peak due to lauryl iodide is less than 10 per cent of the area of the peak due to lauryl iodide; disregard the peak due to the solvent.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 5.0 g in *ethanol (96 per cent) R* and dilute to 50 mL with the same solvent.

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of *ethanol (96 per cent) R* and 10 mL of *water R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (*2.5.1*)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

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Ethylene oxide units per molecule (nominal value)	Hydroxyl value
3	165 - 180
4	145 - 165
5	130 - 140
9	90 - 100
10	85 - 95
12	73 - 83
15	64 - 74
20 - 23	40 - 60

Iodine value (*2.5.4*)

Maximum 2.0.

Saponification value (*2.5.6*)

Maximum 3.0, determined on 10.0 g.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent.

Ignite a silica crucible at 600 ± 50 °C for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.0 g in the crucible and weigh again. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C until the substance is thoroughly charred. Carry out the test for sulfated ash on the residue obtained, starting from “Moisten the substance to be examined...”.

STORAGE

In an airtight container.

LABELLING

The label states the number of moles of ethylene oxide reacted per mole of $C_{12}H_{26}O$ (nominal value).

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Macrogol Oleate

General Notices

(Ph. Eur. monograph 1618)

Action and use

Non-ionic surfactant.

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DEFINITION

A mixture of monoesters and diesters of mainly oleic (*cis*-9-octadecenoic) acid and macrogols. It may be obtained by ethoxylation of *Oleic acid (0799)* or by esterification of macrogols with oleic acid of animal or vegetable origin. It may contain free macrogols. The average polymer length is equivalent to 5-6 or 10 moles of ethylene oxide per mole (nominal value). A suitable antioxidant may be added.

CHARACTERS

Appearance

Slightly yellowish, viscous liquid.

Solubility

Dispersible in water, soluble in ethanol (96 per cent) and in 2-propanol, dispersible in oils, miscible with fatty oils and with waxes.

Refractive index

About 1.466.

IDENTIFICATION

First identification: A, C.

Second identification: A, B.

A. Saponification value (see Tests).

B. Thin-layer chromatography (*2.2.27*).

Test solution To 20 mg add 10 mL of *methylene chloride R* and mix.

Plate *TLC silica gel F_{254} plate R*.

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Mobile phase 25 per cent *V/V* solution of *concentrated ammonia R*, *2-propanol R* (20:80 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with *potassium iodobismuthate solution R4*; examine the plate about 10 min later.

Results The chromatogram obtained shows 3 principal spots, corresponding, in order of increasing R_F value, to free macrogol, macrogol mono-oleate and macrogol dioleate.

C. Composition of fatty acids (see Tests).

TESTS

Alkalinity

Dissolve 2.0 g in *ethanol (96 per cent) R* and dilute to 20 mL with the same solvent. To 2 mL of this solution add 0.05 mL of *phenol red solution R*. The solution is not red.

Acid value (*2.5.1*)

Maximum 2.0.

Hydroxyl value (*2.5.3, Method A*)

See Table 1618.-1.

Iodine value (*2.5.4, Method A*)

See Table 1618.-1.

Peroxide value (*2.5.5, Method A*)

Maximum 12.0.

Saponification value (*2.5.6*)

See Table 1618.-1.

Table 1618.-1

	5-6 moles of ethylene oxide	10 moles of ethylene oxide
Hydroxyl value	50 - 70	65 - 90

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	5-6 moles of ethylene oxide	10 moles of ethylene oxide
Iodine value	50 - 60	27 - 34
Saponification value	105 - 120	68 - 85

Composition of fatty acids

Gas chromatography (*2.4.22, Method A*).

Composition of the fatty-acid fraction of the substance:

— *myristic acid*: maximum 5.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *palmitic acid*: maximum 16.0 per cent;

— *palmitoleic acid*: maximum 8.0 per cent;

— *oleic acid*: 65.0 per cent to 88.0 per cent;

— *linoleic acid*: maximum 18.0 per cent;

— *linolenic acid*: maximum 4.0 per cent;

— *fatty acids with a chain length greater than* C_{18}: maximum 4.0 per cent.

Residual ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of residual ethylene oxide and 10 ppm of residual dioxan.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 1.00 g using *anhydrous methanol R* as the solvent.

Total ash (*2.4.16*)

Maximum 0.3 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

LABELLING

The label states the number of moles of ethylene oxide per mole (nominal value).

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Macrogol Oleyl Ether

General Notices

(Ph. Eur. monograph 1125)

Action and use

Non-ionic surfactant.

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DEFINITION

Mixture of ethers of mixed macrogols with linear fatty alcohols, mainly oleyl alcohol. It contains a variable quantity of free oleyl alcohol and it may contain free macrogols. The number of moles of ethylene oxide reacted per mole of oleyl alcohol is 2 to 20 (nominal value). A suitable antioxidant may be added.

CHARACTERS

— Macrogol oleyl ether with 2 to 5 units of ethylene oxide per molecule.

Appearance

Yellow liquid.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent), practically insoluble in light petroleum.

— Macrogol oleyl ether with 10 to 20 units of ethylene oxide per molecule.

Appearance

Yellowish-white waxy mass.

Solubility

Dispersible or soluble in water, soluble in ethanol (96 per cent), practically insoluble in light petroleum.

IDENTIFICATION

A. Hydroxyl value (see Tests).

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B. Iodine value (see Tests).

C. Saponification value (see Tests).

D. Dissolve or disperse 0.1 g in 5 mL of *alcohol R*, add 2 mL of *water R*, 10 mL of *dilute hydrochloric acid R*, 10 mL of *barium chloride solution R1* and 10 mL of a 100 g/L solution of *phosphomolybdic acid R*. A precipitate is formed.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 5.0 g in *alcohol R* and dilute to 50 mL with the same solvent.

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of *water R* and 10 mL of *alcohol R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (*2.5.1*)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

See Table 1125.-1.

Iodine value (*2.5.4*)

See Table 1125.-1.

Table 1125.-1

Ethylene oxide units per molecule (nominal value)	Hydroxyl value	Iodine value
2	158 - 178	48 - 74*
5	110 - 125	48 - 56
10	75 - 95	24 - 38
20	40 - 65	14 - 24

* This broad range is needed since 2 different grades of oleyl alcohol may be used for the synthesis. The iodine value does not differ by more than 5 units from the nominal iodine value and is within the limits stated in the table.

Peroxide value (*2.5.5*)

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Maximum 10.0.

Saponification value (*2.5.6*)

Maximum 3.0.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 2.00 g.

Total ash (*2.4.16*)

Maximum 0.2 per cent, determined on 2.0 g.

STORAGE

In an airtight container, protected from light.

LABELLING

The label states:

— the number of moles of ethylene oxide reacted per mole of oleyl alcohol (nominal value),

— the nominal iodine value for the type with 2 units of ethylene oxide per molecule.

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Macrogol Poly(vinyl alcohol) Grafted Copolymer

General Notices

(Ph. Eur. monograph 2523)

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DEFINITION

Grafted copolymer of macrogol and poly(vinyl alcohol), having a mean relative molecular mass of about 45 000.

It consists of about 75 per cent of poly(vinyl alcohol) units and 25 per cent of macrogol units. It may contain *Anhydrous colloidal silica (0434)* to improve flowability.

CHARACTERS

Appearance

White or slightly yellowish powder; opalescent solutions may be obtained during testing due to the presence of anhydrous colloidal silica.

Solubility

Very soluble in water, practically insoluble in anhydrous ethanol and in acetone. It dissolves in dilute acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *macrogol poly(vinyl alcohol) grafted copolymer CRS*.

Preparation Dissolve 0.2 g in 20 mL of *water R*, spread a few drops of the solution on a thallium bromoiodide plate and evaporate the solvent at 110 °C for 30 min.

B. Dissolve 0.4 g in 2 mL of *water R*. Place 1 mL of the solution on a glass plate and allow to dry. A transparent film is formed.

TESTS

pH (*2.2.3*)

5.0 to 8.0.

D *dioxide-free water R* and dilute to 25.0 mL with the same solvent.

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Ester value

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Ester value

10 to 75.

Determine the acid value (I_A) as follows. Dissolve 5.00 g in 100 mL of *distilled water R* while stirring with a magnetic stirrer. Titrate with *0.01 M alcoholic potassium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank test under the same conditions.

$$I_A = \frac{0.561\left(n_1 - n_2\right)}{m}$$

n_1 = volume of titrant used in the test, in millilitres;

n_2 = volume of titrant used in the blank test, in millilitres;

m = mass of the sample, in grams.

Determine the saponification value (I_S) (*2.5.6*) on 5.00 g, using 50.0 mL of *0.5 M alcoholic potassium hydroxide* and stirring vigorously with a magnetic stirrer.

The ester value (I_E) is calculated from the saponification value (I_S) and the acid value (I_A):

$$I_E = I_S - I_A$$

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Impurity A

Liquid chromatography (*2.2.29*).

Test solution Introduce 0.250 g of the substance to be examined into a 10 mL volumetric flask and add about 1 mL of *methanol R*. Sonicate. Add about 8 mL of *water R* and dilute to 10.0 mL with the same solvent. Filter.

Reference solution (a) Dissolve 5.0 mg of *vinyl acetate CRS* (impurity A) in *methanol R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 5 mg of *vinyl acetate R* (impurity A) and 5 mg of *1-vinylpyrrolidin-2-one R* in 10 mL of *methanol R* and dilute to 50 mL with *water R*. Dilute 1 mL of the solution to 20 mL with *water R*.

A precolumn containing *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) may be used if a matrix effect is observed.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

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Mobile phase:

— *mobile phase A*: *acetonitrile R1*, *methanol R2*, *water for chromatography R* (5:5:90 *V/V/V*);

— *mobile phase B*: *methanol R2*, *acetonitrile R1*, *water for chromatography R* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 40	100 → 85	0 → 15
40 - 42	85 → 0	15 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL.

Retention time Impurity A = about 19 min; 1-vinylpyrrolidin-2-one = about 25 min.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and 1-vinylpyrrolidin-2-one.

Limit:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (100 ppm).

Impurity B

Liquid chromatography (*2.2.29*).

Test solution Mix 0.200 g of the substance to be examined with *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 30 mg of *citric acid monohydrate R* and 0.100 g of *acetic acid R* (impurity B) in the mobile phase. Shake gently to dissolve and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 0.50 g/L solution of *sulfuric acid R*.

Flow rate 1.0 mL/min.

Processing math: 100%

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Detection Spectrophotometer at 205 nm.

Injection 20 µL. After each injection, rinse the column with a mixture of equal volumes of *acetonitrile R1* and a 0.50 g/L solution of *sulfuric acid R*.

Retention time Impurity B = about 5 min; citric acid = about 7 min.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to impurity B and citric acid.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (1.5 per cent).

Sulfated ash (*2.4.14*)

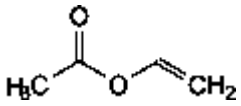
Maximum 3.0 per cent, determined on 5.0 g.

Loss on drying (*2.2.32*)

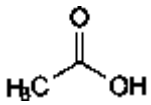
Maximum 5.0 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C.

IMPURITIES

Specified impurities *A, B.*



A. ethenyl acetate,



B. acetic acid.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the

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purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for macrogol poly(vinyl alcohol) grafted copolymer used as film former in film-coated tablets.

Viscosity (*2.2.10*)

Typically less than 250 mPa·s, determined on a 20 per cent *m/m* solution, using a rotating viscometer at 25 °C and rotation speed of 100 r/min.

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Macrogol Stearate

General Notices

(Ph. Eur. monograph 1234)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of monoesters and diesters of mainly stearic (octadecanoic) acid and/or palmitic (hexadecanoic) acid and macrogols. It may be obtained by ethoxylation or by esterification of macrogols with stearic acid 50 (type I) or stearic acid 95 (type II) (see *Stearic acid (1474)*). It may contain free macrogols. The average polymer length is equivalent to 6 to 100 ethylene oxide units per molecule (nominal value).

CHARACTERS

Appearance

White or slightly yellowish, waxy mass.

Solubility

Soluble in ethanol (96 per cent) and in 2-propanol. Macrogol stearate corresponding to a product with 6-9 units of ethylene oxide per molecule is practically insoluble, but freely dispersible in water and miscible with fatty oils and with waxes. Macrogol stearate corresponding to a product with 20-100 units of ethylene oxide per molecule is soluble in water and practically insoluble in fatty oils and in waxes.

IDENTIFICATION

A. Saponification value (see Tests).
B. Composition of fatty acids (see Tests).

TESTS

Alkalinity

Dissolve 2.0 g in *ethanol (96 per cent) R* and dilute to 20 mL with the same solvent. To 2 mL of this solution add 0.05 mL of *phenol red solution R*. The solution is not red.

Melting point (*2.2.15*)

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See Table 1234.-1.

Melt about 10 g at 80-90 °C. Introduce a sufficient amount of the substance into the tube by capillary action to form a column of the prescribed height. Allow to stand at 0 °C for 2 h.

Acid value (*2.5.1*)

Maximum 4.0, determined on 2.0 g.

Hydroxyl value (*2.5.3, Method A*)

See Table 1234.-1.

Iodine value (*2.5.4*)

Maximum 2.0.

Saponification value (*2.5.6*)

See Table 1234.-1.

Table 1234.-1

Ethylene oxide units per molecule (nominal value)	Melting point (°C)	Hydroxyl value	Saponification value
6	26 - 37	80 - 110	85 - 115
8 - 9	26 - 35	80 - 105	88 - 100
20	33 - 40	50 - 62	46 - 56
32	46 - 50	20 - 40	30 - 45
40 - 50	38 - 52	23 - 40	20 - 35
100	48 - 60	15 - 30	5 - 20

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*).

Composition of the fatty acid fraction of the substance:

	Type of fatty acid used	Composition of fatty acids
Macrogol stearate type I	Stearic acid 50	*Stearic acid*: 40.0 per cent to 60.0 per cent, *Sum of the contents of palmitic and stearic acids*: not less than 90.0 per cent.

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	Type of fatty acid used	Composition of fatty acids
Macrogol stearate type II	Stearic acid 95	*Stearic acid*: 90.0 per cent to 99.0 per cent, *Sum of the contents of palmitic and stearic acids*: not less than 96.0 per cent.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.50 g. Use as the solvent a mixture of equal volumes of *anhydrous methanol R* and *methylene chloride R*.

Total ash (*2.4.16*)

Maximum 0.3 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

LABELLING

The label states:

— the number of ethylene oxide units per molecule (nominal value);

— the type of macrogol stearate.

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Macrogol Stearyl Ether

General Notices

(Ph. Eur. monograph 1340)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of ethers obtained by ethoxylation of stearyl alcohol. It may contain some free macrogols and various amounts of free stearyl alcohol. The number of moles of ethylene oxide reacted per mole of stearyl alcohol is 2 to 20 (nominal value).

CHARACTERS

Appearance

White or yellowish-white, waxy, unctuous mass, pellets, microbeads or flakes.

Solubility

— macrogol stearyl ether with 2 moles of ethylene oxide reacted per mole: practically insoluble in water, soluble in ethanol (96 per cent) with heating and in methylene chloride;

— macrogol stearyl ether with 10 moles of ethylene oxide reacted per mole: soluble in water and in ethanol (96 per cent);

— macrogol stearyl ether with 20 moles of ethylene oxide reacted per mole: soluble in water, in ethanol (96 per cent) and in methylene chloride.

After melting, it solidifies at about 45 °C.

IDENTIFICATION

A. Hydroxyl value (see Tests).
B. Iodine value (see Tests).
C. Saponification value (see Tests).
D. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10.0 g in a mixture of 1 volume of *water R* and 9 volumes of *methanol R* and dilute to 75 mL with the same mixture of solvents. Add 60 mL of *heptane R* and shake for 3 min. The formation of foam can be reduced by the addition of a few drops of *ethanol*

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(96 per cent) R. Filter the upper layer through *anhydrous sodium sulfate R*, wash the filter with 3 quantities, each of 10 mL, of *heptane R* and evaporate the combined filtrates to dryness. Dissolve 50 mg of the residue in 10 mL of *methanol R* (the solution may be opalescent).

Reference solution Dissolve 25 mg of *stearyl alcohol CRS* in *methanol R* and dilute to 25 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *ethyl acetate R*.

Application 20 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with vanillin-sulfuric acid reagent prepared as follows: dissolve 0.5 g of *vanillin R* in 50 mL of *ethanol (96 per cent) R* and dilute to 100 mL with *sulfuric acid R*; allow to dry in air; heat at about 130 °C for 15 min and allow to cool in air.

Results The chromatogram obtained with the test solution shows several spots; one of these spots corresponds to the principal spot in the chromatogram obtained with the reference solution.

E. Dissolve or disperse 0.1 g in 5 mL of *ethanol (96 per cent) R*, add 2 mL of *water R*, 10 mL of *dilute hydrochloric acid R*, 10 mL of *barium chloride solution R1* and 10 mL of a 100 g/L solution of *phosphomolybdic acid R*. A precipitate is formed.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 5.0 g in *ethanol (96 per cent) R* and dilute to 50 mL with the same solvent.

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of *ethanol (96 per cent) R* and 10 mL of *water R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (*2.5.1*)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

Number of moles of ethylene oxide reacted per mole (nominal value)	Hydroxyl value
2	150 - 180

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Number of moles of ethylene oxide reacted per mole (nominal value)	Hydroxyl value
10	75 - 90
20	40 - 60

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Saponification value (*2.5.6*)

Maximum 3.0, determined on 10.0 g.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.00 g.

STORAGE

In an airtight container.

LABELLING

The label states the number of moles of ethylene oxide reacted per mole of stearyl alcohol (nominal value).

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Macrogols

General Notices

(Ph. Eur. monograph 1444)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixtures of polymers with the general formula H-[OCH_2-CH_2]$_n$-OH where *n* represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

CHARACTERS

Type of macrogol	Appearance	Solubility
300 400 600	clear, viscous, colourless or almost colourless, hygroscopic liquid	miscible with water, very soluble in acetone, in ethanol (96 per cent) and in methylene chloride, practically insoluble in fatty oils and in mineral oils
1000	white or almost white, hygroscopic solid with a waxy or paraffin-like appearance	very soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride, practically insoluble in fatty oils and in mineral oils
1500	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, freely soluble in ethanol (96 per cent), practically insoluble in fatty oils and in mineral oils
3000 3350	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils and in mineral oils
4000 6000 8000	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, practically insoluble in ethanol (96 per cent), in fatty oils and in mineral oils

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Type of macrogol	Appearance	Solubility
20 000 35 000	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water, soluble in methylene chloride, practically insoluble in ethanol (96 per cent), in fatty oils and in mineral oils

IDENTIFICATION

A. Viscosity (see Tests).

B. To 1 g in a test-tube add 0.5 mL of *sulfuric acid R*, close the test-tube with a stopper fitted with a bent delivery tube and heat until white fumes are evolved. Collect the fumes via the delivery tube into 1 mL of *mercuric chloride solution R*. An abundant, white, crystalline precipitate is formed.

C. To 0.1 g add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R* and mix thoroughly with a glass rod. Add 5 mL of *methylene chloride R* and shake. The liquid phase becomes blue.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 12.5 g in *water R* and dilute to 50 mL with the same solvent.

Acidity or alkalinity

Dissolve 5.0 g in 50 mL of *carbon dioxide-free water R* and add 0.15 mL of *bromothymol blue solution R1*. The solution is yellow or green. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Viscosity (*2.2.9*)

The viscosity is calculated using a density given in Table 1444.-1.

For macrogols with a relative molecular mass greater than 400, determine the viscosity on a 50 per cent *m/m* solution of the substance to be examined.

Freezing point (*2.2.18*)

See Table 1444.-2.

Hydroxyl value

Introduce *m* g (see Table 1444.-3) into a dry conical flask fitted with a reflux condenser. Add 25.0 mL of *phthalic anhydride solution R*, swirl to dissolve and boil under a reflux condenser on a hot plate for 60 min. Allow to cool. Rinse the condenser first with 25 mL of *pyridine R* and then with 25 mL of *water R*, add 1.5 mL of *phenolphthalein solution R* and titrate with *1 M sodium hydroxide* until a faint pink colour is obtained (n_1 mL). Carry out a blank test (n_2 mL). Calculate the hydroxyl value using the following expression:

$$\frac{56.1 \times \left(n_2 - n_1\right)}{m}$$

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For macrogols with a relative molecular mass greater than 1000, if the water content is more than 0.5 per cent, dry a sample of suitable mass at 100-105 °C for 2 h and carry out the determination of the hydroxyl value on the dried sample.

Table 1444.-1

Type of macrogol	Kinematic viscosity ($mm^2 \cdot s^{-1}$)	Dynamic viscosity (mPa·s)	Density* (g/mL)
300	71 - 94	80 - 105	1.120
400	94 - 116	105 - 130	1.120
600	13.9 - 18.5	15 - 20	1.080
1000	20.4 - 27.7	22 - 30	1.080
1500	31 - 46	34 - 50	1.080
3000	69 - 93	75 - 100	1.080
3350	76 - 110	83 - 120	1.080
4000	102 - 158	110 - 170	1.080
6000	185 - 250	200 - 270	1.080
8000	240 - 472	260 - 510	1.080
20 000	2500 - 3200	2700 - 3500	1.080
35 000	10 000 - 13 000	11 000 - 14 000	1.080

*Density of the substance for macrogols 300 and 400. Density of the 50 per cent *m/m* solution for the other macrogols.

Table 1444.-2

Type of macrogol	Freezing point (°C)
600	15 - 25
1000	35 - 40
1500	42 - 48
3000	50 - 56
3350	53 - 57
4000	53 - 59

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Type of macrogol	Freezing point (°C)
6000	55 - 61
8000	55 - 62
20 000	minimum 57
35 000	minimum 57

Table 1444.-3

Type of macrogol	Hydroxyl value	*m* (g)
300	340 - 394	1.5
400	264 - 300	1.9
600	178 - 197	3.5
1000	107 - 118	5.0
1500	70 - 80	7.0
3000	34 - 42	12.0
3350	30 - 38	12.0
4000	25 - 32	14.0
6000	16 - 22	18.0
8000	12 - 16	24.0
20 000	-	-
35 000	-	-

Reducing substances

Dissolve 1 g in 1 mL of a 10 g/L solution of *resorcinol R* and warm gently if necessary. Add 2 mL of *hydrochloric acid R*. After 5 min the solution is not more intensely coloured than reference solution R_3 (*2.2.2, Method I*).

Formaldehyde

Maximum 30 ppm.

Test solution To 1.00 g add 0.25 mL of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 mL of *sulfuric acid R*. Allow to stand for 15 min and dilute slowly to 10 mL with *water R*.

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Reference solution Dilute 0.860 g of *formaldehyde solution R* to 100 mL with *water R*. Dilute 1.0 mL of this solution to 100 mL with *water R*. In a 10 mL flask, mix 1.00 mL of this solution and 0.25 mL of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 mL of *sulfuric acid R*. Allow to stand for 15 min and dilute slowly to 10 mL with *water R*.

Blank solution In a 10 mL flask mix 1.00 mL of *water R* and 0.25 mL of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 mL of *sulfuric acid R*. Dilute slowly to 10 mL with *water R*.

Determine the absorbance (*2.2.25*) of the test solution at 567 nm, against the blank solution. It is not higher than that of the reference solution.

If the use of macrogols with a higher content of formaldehyde may have adverse effects, the competent authority may impose a limit of not more than 15 ppm.

Ethylene glycol and diethylene glycol

carry out this test only if the macrogol has a relative molecular mass below 1000.

Gas chromatography (*2.2.28*).

Test solution Dissolve 5.00 g of the substance to be examined in *acetone R* and dilute to 100.0 mL with the same solvent.

Reference solution Dissolve 0.10 g of *ethylene glycol R* and 0.50 g of *diethylene glycol R* in *acetone R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *acetone R*.

Column:

— *material*: glass;

— *size*: *l* = 1.8 m, Ø = 2 mm;

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R*, impregnated with 5 per cent *m/m* of *macrogol 20 000 R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: if necessary, precondition the column by heating at 200 °C for about 15 h; adjust the initial temperature of the column to obtain a retention time of 14-16 min for diethylene glycol; raise the temperature of the column by about 30 °C at a rate of 2 °C/min but without exceeding 170 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Injection 2 µL.

Carry out 5 replicate injections to check the repeatability of the response.

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Limit Maximum 0.4 per cent, calculated as the sum of the contents of ethylene glycol and diethylene glycol.

Ethylene oxide and dioxan (2.4.25)

Maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Water (2.5.12)

Maximum 2.0 per cent for macrogols with a relative molecular mass not greater than 1000 and maximum 1.0 per cent for macrogols with a relative molecular mass greater than 1000, determined on 2.00 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

LABELLING

The label states:

— the type of macrogol;

— the content of formaldehyde.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for macrogols used as solvent.

Viscosity

(see Tests).

The following characteristics may be relevant for macrogols used as suspension stabiliser and thickener.

Viscosity

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(see Tests).

The following characteristic may be relevant for macrogols used as lubricant in tablets.

Particle-size distribution (*2.9.31*)

The following characteristics may be relevant for macrogols used as suppository base and for macrogols used in hydrophilic ointments.

Viscosity

(see Tests).

Melting point (*2.2.15*)

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Magaldrate

General Notices

(Ph. Eur. monograph 1539)

$Al_5Mg_{10}(OH)_{31}(SO_4)_2,xH_2O$ 1097 (anhydrous substance) *74978-16-8*

Action and use

Antacid.

Preparation

Magaldrate Oral Suspension

Ph Eur

DEFINITION

Magaldrate is composed of aluminium and magnesium hydroxides and sulfates. Its composition corresponds approximately to the formula $Al_5Mg_{10}(OH)_{31}(SO_4)_2,xH_2O$.

Content

90.0 per cent to 105.0 per cent (dried substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It is soluble in dilute mineral acids.

IDENTIFICATION

A. Dissolve 0.6 g in 20 mL of *3 M hydrochloric acid R*, add about 30 mL of *water R* and heat to boiling. Adjust to pH 6.2 with *dilute ammonia R1*, continue boiling for a further 2 min, filter and retain the precipitate and the filtrate. To 2 mL of the filtrate add 2 mL of *ammonium chloride solution R* and neutralise with a solution prepared by dissolving 2 g of *ammonium carbonate R* and 2 mL of *dilute*

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ammonia R1 in 20 mL of *water R*; no precipitate is produced. Add *disodium hydrogen phosphate solution R*; a white, crystalline precipitate is produced which does not dissolve in *dilute ammonia R1*.

B. The precipitate retained in identification test A gives the reaction of aluminium (*2.3.1*).

C. The filtrate retained in identification test A gives reaction (a) of sulfates (*2.3.1*).

TESTS

Soluble chlorides

Maximum 3.5 per cent.

To 0.5 g add 25 mL of *dilute nitric acid R* and shake until completely dissolved. Add 10.0 mL of *0.1 M silver nitrate* and 2 mL of *ferric ammonium sulfate solution R2* as indicator. Titrate with *0.1 M ammonium thiocyanate*, shaking vigorously until a persistent brownish-red colour is obtained.

1 mL of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Soluble sulfates

Maximum 1.9 per cent.

Disperse 0.5 g in 25 mL of *water R*, boil for 5 min, cool, dilute to 25.0 mL with *water R*, mix and filter. To 2.5 mL of the filtrate, add 30 mL of *water R*, neutralise to *blue litmus paper R* with *hydrochloric acid R*, add 3 mL of *1 M hydrochloric acid*, 3 mL of a 120 g/L solution of *barium chloride R* and dilute to 50 mL with *water R*. Mix and allow to stand for 10 min. Any opalescence in the solution is not more intense than that in a standard prepared at the same time in the same manner using 1 mL of *0.01 M sulfuric acid* instead of 2.5 mL of filtrate.

Sulfates

16.0 per cent to 21.0 per cent (dried substance).

Dissolve 0.875 g in a mixture of 5 mL of *glacial acetic acid R* and 10 mL of *water R* and dilute to 25.0 mL with *water R*. Prepare a chromatographic column of 1 cm in internal diameter containing 15 mL of *cation-exchange resin R* (150-300 µm), previously washed with 30 mL of *water R*. Transfer 5.0 mL of the solution to be examined to the column and elute with 15 mL of *water R*. To the eluate add 5 mL of a 53.6 g/L solution of *magnesium acetate R*, 32 mL of *methanol R* and 0.2 mL of *alizarin S solution R*. Add from a burette about 4.0 mL of *0.05 M barium chloride*, add a further 0.2 mL of *alizarin S solution R* and slowly complete the titration until the yellow colour disappears and a violet-red tinge is visible.

1 mL of *0.05 M barium chloride* is equivalent to 4.803 mg of SO_4.

Aluminium hydroxide

32.1 per cent to 45.9 per cent (dried substance).

Dissolve 0.800 g in 10 mL of *dilute hydrochloric acid R*, heating on a water-bath. Cool and dilute to 50.0 mL with *water R*. To 10.0 mL of this solution, add *dilute ammonia R1* until a precipitate begins to appear. Add the smallest quantity of *dilute hydrochloric acid R* needed to dissolve the precipitate and dilute to 20 mL with *water R*. Carry out the complexometric titration of aluminium (*2.5.11*).

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1 mL of *0.1 M sodium edetate* is equivalent to 7.80 mg of $Al(OH)_3$.

Magnesium hydroxide

49.2 per cent to 66.6 per cent (dried substance).

Dissolve 0.100 g in 2 mL of *dilute hydrochloric acid R* and transfer to a 500 mL conical flask with the aid of *water R*. Dilute to 200 mL with *water R*, add 20 mL of *triethanolamine R* with shaking, 10 mL of *ammonium chloride buffer solution pH 10.0 R* and about 50 mg of *mordant black 11 triturate R*. Titrate with *0.1 M sodium edetate* until the colour changes from violet to pure blue.

1 mL of *0.1 M sodium edetate* is equivalent to 5.832 mg of $Mg(OH)_2$.

Sodium

Maximum 0.10 per cent.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Weigh 2.00 g into a 100 mL volumetric flask, place in an ice-bath, add 5 mL of *nitric acid R* and swirl to mix. Allow to warm to room temperature and dilute to 100 mL with *water R*. Filter, if necessary, to obtain a clear solution. Dilute 10.0 mL of the filtrate to 100.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluted as necessary with *dilute nitric acid R*.

Source Sodium hollow-cathode lamp.

Wavelength 589 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

10.0 per cent to 20.0 per cent, determined on 1.000 g by drying in an oven at 200 °C for 4 h.

ASSAY

To 1.500 g add 50.0 mL of *1 M hydrochloric acid*. Titrate the excess hydrochloric acid with *1 M sodium hydroxide* to pH 3.0, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *1 M hydrochloric acid* is equivalent to 35.40 mg of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$.

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Magaldrate Oral Suspension

General Notices

Action and use

Antacid.

DEFINITION

Magaldrate Oral Suspension contains Magaldrate in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous magaldrate, $Al_5Mg_{10}(OH)_{31}(SO_4)_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the oral suspension containing the equivalent of 0.8 g of anhydrous magaldrate in 20 mL of *3M hydrochloric acid*, add 30 mL of *water* and heat to boiling. Add 6M *ammonia* until a pH of 6.2 is obtained, continue boiling for a further 2 minutes, filter and retain the precipitate and the filtrate. To 2 mL of the filtrate add 2 mL of *ammonium chloride solution* and neutralise with a solution prepared by dissolving 2 g of *ammonium carbonate* and 2 mL of 6M *ammonia* in sufficient *water* to produce 20 mL; no precipitate is produced. Add *disodium hydrogen phosphate solution*; a white, crystalline precipitate is produced which is insoluble in 6M *ammonia*.

B. The precipitate retained in test A yields the reaction characteristic of *aluminium salts*, Appendix VI.

C. The filtrate obtained in test A yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Neutralising capacity

Disperse a quantity containing the equivalent of 0.8 g of anhydrous magaldrate in 70 mL of water, heat to 37° and mix for 1 minute. Maintain the temperature at 37° and, while stirring continuously, add from a pipette 30 mL of *1M hydrochloric acid VS*. Stir for 15 minutes and, over a period not exceeding 5 minutes, titrate the excess acid with *1M sodium hydroxide VS* to a pH of 3.5 which is stable for a period of 10 to 15 seconds. Not more than 12 mL of *1M sodium hydroxide VS* is required.

Magnesium hydroxide

Not less than 49.2% and not more than 66.6% of the content of anhydrous magaldrate when determined by the following method. Mix a quantity of the oral suspension containing the equivalent of 1 g of magaldrate in 30 mL of *2M hydrochloric acid* and add sufficient *water* to produce 100 mL (solution A). Dilute 10 mL of this solution to 200 mL with *water*. Add, while stirring, 1 g of *ammonium chloride*, 20 mL of

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triethanolamine, 10 mL of *ammonia buffer pH 10.9* and 0.4 mL of *mordant black 11 solution*. Titrate with 0.05M *disodium edetate VS* until a blue colour is obtained. Repeat the procedure without the substance being examined. The difference between the titrations represents the amount of disodium edetate required. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.916 g of $Mg(OH)_2$.

Aluminium hydroxide

Not less than 32.1% and not more than 45.9% of the stated content of anhydrous magaldrate when determined by the following method. Dilute 10 mL of solution A obtained in the test for Magnesium hydroxide with 20 mL of *water*. Add 25 mL of 0.05M *disodium edetate VS*, mix, allow to stand for 5 minutes and add 20 mL of *acetate buffer pH 4.4*, 60 mL of *ethanol (96%)* and 2 mL of a 0.026% w/v solution of *dithizone* in *ethanol (96%)*. Titrate with *0.05M zinc sulfate VS* until a bright pink colour is obtained. Repeat the procedure without the substance being examined. The difference between the titrations represents the amount of disodium edetate required. Each mL of 0.05M *disodium edetate VS* is equivalent to 3.90 g of $Al(OH)_3$.

Microbial contamination

Carry out a quantitative evaluation for Enterobacteria and certain other Gram-negative bacteria, Appendix XVI B1. 0.01 mL of the preparation gives a negative result, Table 1 (most probable number of bacteria per gram fewer than 10^2).

ASSAY

To a quantity of the oral suspension containing the equivalent of 3 g of anhydrous magaldrate add 100 mL of *1M hydrochloric acid VS* and mix using a magnetic stirrer to achieve dissolution. Titrate the excess acid with *1M sodium hydroxide VS* to pH 3, determined potentiometrically. Repeat the procedure without the preparation being examined. The difference between the titrations represents the amount of hydrochloric acid required. Each mL of *1M hydrochloric acid VS* is equivalent to 35.40 mg of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of anhydrous magaldrate.

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Magnesium Acetate Tetrahydrate

General Notices

(Ph. Eur. monograph 2035)

$Mg(CH_3COO)_2,4H_2O$ 214.5 *16674-78-5*

Action and use

Used in dialysis solutions.

Ph Eur

DEFINITION

Content

98.0 per cent to 101.0 per cent of magnesium acetate (anhydrous substance).

CHARACTERS

Appearance

Colourless crystals or white or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve about 100 mg in 2 mL of *water R*. Add 1 mL of *dilute ammonia R1* and heat. A white precipitate is formed that dissolves slowly on addition of 5 mL of *ammonium chloride solution R*. Add 1 mL of *disodium hydrogen phosphate solution R*. A white crystalline precipitate is formed.

B. It gives reaction (b) of acetates (*2.3.1*).

TESTS

pH (*2.2.3*)

7.5 to 8.5.

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Chloride (*2.4.4*)

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Chlorides (*2.4.4*)

Maximum 330 ppm.

Dissolve 1.0 g in *water R* and dilute to 100 mL with the same solvent.

Nitrates

Maximum 3 ppm.

Dissolve 1.0 g in *distilled water R* and dilute to 10 mL with the same solvent, add 5 mg of *sodium chloride R*, 0.05 mL of *indigo carmine solution R* and while stirring, 10 mL of *nitrogen-free sulfuric acid R*. A blue colour is produced which persists for at least 10 min.

Sulfates (*2.4.13*)

Maximum 600 ppm.

Dissolve 0.25 g in *distilled water R* and dilute to 15 mL with the same solvent.

Aluminium (*2.4.17*)

Maximum 1 ppm.

Prescribed solution Dissolve 4.0 g in *water R* and dilute to 100 mL with the same solvent. Add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Calcium (*2.4.3*)

Maximum 100 ppm.

Dissolve 1.0 g in *distilled water R* and dilute to 15 mL with the same solvent.

Potassium

Maximum 0.1 per cent.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution Dissolve 0.5 g in *water R* and dilute to 100 mL with the same solvent.

Reference solutions Prepare the reference solutions using *potassium standard solution (600 ppm K) R*, diluted as necessary with *water R*.

Wavelength 766.5 nm.

Sodium

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Maximum 0.5 per cent.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution Dissolve 1.0 g in *water R* and dilute to 100 mL with the same solvent.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluted as necessary with *water R*.

Wavelength 589.0 nm.

Readily oxidisable substances

Dissolve 2.0 g in 100 mL of boiling *water R*, add 6 mL of a 150 g/L solution of *sulfuric acid R* and 0.3 mL of *0.02 M potassium permanganate*. Mix and boil gently for 5 min. The pink colour is not completely discharged.

Water (*2.5.12*)

33.0 per cent to 35.0 per cent, determined on 0.100 g.

ASSAY

Dissolve 0.150 g in 300 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 14.24 mg of $C_4H_6MgO_4$.

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Magnesium Aluminometasilicate

General Notices

(Ph. Eur. monograph 2854)

Action and use

Excipient.

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DEFINITION

Magnesium aluminometasilicate of synthetic origin exists in 2 forms (type A and type B), which differ in their apparent pH. It contains a variable quantity of water.

Content (type A and type B):

— *silicon dioxide* (SiO_2; M_r 60.1): 29.2 per cent to 35.6 per cent (dried substance);

— *aluminium oxide* (Al_2O_3; M_r 102.0): 29.1 per cent to 35.5 per cent (dried substance);

— *magnesium oxide* (MgO; M_r 40.30): 11.4 per cent to 14.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder or granules.

Solubility

Practically insoluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. To 0.5 g add 5 mL of a mixture of 1 volume of *sulfuric acid R* and 2 volumes of *water R* and heat until white fumes evolve. Cool, add 20 mL of *water R* and filter. Use the filtrate for identification tests B and C. Wash the residue with *water R*. The residue gives the reaction of silicates (*2.3.1*).

B. Neutralise the filtrate obtained in identification test A with *ammonia R*. A white, gelatinous precipitate is formed. Centrifuge and keep the supernatant for identification test C. Dissolve the precipitate in *dilute hydrochloric acid R*. Add dropwise *dilute sodium hydroxide solution R*. A white, gelatinous precipitate is formed. Filter and add a few drops of *phenolphthalein solution R* to the residue. The residue turns pink. Wash the residue with *water R* until the pink colour is completely discharged and the residue remains white upon addition of a drop of

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phenolphthalein solution R. Sprinkle a few crystals of *sodium fluoride R* on the residue. The residue, in contact with the crystals, turns pink again in a short time.

C. To 2 mL of the supernatant obtained after centrifugation in identification test B, add 1 mL of *dilute ammonia R1* and 1 mL of *ammonium chloride solution R*. Upon the addition of *dilute ammonia R1* a white precipitate may form, which dissolves after addition of the *ammonium chloride solution R*. Add 1 mL of *disodium hydrogen phosphate solution R*. A white precipitate is formed.

TESTS

Solution S

Disperse 10.0 g in 100.0 mL of *water R* and boil gently for 15 min with shaking. After cooling, dilute to 100.0 mL with *water R* and centrifuge. Dilute 50.0 mL of the clear supernatant to 100.0 mL with *water R*.

pH (*2.2.3*)

6.0 to 8.5 for type A; 8.5 to 10.5 for type B.

Disperse 2.0 g in 50 mL of *carbon dioxide-free water R*. Read the pH after the electrode has been immersed in the suspension for 2 min.

Water-soluble salts

Maximum 1.5 per cent.

Evaporate 25 mL of solution S to dryness on a water-bath and heat at 700 °C for 2 h. The residue weighs a maximum of 19 mg.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dilute 2 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.5 per cent.

Dilute 10 mL of solution S to 100 mL with *distilled water R*. Dilute 6 mL of the solution to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 300 ppm.

Disperse 0.10 g in 8 mL of *dilute nitric acid R*, boil for 1 min, cool and dilute to 30.0 mL with *water R*. Centrifuge and use 10 mL of the clear supernatant.

Loss on drying (*2.2.32*)

Maximum 20.0 per cent, determined on 1.000 g by drying in an oven at 110 °C for 7 h.

Neutralising capacity

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Minimum 210 mL of *0.1 M hydrochloric acid* per gram of dried substance.

To 0.200 g in a glass-stoppered flask add 100.0 mL of *0.1 M hydrochloric acid*. Stopper the flask tightly, shake at 37 ± 2 °C for 1 h and filter. Titrate 50.0 mL of the filtrate with *0.1 M sodium hydroxide* to pH 3.5 while stirring thoroughly. Carry out a blank determination.

ASSAY

Silicon dioxide

In a suitable container, disperse 1.000 g (*m*) in 30 mL of *dilute hydrochloric acid R* and evaporate to dryness on a water-bath. Moisten the residue with *hydrochloric acid R* and evaporate to dryness on a water-bath. To the residue add 8 mL of *hydrochloric acid R*, stir, add 25 mL of boiling *water R* and stir again. Allow to stand, then filter the supernatant through filter paper. To the residue in the container add 10 mL of boiling *water R*, stir, allow to stand, then filter the supernatant through the filter paper. Wash the residue in the container with 3 quantities, each of 10 mL, of boiling *water R*, each time filtering the washings through the filter paper. Add 50 mL of *water R* to the residue in the container, heat on a water-bath for 15 min and filter through the filter paper. Wash the residue on the filter paper with boiling *water R* until no further precipitate is formed when 1 mL of *silver nitrate solution R1* is added to 5 mL of the washings. Transfer the residue and the filter paper to a platinum crucible that has been weighed prior to the transfer (*a*). Heat strongly to incinerate and continue to heat at 775-825 °C for 1 h. Cool and weigh (*b*).

Calculate the percentage content of silicon dioxide (SiO_2) using the following expression:

$$\frac{b-a}{m} \times 100$$

Aluminium oxide

In a conical flask disperse 1.250 g in 15 mL of *dilute hydrochloric acid R* and 50 mL of *water R* and heat on a water-bath for 15 min. To this solution add 8 mL of *hydrochloric acid R* and heat on a water-bath for 10 min. After cooling, transfer the solution to a 250 mL volumetric flask, rinse the conical flask with *water R* and add the washings to the volumetric flask. Dilute to volume with *water R*. Centrifuge and use the supernatant as the test solution. Retain a portion for use in the assay for magnesium oxide.

Carry out the complexometric titration of aluminium (*2.5.11*). Carry out a blank determination.

1 mL of *0.1 M sodium edetate* is equivalent to 5.098 mg of Al_2O_3.

Magnesium oxide

Transfer 100.0 mL of the test solution obtained in the assay for aluminium oxide to a conical flask, add 25 mL of a 50 per cent *V/V* solution of *triethanolamine R* and shake. Add 25 mL of *ammonium chloride buffer solution pH 10.7 R* and 40 mg of *mordant black 11 triturate R*. Titrate with *0.1 M sodium edetate* until the colour changes from violet to pure blue.

1 mL of *0.1 M sodium edetate* is equivalent to 4.030 mg of MgO.

STORAGE

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In an airtight container.

LABELLING

The label states the type of magnesium aluminometasilicate.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for magnesium aluminometasilicate used as glidant in tablets and capsules.

Particle-size distribution (*2.9.31*)

Specific surface area (*2.9.26, Method I*)

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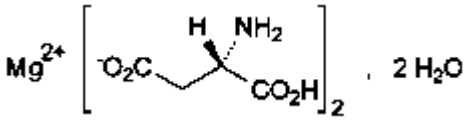
Magnesium Aspartate

General Notices

(Magnesium Aspartate Dihydrate, Ph. Eur. monograph 1445)



$C_8H_{12}MgN_2O_8,2H_2O$ 324.5 *215533-00-9*

Ph Eur

DEFINITION

Magnesium bis[(3*S*)-3-amino-3-carboxypropanoate] dihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water.

IDENTIFICATION

Carry out either tests A, C, D, E or tests B, C, D, E.

A. Specific optical rotation (2.2.7): + 22.0 to + 24.0 (anhydrous substance).

Dissolve 0.50 g in a 515 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same acid.

B. Enantiomeric purity (see Tests).

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 50 mL with the same solvent.

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Reference solution Dissolve 10 mg of *magnesium aspartate dihydrate CRS* in *water R* and dilute to 50 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Ignite about 15 mg until a white residue is obtained. Dissolve the residue in 1 mL of *dilute hydrochloric acid R*, neutralise to *red litmus paper R* by adding *dilute sodium hydroxide solution R* and filter if necessary. The solution gives the reaction of magnesium (*2.3.1*).

E. Water (see Tests).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 8.0 for solution S.

Enantiomeric purity

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.120 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 0.100 g of *D-aspartic acid R* (impurity A) in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 0.120 g of the substance to be examined in 90 mL of *water R*, add 0.3 mL of reference solution (a) and dilute to 100 mL with *water R*.

Reference solution (c) Dilute 0.3 mL of reference solution (a) to 100.0 mL with *water R*.

Column:

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— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *L-penicillamine coated silica gel for chiral separations R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *2-propanol R*, 0.5 g/L solution of *copper sulfate pentahydrate R* (5:95 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to magnesium aspartate (retention time = about 12 min): impurity A = about 0.85.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and magnesium aspartate.

Calculation of percentage content:

— for impurity A, use the concentration of impurity A in reference solution (c).

Limit:

— *impurity A*: maximum 0.3 per cent.

Other dicarboxylic acids

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.600 g of the substance to be examined in 2.0 mL of a 618 g/L solution of *hydrochloric acid R* and dilute to 10.0 mL with *water R*.

Reference solution (a) Dissolve 20.0 mg of *malic acid R* (impurity B) in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dissolve 10.0 mg of *maleic acid R* (impurity I) in *water R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solution (c) Dilute 1 mL of reference solution (b) to 10 mL with reference solution (a).

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *water R*.

Reference solution (e) Dissolve 10 mg of *fumaric acid R* (impurity C) in *water R* and dilute to 10 mL with the same solvent. Dilute 1 mL of the solution to 100 mL with *water R*.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

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— *stationary phase*: *cation-exchange resin R* (9 µm);

— *temperature*: 30 °C.

Mobile phase 0.39 g/L solution of *sulfuric acid R*.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL.

Run time 4 times the retention time of impurity I.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B and I; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity C.

Relative retention With reference to impurity I (retention time = about 7.5 min): impurity B = about 1.2; impurity C = about 2.0.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities I and B.

Calculation of percentage contents:

— for impurities C and I, use the concentration of impurity I in reference solution (b).

— for impurities other than C and I, use the concentration of impurity B in reference solution (d).

Limits:

— *impurity C*: maximum 0.10 per cent;

— *impurity I*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Ninhydrin-positive substances

Amino acid analysis (*2.2.56*). For analysis, use Method 1.

The concentrations of the test and reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter *2.2.46* are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A *dilute hydrochloric acid R1* or a sample preparation buffer suitable for the apparatus used.

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Test solution Dissolve 35.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* and 30 mg of *leucine R* in solution A and dilute to 50 mL with solution A. Dilute 1 mL of the solution to 200 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test solution, blank solution and reference solutions (a), (b) and (d) into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of magnesium aspartate dihydrate in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 500 ppm.

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Dilute 12 mL of solution S to 15 mL with *distilled water R*. Carry out the evaluation of the test after 30 min.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modification.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.04 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 50 ppm.

In a separating funnel, dissolve 0.20 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Water (*2.5.12*)

10.0 per cent to 16.0 per cent, determined on 0.100 g.

Dissolve the substance to be examined in a mixture of 2 mL of *anhydrous methanol R* and 10 mL of *formamide R1* at 50 °C protected from moisture. Allow to cool. Carry out a blank determination.

ASSAY

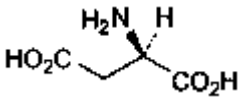
Dissolve 0.260 g in 10 mL of *water R* and carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 28.85 mg of $C_8H_{12}MgN_2O_8$.

IMPURITIES

Specified impurities *A, C, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E, F, G, H.*



A. (2*R*)-2-aminobutanedioic acid (D-aspartic acid),

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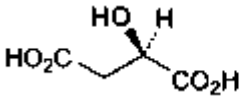
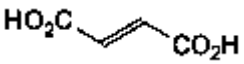
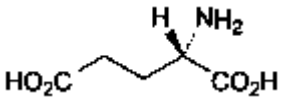

and enantiomer

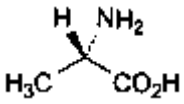
B. (2*RS*)-2-hydroxybutanedioic acid (malic acid),



C. (2*E*)-but-2-enedioic acid (fumaric acid),

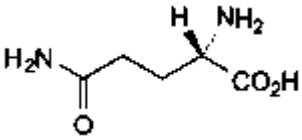


D. (2*S*)-2-aminopentanedioic acid (glutamic acid),

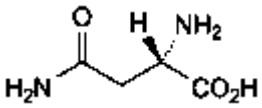


E. (2*S*)-2-aminopropanoic acid (alanine),

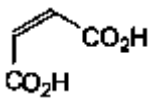
F. butanedioic acid (succinic acid),



G. (2*S*)-2,5-diamino-5-oxopentanoic acid (L-glutamine),



H. (2*S*)-2,4-diamino-4-oxobutanoic acid (asparagine),



I. (2*Z*)-but-2-enedioic acid (maleic acid).

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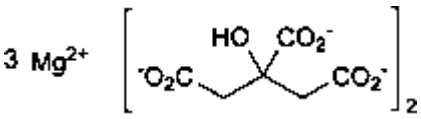
Magnesium Citrate

General Notices

Anhydrous Magnesium Citrate

(Ph. Eur. monograph 2339)



$Mg_3(C_6H_5O_7)_2$ 451.1 *3344-18-1*

Ph Eur

DEFINITION

Trimagnesium bis(2-hydroxypropane-1,2,3-tricarboxylate).

Content

15.0 per cent to 16.5 per cent of Mg (dried substance).

CHARACTERS

Appearance

White or almost white, fine, slightly hygroscopic powder.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute hydrochloric acid.

IDENTIFICATION

A. It gives the reaction of citrates (*2.3.1*).

B. It gives the reaction of magnesium (*2.3.1*).

C. pH (see Tests).

D. Loss on drying (see Tests).

TESTS

Solution S

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Dissolve 5.0 g in *carbon dioxide-free water R*, heating at 60 °C, cool and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solutions Y_7 or BY_6 (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 8.5 for solution S.

Oxalates

Maximum 280 ppm.

Dissolve 0.50 g in 4 mL of *water R*. Add 3 mL of *hydrochloric acid R* and 1 g of *activated zinc R*. Allow to stand for 5 min. Transfer the liquid to a tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R*. Heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of *potassium ferricyanide solution R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 4 mL of a 50 mg/L solution of *oxalic acid R*.

Sulfates (*2.4.13*)

Maximum 0.2 per cent.

Dilute 1.5 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 0.2 per cent.

Dilute 1.0 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 2.0 mL of solution S to 10 mL with *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 3.5 per cent, determined on 1.000 g by drying in an oven at 180 ± 10 °C for 5 h.

ASSAY

Dissolve 0.150 g in 50 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

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STORAGE

In a non-metallic, airtight container.

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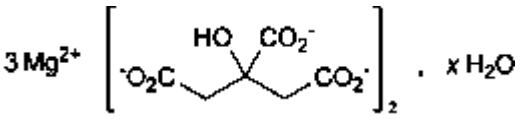
Magnesium Citrate Dodecahydrate

General Notices

(Ph. Eur. monograph 2401)



$Mg_3(C_6H_5O_7)_2,xH_2O$ with $x \approx 12$ 451.1 (anhydrous substance)

Ph Eur

DEFINITION

Trimagnesium bis(2-hydroxypropane-1,2,3-tricarboxylate) dodecahydrate.

Content

15.0 per cent to 16.5 per cent of Mg (dried substance).

CHARACTERS

Appearance

White or almost white, fine powder.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute hydrochloric acid.

IDENTIFICATION

A. It gives the reaction of citrates (*2.3.1*).

B. It gives the reaction of magnesium (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 2.5 g in 15 mL of *dilute hydrochloric acid R* with heating. Cool and dilute to 100 mL with *distilled water R*.

Appearance of solution

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Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 8.5.

Disperse 5.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent. Centrifuge and measure the pH of the clear supernatant.

Oxalates

Maximum 280 ppm.

Dissolve 0.50 g in a mixture of 3 mL of *hydrochloric acid R* and 4 mL of *water R* and add 1 g of *activated zinc R*. Allow to stand for 5 min. Transfer the liquid to a tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R*. Heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of *potassium ferricyanide solution R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that of a standard prepared at the same time and in the same manner using 4 mL of a 50 mg/L solution of *oxalic acid R*.

Sulfates (*2.4.13*)

Maximum 0.2 per cent.

Dilute 3.0 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 0.2 per cent.

To a mixture of 2 mL of solution S and 8 mL of *distilled water R*, add about 0.2 mL of *ammonia R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 4.0 mL of solution S to 10 mL with *distilled water R*.

Loss on drying (*2.2.32*)

29.0 per cent to 36.0 per cent, determined on 1.000 g by drying in an oven at 180 ± 10 °C for 5 h.

ASSAY

Dissolve 0.200 g in 5 mL of *dilute hydrochloric acid R* with heating. Cool and add 50 mL of *water R*. Adjust to pH 7.0 with *ammonia R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

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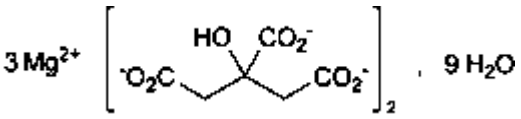
Magnesium Citrate Nonahydrate

General Notices

(Ph. Eur. monograph 2402)



$Mg_3(C_6H_5O_7)_2,9H_2O$ 613 *153531-96-5*

Ph Eur

DEFINITION

Trimagnesium bis(2-hydroxypropane-1,2,3-tricarboxylate) nonahydrate.

Content

15.0 per cent to 16.5 per cent of Mg (dried substance).

CHARACTERS

Appearance

White or almost white, fine powder.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute hydrochloric acid.

IDENTIFICATION

A. It gives the reaction of citrates (*2.3.1*).

B. It gives the reaction of magnesium (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 2.5 g in 15 mL of *dilute hydrochloric acid R* with heating. Cool and dilute to 100 mL with *distilled water R*.

Appearance of solution

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Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 8.5.

Disperse 5.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent. Centrifuge and measure the pH of the clear supernatant.

Oxalates

Maximum 280 ppm.

Dissolve 0.50 g in a mixture of 3 mL of *hydrochloric acid R* and 4 mL of *water R* and add 1 g of *activated zinc R*. Allow to stand for 5 min. Transfer the liquid to a tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R*. Heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of *potassium ferricyanide solution R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that of a standard prepared at the same time and in the same manner using 4 mL of a 50 mg/L solution of *oxalic acid R*.

Sulfates (*2.4.13*)

Maximum 0.2 per cent.

Dilute 3.0 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 0.2 per cent.

To a mixture of 2 mL of solution S and 8 mL of *distilled water R*, add about 0.2 mL of *ammonia R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 4.0 mL of solution S to 10 mL with *distilled water R*.

Loss on drying (*2.2.32*)

24.0 to 28.0 per cent, determined on 1.000 g by drying in an oven at 180 ± 10 °C for 5 h.

ASSAY

Dissolve 0.200 g in 5 mL of *dilute hydrochloric acid R* with heating. Cool and add 50 mL of *water R*. Adjust to pH 7.0 with *ammonia R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

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Magnesium Chloride Hexahydrate

General Notices

(Ph. Eur. monograph 0402)

$MgCl_2,6H_2O$ 203.3 *7791-18-6*

Action and use

Used in the treatment of electrolyte deficiencies and in dialysis solutions.

Preparation

Magnesium Chloride Injection

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DEFINITION

Content

98.0 per cent to 101.0 per cent of $MgCl_2,6H_2O$.

CHARACTERS

Appearance

Colourless crystals, hygroscopic.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Water (see Tests).

B. It gives reaction (a) of chlorides (*2.3.1*).

C. It gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent.

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Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 5 mL of solution S add 0.05 mL of *phenol red solution R*. Not more than 0.3 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromides

Maximum 500 ppm.

Dilute 2.0 mL of solution S to 10.0 mL with *water R*. To 1.0 mL of this solution add 4.0 mL of *water R*, 2.0 mL of *phenol red solution R3* and 1.0 mL of *chloramine solution R2* and mix immediately. After exactly 2 min, add 0.30 mL of *0.1 M sodium thiosulfate*, mix and dilute to 10.0 mL with *water R*. The absorbance (*2.2.25*) of the solution measured at 590 nm, using *water R* as the compensation liquid, is not greater than that of a standard prepared at the same time and in the same manner using 5.0 mL of a 3 mg/L solution of *potassium bromide R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Aluminium (*2.4.17*)

Maximum 1 ppm, if intended for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions, or haemofiltration solutions.

Prescribed solution Dissolve 4 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Calcium (*2.4.3*)

Maximum 0.1 per cent.

Dilute 1 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Potassium

Maximum 500 ppm, if intended for use in the manufacture of parenteral preparations.

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Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using the following solution, diluted as necessary with *water R*: dissolve 1.144 g of *potassium chloride R*, previously dried at 100-105 °C for 3 h in *water R* and dilute to 1000.0 mL with the same solvent (600 µg of K per millilitre).

Wavelength 766.5 nm.

Water (*2.5.12*)

51.0 per cent to 55.0 per cent, determined on 50.0 mg.

ASSAY

Dissolve 0.300 g in 50 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 20.33 mg of $MgCl_2,6H_2O$.

STORAGE

In an airtight container.

LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions or haemofiltration solutions,

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Magnesium Chloride Injection

General Notices

DEFINITION

Magnesium Chloride Injection is a sterile solution of Magnesium Chloride Hexahydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of magnesium chloride hexahydrate, $MgCl_2,6H_2O$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

Yields the reactions characteristic of *magnesium salts* and of *chlorides*, Appendix VI.

Acidity or alkalinity

pH, 5.0 to 8.0, Appendix V L.

ASSAY

Dilute a volume containing 2.5 g of Magnesium Chloride Hexahydrate to 100 mL with *water*. To 20 mL of this solution add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.1M *disodium edetate VS* using 0.1 g of *mordant black 11 triturate* as indicator, until the pink tint is discharged from the blue colour. Each mL of 0.1M *disodium edetate VS* is equivalent to 20.33 mg of $MgCl_2,6H_2O$.

LABELLING

The strength is stated as the percentage w/v of Magnesium Chloride Hexahydrate and as the approximate concentration of magnesium ions (Mg^{2+}) in millimoles per mL.

For a preparation containing 10% w/v of Magnesium Chloride Hexahydrate, the concentration of magnesium ions is approximately 0.5 millimoles per millilitre (0.5 mmol Mg^{2+}/mL).

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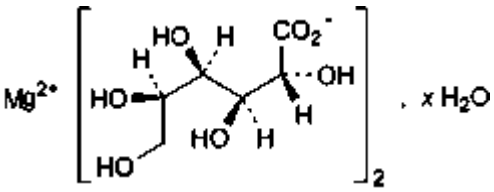
Magnesium Gluconate

General Notices

(Ph. Eur. monograph 2161)



$C_{12}H_{22}MgO_{14},xH_2O$ 414.6 (anhydrous substance)

Ph Eur

DEFINITION

Anhydrous or hydrated magnesium bis[(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate] (anhydrous or hydrated magnesium di(D-gluconate)).

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, amorphous, hygroscopic, crystalline or granular powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *water R*.

Reference solution Dissolve 20 mg of *calcium gluconate CRS* in 1 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Plate *TLC silica gel plate R* (5-40 µm) [or *TLC silica gel plate R* (2-10 µm)].

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Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *water R*, *ethanol (96 per cent) R* (10:10:30:50 *V/V/V/V*).

Application 1 µL.

Development Over 3/4 of the plate.

Drying At 105 °C for 20 min, then allow to cool to room temperature.

Detection Spray with a solution containing 25 g/L of *ammonium molybdate R* and 10 g/L of *cerium sulfate R* in *dilute sulfuric acid R*, then heat at 105 °C for about 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. To 10 mL of solution S (see Tests) add 3 mL of *ammonium chloride solution R*. A slight opalescence may be observed. Add 10 mL of *disodium hydrogen phosphate solution R*. A white precipitate is formed that does not dissolve upon the addition of 2 mL of *dilute ammonia R1*.

TESTS

Solution S

Dissolve 1.0 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Sucrose and reducing sugars

Dissolve 0.5 g in a mixture of 2 mL of *hydrochloric acid R1* and 10 mL of *water R*. Boil for 5 min, allow to cool, add 10 mL of *sodium carbonate solution R* and allow to stand for 10 min. Dilute to 25 mL with *water R* and filter. To 5 mL of the filtrate add 2 mL of *cupri-tartaric solution R* and boil for 1 min. Allow to stand for 2 min. No red precipitate is formed.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

Dissolve 2.0 g in a mixture of 10 mL of *acetic acid R* and 90 mL of *distilled water R*.

Water (*2.5.32*)

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Maximum 12.0 per cent, determined on 80 mg.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

ASSAY

Dissolve 0.350 g in 100 mL of *water R* and carry out the complexometric titration of magnesium (2.5.11).

1 mL of *0.1 M sodium edetate* is equivalent to 41.46 mg of $C_{12}H_{22}MgO_{14}$.

STORAGE

In an airtight container.

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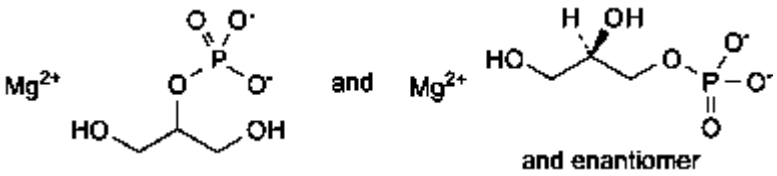
Magnesium Glycerophosphate

General Notices

(Ph. Eur. monograph 1446)



$C_3H_7MgO_6P$ 194.4

Action and use

Excipient.

Preparations

Magnesium Glycerophosphate Chewable Tablets

Magnesium Glycerophosphate Oral Solution

Ph Eur

DEFINITION

Mixture, in variable proportions, of magnesium salts of (*RS*)-2,3-dihydroxypropyl phosphate and 2-hydroxy-1-(hydroxymethyl)ethyl phosphate, which may be hydrated.

Content

11.0 per cent to 12.5 per cent of Mg (dried substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of acids.

IDENTIFICATION

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A. Mix 1 g with 1 g of *potassium hydrogen sulfate R* in a test tube fitted with a glass tube. Heat strongly and direct the white vapour towards a piece of filter paper impregnated with a freshly prepared 10 g/L solution of *sodium nitroprusside R*. The filter paper develops a blue colour in contact with *piperidine R*.

B. Ignite 0.1 g in a crucible. Take up the residue with 5 mL of *nitric acid R* and heat on a water-bath for 1 min. Filter. The filtrate gives reaction (b) of phosphates (*2.3.1*).

C. It gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*).

Acidity

Dissolve 1.0 g in 100 mL of *carbon dioxide-free water R*. Add 0.1 mL of *phenolphthalein solution R*. Not more than 1.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Glycerol and ethanol (96 per cent)-soluble substances

Maximum 1.5 per cent.

Shake 1.0 g with 25 mL of *ethanol (96 per cent) R* for 2 min. Filter and wash the residue with 5 mL of *ethanol (96 per cent) R*. Combine the filtrate and the washings, evaporate to dryness on a water-bath and dry the residue at 70 °C for 1 h. The residue weighs a maximum of 15 mg.

Chlorides (*2.4.4*)

Maximum 0.15 per cent.

Dissolve 1.0 g in *water R* and dilute to 100 mL with the same solvent. Dilute 3.5 mL of this solution to 15 mL with *water R*.

Phosphates (*2.4.11*)

Maximum 0.5 per cent.

Dilute 4 mL of solution S to 100 mL with *water R*. Dilute 1 mL of this solution to 100 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.1 per cent.

Dilute 3 mL of solution S to 15 mL with *distilled water R*.

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Iron (*2.4.9*)

Maximum 150 ppm.

Dissolve 67 mg in *water R* and dilute to 10 mL with the same solvent.

Loss on drying (*2.2.32*)

Maximum 12.0 per cent, determined on 1.000 g by drying in an oven at 150 °C for 4 h.

ASSAY

Dissolve 0.200 g in 40 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

STORAGE

In an airtight container.

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Magnesium Glycerophosphate Chewable Tablets

General Notices

Chewable Magnesium Glycerophosphate Tablets

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in the treatment of magnesium deficiency.

DEFINITION

Magnesium Glycerophosphate Chewable Tablets contain Magnesium Glycerophosphate.

The tablets comply with the requirements stated under Tablets and with the following requirements. Where appropriate, the tablets also comply with the requirements stated under Unlicensed Medicines.

Content of magnesium, Mg

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing the equivalent of about 25 mg of magnesium in a test tube fitted with a glass tube add 1 g of *potassium hydrogen sulfate*. Heat strongly and direct the white vapour towards a piece of filter paper impregnated with a freshly prepared 1% w/v solution of *sodium nitroprusside*. The filter paper develops a blue colour in contact with *piperidine*.

B. Place a quantity of the powdered tablets containing the equivalent of about 25 mg of magnesium in a crucible and ignite. Take up the residue with 5 mL of *nitric acid*, heat on a water-bath for 1 minute and filter. The filtrate yields reaction B characteristic of *phosphates*, Appendix VI.

C. Dissolve a quantity of the powdered tablets containing the equivalent of about 25 mg of magnesium in 10 mL of *water* and filter. The filtrate yields reaction A characteristic of *magnesium salts*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Chewable Magnesium Glycerophosphate Tablets.

Phosphate

Dissolve a quantity of the powdered tablets containing the equivalent of about 25 mg of magnesium in 100 mL of *water* and dilute 1 mL of the solution to 100 mL with *water*. The resulting solution complies with the *limit test for phosphates*, Appendix VII (0.5%).

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ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing the equivalent of about 120 mg of magnesium in 25 mL of *water*. Transfer 10 mL of the solution into a 500 mL conical flask and carry out the *complexometric titration of magnesium*, Appendix VIII D, beginning at the words '… and dilute to 300 mL with *water*'. Each mL of 0.1M *disodium edetate VS* is equivalent to 2.431 mg of Mg.

LABELLING

The label states the quantity of active ingredient both in terms of the amount of Magnesium Glycerophosphate and in terms of the equivalent amount of magnesium or magnesium ions (Mg^{2+}).

Tablets containing 1 gram of Magnesium Glycerophosphate contain approximately 97 mg of magnesium and approximately 4 millimoles of magnesium ions (4 mmol Mg^{2+}) per tablet.

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Magnesium Glycerophosphate Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Used in the treatment of magnesium deficiency.

DEFINITION

Magnesium Glycerophosphate Oral Solution is a solution of Magnesium Glycerophosphate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of magnesium, Mg

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the oral solution containing the equivalent of about 25 mg of magnesium in a test tube fitted with a glass tube add 1 g of *potassium hydrogen sulfate*. Heat strongly and direct the white vapour towards a piece of filter paper impregnated with a freshly prepared 1% w/v solution of *sodium nitroprusside*. The filter paper develops a blue colour in contact with *piperidine*.

B. Reduce a quantity of the oral solution containing the equivalent of about 25 mg of magnesium in a crucible and ignite. Add 5 mL of *nitric acid* to the residue, heat on a water-bath for 1 minute and filter. The filtrate yields reaction B characteristic of *phosphates*, Appendix VI.

C. Yields reaction A characteristic of *magnesium salts*, Appendix VI.

TESTS

Acidity

Dilute a quantity of the oral solution containing the equivalent of about 25 mg of magnesium to 100 mL with *carbon dioxide-free water*. Add 0.1 mL of *phenolphthalein solution*. Not more than 2.0 mL of 0.1M *sodium hydroxide* is required to change the colour of the solution.

Phosphate

Dilute a quantity of the oral solution containing the equivalent of about 25 mg of magnesium to 100 mL with *water* and dilute 1 mL of the solution to 100 mL with *water*. The resulting solution complies with the *limit test for phosphates*, Appendix VII (0.5%).

ASSAY

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To a quantity of the oral solution containing the equivalent of about 120 mg of magnesium add 25 mL of *water*. Transfer 10 mL of the solution into a 500 mL conical flask and carry out the *complexometric titration of magnesium*, Appendix VIII D, beginning at the words 'and dilute to 300 mL with *water*…'. Each mL of 0.1M *disodium edetate VS* is equivalent to 2.431 mg of Mg.

LABELLING

The quantity of the active ingredient is stated both as the amount of Magnesium Glycerophosphate and in terms of the equivalent amount of magnesium or magnesium ions (Mg^{2+}).

For a preparation containing 250 milligrams per mL of Magnesium Glycerophosphate, the concentration of magnesium is approximately 24.25 milligrams per mL and the concentration of magnesium ions is approximately 1 millimole per millilitre (1 mmol Mg^{2+}/mL).

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Magnesium Hydroxide

General Notices

(Ph. Eur. monograph 0039)

$Mg(OH)_2$ 58.32 *1309-42-8*

Action and use

Antacid; osmotic laxative.

Preparations

Co-magaldrox Oral Suspension

Co-magaldrox Tablets

Magnesium Hydroxide Mixture

Ph Eur

DEFINITION

Content

95.0 per cent to 100.5 per cent of $Mg(OH)_2$.

CHARACTERS

Appearance

White or almost white, fine, amorphous powder.

Solubility

Practically insoluble in water. It dissolves in dilute acids.

IDENTIFICATION

A. Dissolve about 15 mg in 2 mL of *dilute nitric acid R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives the reaction of magnesium (*2.3.1*).

B. Loss on ignition (see Tests).

TESTS

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Solution S

Dissolve 5.0 g in a mixture of 50 mL of *acetic acid R* and 50 mL of *distilled water R*. Not more than slight effervescence is produced. Boil for 2 min, cool and dilute to 100 mL with *dilute acetic acid R*. Filter, if necessary, through a previously ignited and tared porcelain or silica filter crucible of suitable porosity to give a clear filtrate. Keep the residue for the test for substances insoluble in acetic acid.

Appearance of solution

Solution S is not more intensely coloured than reference solution B_3 (*2.2.2, Method II*).

Soluble substances

Maximum 2.0 per cent.

Mix 2.00 g with 100 mL of *water R* and boil for 5 min. Filter whilst hot through a sintered-glass filter (40) (*2.1.2*), allow to cool and dilute to 100 mL with *water R*. Evaporate 50 mL of the filtrate to dryness and dry at 100-105 °C. The residue weighs a maximum of 20 mg.

Substances insoluble in acetic acid

Maximum 0.1 per cent.

Any residue obtained during the preparation of solution S, washed, dried, and ignited at 600 ± 50 °C, weighs not more than 5 mg.

Chlorides (*2.4.4*)

Maximum 0.1 per cent.

Dilute 1 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 1.0 per cent.

Dilute 0.3 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 1.5 per cent.

Dilute 1.3 mL of solution S to 150 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 0.07 per cent.

Dissolve 0.15 g in 5 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. Dilute 1 mL of the solution to 10 mL with *water R*.

Loss on ignition

29.0 per cent to 32.5 per cent.

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Heat 0.5 g gradually to 900 ± 50 °C and ignite to constant mass.

ASSAY

Dissolve 0.100 g in a mixture of 2 mL of *dilute hydrochloric acid R* and 20 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 5.832 mg of $Mg(OH)_2$.

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Magnesium Hydroxide Mixture

General Notices

Magnesium Hydroxide Oral Suspension

DEFINITION

Magnesium Hydroxide Mixture is an aqueous *oral suspension* of Magnesium Hydroxide in a suitable vehicle.

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of magnesium hydroxide, $Mg(OH)_2$

7.45 to 8.35% w/w.

CHARACTERISTICS

A white, uniform suspension which does not separate readily on standing.

TESTS

Sulfate

Dissolve 2.5 mL in 20 mL of *hydrochloric acid* and dilute to 500 mL with *water*. 15 mL of the solution, filtered if necessary, complies with the *limit test for sulfates*, Appendix VII (0.2%).

ASSAY

Mix 10 g with 50 mL of *water*, add 50 mL of *0.5M sulfuric acid VS* and titrate the excess of acid with *1M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *0.5M sulfuric acid VS* is equivalent to 29.16 mg of $Mg(OH)_2$.

STORAGE

Magnesium Hydroxide Mixture should not be refrigerated.

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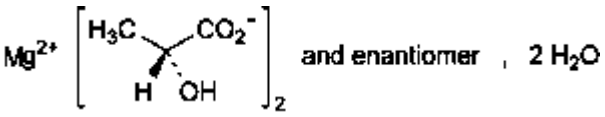
Magnesium Lactate Dihydrate

General Notices

(Ph. Eur. monograph 2160)



$C_6H_{10}MgO_6,2H_2O$ 238.5

Ph Eur

DEFINITION

Magnesium bis(2-hydroxypropanoate) or mixture of magnesium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoate dihydrate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or granular powder.

Solubility

Slightly soluble in water, soluble in boiling water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives the reaction of lactates (*2.3.1*).

B. It gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g with heating in *carbon dioxide-free water R* prepared from *distilled water R*, allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution

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Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

pH (*2.2.3*)

6.5 to 8.5 for solution S.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

14.0 per cent to 17.0 per cent, determined on 0.500 g by drying in an oven at 125 °C.

ASSAY

Dissolve 0.180 g in *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 20.25 mg of $C_6H_{10}MgO_6$.

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Magnesium Peroxide

General Notices

(Ph. Eur. monograph 1540)

Ph Eur

DEFINITION

Mixture of magnesium peroxide and magnesium oxide.

Content

22.0 per cent to 28.0 per cent of MgO_2 (M_r 56.30).

CHARACTERS

Appearance

White or slightly yellow, amorphous, light powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute mineral acids.

IDENTIFICATION

A. Dissolve about 15 mg in 2 mL of *dilute nitric acid R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives the reaction of magnesium (*2.3.1*).

B. Dissolve 50 mg in 2 mL of *dilute sulfuric acid R*. Add 2 mL of a 5 g/L solution of *potassium permanganate R* and shake. The solution becomes colourless with evolution of gas.

TESTS

Solution S1

Dissolve cautiously 5.0 g in 40 mL of *hydrochloric acid R1*. Cautiously evaporate the solution to 10 mL and dilute to 100 mL with a mixture of equal volumes of *acetic acid R* and *distilled water R*. Filter, if necessary, through a previously ignited and tared porcelain or silica filter crucible of suitable porosity to give a clear filtrate. Keep the residue for the test for acid insoluble substances.

Solution S2

Dilute 5 mL of solution S1 to 25 mL with *distilled water R*.

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Appearance of solution

Solution S1 is not more intensely coloured than reference solution B_4 (*2.2.2, Method II*).

Acidity or alkalinity

To 2.0 g add 100 mL of *carbon dioxide-free water R* and heat to boiling for 5 min. Filter whilst hot through a sintered-glass filter (40) (*2.1.2*), allow to cool and dilute to 100 mL with *carbon dioxide-free water R*. To 15 mL of the filtrate, add 0.1 mL of *phenolphthalein solution R*. The solution is red. Not more than 0.2 mL of *0.1 M hydrochloric acid* is necessary to change the colour of the indicator. Keep the filtrate for the test for soluble substances.

Acid insoluble substances

Maximum 0.1 per cent.

Any residue obtained during the preparation of solution S1, washed, dried and ignited at 600 ± 50 °C, weighs a maximum of 5 mg.

Soluble substances

Maximum 1.5 per cent.

Take 50 mL of the filtrate obtained in the test for acidity or alkalinity, evaporate to dryness and dry at 100-105 °C. The residue weighs a maximum of 15 mg.

Chlorides (*2.4.4*)

Maximum 0.1 per cent.

Dissolve 50 mg in 5 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.5 per cent.

Dilute 3 mL of solution S2 to 15 mL with *distilled water R*.

Arsenic (*2.4.2, Method A*)

Maximum 4 ppm, determined on 5 mL of solution S1.

Calcium (*2.4.3*)

Maximum 1.0 per cent.

Dilute 1 mL of solution S2 to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 500 ppm.

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Dilute 2 mL of solution S2 to 10 mL with *water R*.

ASSAY

Dissolve 80.0 mg, shaking cautiously, in a mixture, previously cooled to 20 °C, of 10 mL of *sulfuric acid R* and 90 mL of *water R*. Titrate with *0.02 M potassium permanganate* until a pink colour is obtained.

1 mL of *0.02 M potassium permanganate* is equivalent to 2.815 mg of MgO_2.

STORAGE

Protected from light.

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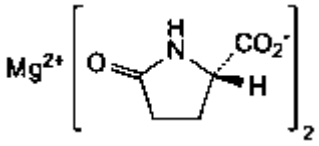
Magnesium Pidolate

General Notices

(Ph. Eur. monograph 1619)



$C_{10}H_{12}MgN_2O_6$ 280.5 *62003-27-4*

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DEFINITION

Magnesium bis[(2*S*)-5-oxopyrrolidine-2-carboxylate].

Content

8.49 per cent to 8.84 per cent of Mg (A_r = 24.31) (anhydrous substance).

CHARACTERS

Appearance

Amorphous, white or almost white powder, hygroscopic.

Solubility

Very soluble in water, soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 60 mg of the substance to be examined in 2 mL of *water R* and dilute to 10 mL with *methanol R*.

Reference solution Dissolve 55 mg of *pidolic acid CRS* in 2 mL of *water R* and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *methanol R*, *glacial acetic acid R*, *methylene chloride R* (15:20:65 *V/V/V*).

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Application 1 µL.

Development Over 2/3 of the plate.

Drying At 100-105 °C for 15 min.

Detection Spray with *strong sodium hypochlorite solution R*. Allow to stand for 10 min and spray abundantly with *glacial acetic acid R*. Allow to stand again for 10 min and dry at 100-105 °C for 2 min. Spray with *potassium iodide and starch solution R* until spots appear.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution. The chromatogram obtained with the test solution may show 2 faint secondary spots.

B. To 0.15 mL of solution S (see Tests) add 1.8 mL of *water R*. The solution gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S

Dissolve 5.00 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method I*).

pH (*2.2.3*)

5.5 to 7.0 for solution S.

Specific optical rotation (*2.2.7*)

-26.5 to -23.3 (anhydrous substance), determined on solution S.

Impurity A

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.250 g of the substance to be examined in 4 mL of *water R* and dilute to 50.0 mL with *methanol R*.

Reference solution (a) Dissolve 60.0 mg of *glutamic acid R* in 50 mL of *water R* and dilute to 100.0 mL with *methanol R*. Dilute 1.0 mL of the solution to 20.0 mL with *methanol R*.

Reference solution (b) Dissolve 10 mg of *aspartic acid R* and 10 mg of *glutamic acid R* in *water R* and dilute to 25 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

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Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.6 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.500 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 50.0 mg of *pidolate impurity B CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 10.0 mL of reference solution (b) to 100.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of *nitrate standard solution (100 ppm NO_3) R* to 100.0 mL with the mobile phase.

Reference solution (e) Dilute 6.0 mL of reference solution (a) to 10.0 mL with reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 1.56 g of *sodium dihydrogen phosphate R* in 1000 mL of *water for chromatography R* and adjust to pH 2.5 with a 10 per cent *V/V* solution of *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (b), (c), (d) and (e).

Run time 4 times the retention time of pidolic acid.

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Retention times Pidolic acid = about 4.5 min; impurity B = about 7.5 min.

System suitability Reference solution (e):

— *resolution*: minimum 10 between the peaks due to pidolic acid and impurity B.

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total of other impurities*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard any peak due to the nitrate ion (NO_3^-).

Chlorides (2.4.4)

Maximum 500 ppm.

Dilute 1.0 mL of solution S to 15.0 mL with *water R*.

Nitrates

Examine the chromatogram obtained with the test solution in the test for related substances.

Limit:

— *nitrates*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (200 ppm).

Sulfates (2.4.13)

Maximum 0.1 per cent.

Dilute 1.5 mL of solution S to 15.0 mL with *distilled water R*.

Iron (2.4.9)

Maximum 200 ppm.

Dilute 0.5 mL of solution S to 10 mL with *water R*.

Water (2.5.12)

Maximum 8.0 per cent, determined on 0.200 g.

ASSAY

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Dissolve 0.300 g in 50 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

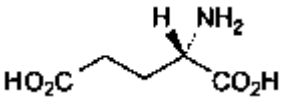
1 mL of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

STORAGE

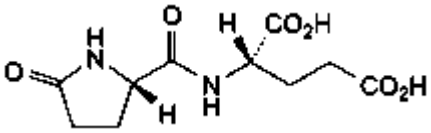
In an airtight container.

IMPURITIES

Specified impurities *A, B.*



A. (2*S*)-2-aminopentanedioic acid (glutamic acid),



B. (2*S*)-2-[(2*S*)-5-oxopyrrolidine-2-carboxamido]pentanedioic acid.

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Magnesium Stearate[1]

General Notices

(Ph. Eur. monograph 0229)

Action and use

Excipient.

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DEFINITION

Compound of magnesium with a mixture of solid organic acids and consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

Content

— *magnesium* (Mg; A_r 24.305): 4.0 per cent to 5.0 per cent (dried substance);

— *stearic acid in the fatty acid fraction*: minimum 40.0 per cent;

— *sum of stearic acid and palmitic acid in the fatty acid fraction*: minimum 90.0 per cent.

♦ CHARACTERS

Appearance

White or almost white, very fine, light powder, greasy to the touch.

Solubility

Practically insoluble in water and in anhydrous ethanol.♦

IDENTIFICATION

First identification: C, D.

◊ *Second identification: A, B, D.*

A. Freezing point (*2.2.18*): minimum 53 °C, determined on the residue obtained in the preparation of solution S (see Tests).

B. Acid value (*2.5.1*): 195 to 210.

Dissolve 0.200 g of the residue obtained in the preparation of solution S in 25 mL of the prescribed mixture of solvents.◊

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C. Examine the chromatograms obtained in the assay of stearic acid and palmitic acid.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 2 principal peaks in the chromatogram obtained with the reference solution.

D. To 1 mL of solution S add 1 mL of *dilute ammonia R1*; a white precipitate is formed that dissolves on addition of 1 mL of *ammonium chloride solution R*. Add 1 mL of a 120 g/L solution of *disodium hydrogen phosphate dodecahydrate R*; a white crystalline precipitate is formed.

TESTS

Solution S

To 5.0 g add 50 mL of *peroxide-free ether R*, 20 mL of *dilute nitric acid R* and 20 mL of *water R* and heat under a reflux condenser until dissolution is complete. Allow to cool. In a separating funnel, separate the aqueous layer and shake the ether layer with 2 quantities, each of 4 mL, of *water R*. Combine the aqueous layers, wash with 15 mL of *peroxide-free ether R* and dilute to 50.0 mL with *water R* (solution S). Evaporate the organic layer to dryness and dry the residue at 100-105 °C. Keep the residue for identification tests A and B.

Acidity or alkalinity

To 1.0 g add 20 mL of *carbon dioxide-free water R* and boil for 1 min with continuous shaking. Cool and filter. To 10 mL of the filtrate add 0.05 mL of *bromothymol blue solution R4*. Not more than 0.05 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides

Maximum 0.1 per cent.

Dilute 10.0 mL of solution S to 40 mL with *water R*. Neutralise if necessary with *nitric acid R* using *litmus R* as indicator. Add 1 mL of *nitric acid R* and 1 mL of *0.1 M silver nitrate* and dilute to 50 mL with *water R*. Mix and allow to stand for 5 min protected from light. The turbidity, if any, is not greater than that produced in a solution containing 1.4 mL of *0.02 M hydrochloric acid*.

Sulfates

Maximum 1.0 per cent.

Dilute 6.0 mL of solution S to 40 mL with *water R*. Neutralise if necessary with *hydrochloric acid R* using *litmus R* as indicator. Add 1 mL of *3 M hydrochloric acid R* and 3 mL of a 120 g/L solution of *barium chloride R* and dilute to 50 mL with *water R*. Mix and allow to stand for 10 min. The turbidity, if any, is not greater than that produced in a solution containing 3.0 mL of *0.02 M sulfuric acid*.

Cadmium

Maximum 3 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

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For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of cadmium, lead and nickel as practicable and store all reagent solutions in containers of borosilicate glass. Clean glassware before use by soaking in a warm 773 g/L solution of nitric acid R for 30 min and by rinsing with deionised water.

Blank solution Dilute 25 mL of *cadmium- and lead-free nitric acid R* to 100.0 mL with *water R*.

Modifier solution Dissolve 20 g of *ammonium dihydrogen phosphate R* and 1 g of *magnesium nitrate R* in *water R* and dilute to 100 mL with the same solvent. Alternatively, use an appropriate matrix modifier as recommended by the graphite furnace atomic absorption (GFAA) spectrometer manufacturer.

Test solution Place 0.100 g of the substance to be examined in a polytetrafluoroethylene digestion bomb and add 2.5 mL of *cadmium- and lead-free nitric acid R*. Close and seal the bomb according to the manufacturer's operating instructions *(when using a digestion bomb, be thoroughly familiar with the safety and operating instructions. Carefully follow the bomb manufacturer's instructions regarding care and maintenance of these digestion bombs. Do not use metal jacketed bombs or liners which have been used with hydrochloric acid due to contamination from corrosion of the metal jacket by hydrochloric acid)*. Heat the bomb in an oven at 170 °C for 3 h. Cool the bomb slowly in air to room temperature according to the bomb manufacturer's instructions. Place the bomb in a fume cupboard and open carefully as corrosive gases may be expelled. Dissolve the residue in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Prepare a solution of 0.0030 µg/mL of Cd by suitable dilutions of a 0.00825 µg/mL solution of *cadmium nitrate tetrahydrate R* in the blank solution.

Dilute 1.0 mL of the test solution to 10.0 mL with the blank solution. Prepare mixtures of this solution, the reference solution and the blank solution in the following proportions: (1.0:0:1.0 *V/V/V*), (1.0:0.5:0.5 *V/V/V*), (1.0:1.0:0 *V/V/V*). To each mixture add 50 µL of modifier solution and mix. These solutions contain respectively 0 µg, 0.00075 µg and 0.0015 µg of cadmium per millilitre from the reference solution (keep the remaining test solution for use in the test for lead and nickel).

Source Cadmium hollow-cathode lamp.

Wavelength 228.8 nm.

Atomisation device Furnace.

Platform Pyrolytically coated with integrated tube.

Operating conditions Use the temperature programme recommended for cadmium by the GFAA spectrometer manufacturer. An example of temperature parameters for GFAA analysis of cadmium is shown below.

Stage	Final temperature (°C)	Ramp time (s)	Hold time (s)
Drying	110	10	20
Ashing	600	10	30
Atomisation	1800	0	5

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Lead

Maximum 10 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of cadmium, lead and nickel as practicable and store all reagent solutions in containers of borosilicate glass. Clean glassware before use by soaking in a warm 773 g/L solution of nitric acid R for 30 min and by rinsing with deionised water.

Blank solution Use the solution described in the test for cadmium.

Modifier solution Use the solution described in the test for cadmium.

Test solution Use the solution described in the test for cadmium.

Reference solution Prepare a solution of 0.100 µg/mL of Pb by suitable dilutions of *lead standard solution (100 ppm Pb) R* with the blank solution.

Prepare mixtures of the test solution, the reference solution and the blank solution in the following proportions: (1.0:0:1.0 *V/V/V*), (1.0:0.5:0.5 *V/V/V*), (1.0:1.0:0 *V/V/V*). To each mixture add 50 µL of modifier solution and mix. These solutions contain respectively 0 µg, 0.025 µg and 0.05 µg of lead per millilitre from the reference solution.

Source Lead hollow-cathode lamp.

Wavelength 283.3 nm.

Atomisation device Furnace.

Platform Pyrolytically coated with integrated tube.

Operating conditions Use the temperature programme recommended for lead by the GFAA spectrometer manufacturer. An example of temperature parameters for GFAA analysis of lead is shown below.

Stage	Final temperature (°C)	Ramp time (s)	Hold time (s)
Drying	110	10	20
Ashing	450	10	30
Atomisation	2000	0	5

Nickel

Maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

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For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of cadmium, lead and nickel as practicable and store all reagent solutions in containers of borosilicate glass. Clean glassware before use by soaking in a warm 773 g/L solution of nitric acid R for 30 min and by rinsing with deionised water.

Blank solution Use the solution described in the test for cadmium.

Modifier solution Dissolve 20 g of *ammonium dihydrogen phosphate R* in *water R* and dilute to 100 mL with the same solvent. Alternatively, use an appropriate matrix modifier as recommended by the GFAA spectrometer manufacturer.

Test solution Use the solution described in the test for cadmium.

Reference solution Prepare a solution of 0.050 µg/mL of Ni by suitable dilutions of a 0.2477 µg/mL solution of *nickel nitrate hexahydrate R* in the blank solution.

Prepare mixtures of the test solution, the reference solution and the blank solution in the following proportions: (1.0:0:1.0 *V/V/V*), (1.0:0.5:0.5 *V/V/V*), (1.0:1.0:0 *V/V/V*). To each mixture add 50 µL of matrix modifier solution and mix. These reference solutions contain respectively 0 µg, 0.0125 µg and 0.025 µg of nickel per millilitre from the reference solution.

Source Nickel hollow-cathode lamp.

Wavelength 232.0 nm.

Atomisation device Furnace.

Platform Pyrolytically coated with integrated tube.

Operating conditions Use the temperature programme recommended for nickel by the GFAA spectrometer manufacturer. An example of temperature parameters for GFAA analysis of nickel is shown below.

Stage	Final temperature (°C)	Ramp time (s)	Hold time (s)
Drying	110	10	20
Ashing	1000	20	30
Atomisation	2300	0	5

Loss on drying (*2.2.32*)

Maximum 6.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

♦ Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

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Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).♦

ASSAY

Magnesium

To 0.500 g in a 250 mL conical flask add 50 mL of a mixture of equal volumes of *anhydrous ethanol R* and *butanol R*, 5 mL of *concentrated ammonia R*, 3 mL of *ammonium chloride buffer solution pH 10.0 R*, 30.0 mL of *0.1 M sodium edetate* and 15 mg of *mordant black 11 triturate R*. Heat at 45-50 °C until the solution is clear and titrate with *0.1 M zinc sulfate* until the colour changes from blue to violet. Carry out a blank titration.

1 mL of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

Stearic acid and palmitic acid

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution In a conical flask fitted with a reflux condenser, dissolve 0.10 g of the substance to be examined in 5 mL of *boron trifluoride-methanol solution R*. Boil under a reflux condenser for 10 min. Add 4 mL of *heptane R* through the condenser and boil again under a reflux condenser for 10 min. Allow to cool. Add 20 mL of *saturated sodium chloride solution R*. Shake and allow the layers to separate. Dry the organic layer over 0.1 g of *anhydrous sodium sulfate R* (previously washed with *heptane R*). Dilute 1.0 mL of the solution to 10.0 mL with *heptane R*.

Reference solution Prepare the reference solution in the same manner as the test solution using 50.0 mg of *palmitic acid CRS* and 50.0 mg of *stearic acid CRS* instead of the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.4 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	70
	2 - 36	70 → 240

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	Time (min)	Temperature (°C)
	36 - 41	240
Injection port		220
Detector		260

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to methyl stearate: methyl palmitate = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to methyl palmitate and methyl stearate;

— *relative standard deviation*: maximum 3.0 per cent for the areas of the peaks due to methyl palmitate and methyl stearate, determined on 6 injections; maximum 1.0 per cent for the ratio of the areas of the peaks due to methyl palmitate to the areas of the peaks due to methyl stearate, determined on 6 injections.

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for magnesium stearate used as lubricant in tablets and capsules.

Particle-size distribution (2.9.31)

Specific surface area (2.9.26, Method I)

Determine the specific surface area in the P/P_o range of 0.05 to 0.15.

Sample outgassing 2 h at 40 °C.

Thermogravimetry (2.2.34)◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Magnesium Sulfate Heptahydrate

General Notices

Epsom Salts

Magnesium Sulphate Heptahydrate

(Ph. Eur. monograph 0044)

$MgSO_4,7H_2O$ 246.5 *10034-99-8*

Action and use

Osmotic laxative; used in treatment of electrolyte deficiency.

Preparations

Magnesium Sulfate Injection

Magnesium Sulfate Mixture

Magnesium Sulfate, Potassium Chloride and Sodium Chloride Infusion

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or brilliant, colourless crystals.

Solubility

Freely soluble in water, very soluble in boiling water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives the reactions of sulfates (*2.3.1*).

B. It gives the reaction of magnesium (*2.3.1*).

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TESTS

Solution S

Dissolve 5.0 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *phenol red solution R*. Not more than 0.2 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*)

Maximum 300 ppm.

Dilute 1.7 mL of solution S to 15 mL with *water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

48.0 per cent to 52.0 per cent, determined on 0.500 g by drying in an oven at 110-120 °C for 1 h and then at 400 °C to constant mass.

ASSAY

Dissolve 0.450 g in 100 mL of *water R* and carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 12.04 mg of $MgSO_4$.

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Magnesium Sulfate Injection

General Notices

Magnesium Sulphate Injection

DEFINITION

Magnesium Sulfate Injection is a sterile solution of Magnesium Sulfate Heptahydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of magnesium sulfate heptahydrate, $MgSO_4,7H_2O$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. Yields reaction A characteristic of *magnesium salts*, Appendix VI.

B. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity or alkalinity

pH of the injection diluted, if necessary, to contain 5% w/v of Magnesium Sulfate Heptahydrate, 5.5 to 7.0, Appendix V L.

ASSAY

Dilute a volume containing 1.25 g of Magnesium Sulfate Heptahydrate to 100 mL with *water*. To 20 mL of this solution add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using 0.1 g of *mordant black 11 triturate* as indicator, until the pink tint is discharged from the blue colour. Each mL of 0.05M *disodium edetate VS* is equivalent to 12.32 mg of $MgSO_4,7H_2O$.

LABELLING

The strength is stated as the percentage w/v of Magnesium Sulfate Heptahydrate and as the approximate concentration of magnesium ions (Mg^{2+}) in millimoles per mL.

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For a preparation containing 50% w/v of Magnesium Sulfate Heptahydrate ($MgSO_4,7H_2O$) the concentration of magnesium ions is approximately 2 millimoles per millilitre (2 mmol Mg^{2+}/mL).

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Magnesium Sulfate Mixture

General Notices

Magnesium Sulphate Mixture

Magnesium Sulfate Oral Suspension

DEFINITION

Magnesium Sulfate Mixture is an *oral suspension* containing 40% w/v of Magnesium Sulfate Heptahydrate and 5% w/v of Light Magnesium Carbonate in a suitable vehicle with a peppermint flavour.

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of magnesium sulfate heptahydrate, $MgSO_4,7H_2O$

36.0 to 44.0% w/v.

Content of magnesium carbonate, calculated as Mg

1.14 to 1.49% w/v.

IDENTIFICATION

A. Filter 10 mL of the mixture and reserve the residue. The filtrate yields reaction A characteristic of *magnesium salts*, Appendix VI. Wash the residue with 10 mL of *water*, dissolve 25 mg in 1 mL of 1M *hydrochloric acid* and adjust the pH to 6 to 7 with 1M *sodium hydroxide*. The resulting solution yields reaction A characteristic of *magnesium salts*, Appendix VI.

B. The residue obtained in test A yields reaction A characteristic of *carbonates*, Appendix VI.

C. The filtrate obtained in test A yields reaction A characteristic of *sulfates*, Appendix VI.

ASSAY

For magnesium sulfate heptahydrate

Boil 0.7 g with 50 mL of a mixture of equal volumes of *ethanol (96%)* and *water*, cool, filter and wash the residue with successive small quantities of the diluted ethanol until the washings are free from sulfate. Reserve the residue for the Assay for magnesium carbonate. To the combined filtrate and washings add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 12.32 mg of $MgSO_4,7H_2O$. Determine the *weight per mL* of the mixture, Appendix V G, and calculate the percentage of $MgSO_4,7H_2O$, weight in volume.

For magnesium carbonate

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Dissolve the residue obtained in the Assay for magnesium sulfate in 10 mL of 1M *hydrochloric acid* and wash the filter with successive small quantities of *water* until the washings are free from chloride. To the combined filtrate and washings add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 1.215 mg of Mg. Using the *weight per mL*, calculate the percentage of Mg, weight in volume.

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Magnesium Sulfate Paste

General Notices

Magnesium Sulphate Paste

Morison's Paste

DEFINITION

Dried Magnesium Sulfate	A sufficient quantity
Phenol	0.5 g
Glycerol, previously heated at 120°	55 g
for 1 hour and cooled	

Extemporaneous preparation

The following directions apply.

Dry about 70 g of Dried Magnesium Sulfate at 150° for 1.5 hours or at 130° for 4 hours and allow to cool in a desiccator. Mix 45 g of the dried material in a warm mortar with the Phenol dissolved in the Glycerol.

In preparing larger quantities of the paste the period of heating the Dried Magnesium Sulfate should be increased, if necessary, to ensure that the dried material contains not less than 85% of magnesium sulfate, calculated as $MgSO_4$.

The paste complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of magnesium sulfate, $MgSO_4$

36.0 to 41.0% w/w.

Content of phenol, C_6H_6O

0.45 to 0.55% w/w.

ASSAY

For magnesium sulfate

Dissolve 5 g in sufficient *water* to produce 100 mL. To 10 mL of the resulting solution add 150 mL of *water* and 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS*, using *mordant black 11 solution* as indicator, to a full blue colour. Each mL of 0.05M *disodium edetate VS* is equivalent to 6.018 mg of $MgSO_4$.

For phenol

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Dissolve 5 g in 25 mL of *water*, add 25 mL of *0.05M bromine VS* and 5 mL of *hydrochloric acid*, stopper the flask, allow to stand for 30 minutes with occasional swirling and then allow to stand for a further 15 minutes. Add 5 mL of a 20% w/v solution of *potassium iodide*, shake thoroughly, titrate with 0.1M *sodium thiosulfate VS* until only a faint yellow colour remains, add 0.25 mL of *starch mucilage* and 10 mL of *chloroform* and complete the titration with vigorous shaking. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of bromine required. Each mL of *0.05M bromine VS* is equivalent to 1.569 mg of C_6H_6O.

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Magnesium Sulfate, Potassium Chloride and Sodium Chloride Infusion

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Hydrating agent; adjunctive therapy for use with platinum based cytotoxics.

DEFINITION

Magnesium Sulfate, Potassium Chloride and Sodium Chloride Infusion is a sterile, isotonic solution containing Magnesium Sulfate Heptahydrate, Potassium Chloride and Sodium Chloride. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the infusion also complies with the requirements stated under Unlicensed Medicines.

Content of magnesium, Mg

95.0 to 105.0% of the stated amount.

Content of potassium, K

95.0 to 105.0% of the stated amount.

Content of sodium, Na

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Yields reaction B characteristic of *magnesium salts* and the reactions characteristic of *potassium salts* and of *sodium salts*, Appendix VI.

B. Yields reaction A characteristic of *chlorides* and reaction A characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

pH, 5.0 to 6.0, Appendix V L.

ASSAY

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For magnesium

Transfer 100 mL into a 500 mL conical flask and carry out the *complexometric titration of magnesium*, Appendix VIII D, beginning at the words 'and dilute to 300 mL with *water*…'. Each mL of 0.1M *disodium edetate VS* is equivalent to 0.1 mmol (2.431 mg) of Mg.

For potassium

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 767 nm and using *potassium standard solution (600 ppm K)*, suitably diluted with *water*, to prepare the standard solutions.

For sodium

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm and using *sodium standard solution (200 ppm Na)*, suitably diluted with *water*, to prepare the standard solutions.

STORAGE

Magnesium Sulfate, Potassium Chloride and Sodium Chloride Infusion should be protected from light.

LABELLING

The strength is stated as the approximate concentration, in millimoles per litre, of Magnesium Sulfate and of Potassium Chloride and as the percentage w/v of Sodium Chloride.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Magnesium Trisilicate

General Notices

(Ph. Eur. monograph 0403)

Action and use

Antacid.

Preparations

Magnesium Trisilicate Mixture

Compound Magnesium Trisilicate Chewable Tablets

Compound Magnesium Trisilicate Oral Powder

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DEFINITION

It has a variable composition corresponding approximately to $Mg_2Si_3O_8,xH_2O$.

Content

— *magnesium oxide* (MgO; M_r 40.30): minimum 29.0 per cent (ignited substance),

— *silicon dioxide* (SiO_2; M_r 60.1): minimum 65.0 per cent (ignited substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. 0.25 g gives the reaction of silicates (*2.3.1*).

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B. 1 mL of solution S (see Tests) neutralised with *dilute sodium hydroxide solution R* gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S

To 2.0 g add a mixture of 4 mL of *nitric acid R* and 4 mL of *distilled water R*. Heat to boiling with frequent shaking. Add 12 mL of *distilled water R* and allow to cool. Filter or centrifuge to obtain a clear solution and dilute to 20 mL with *distilled water R*.

Alkalinity

To 10.0 g in a 200 mL conical flask, add 100.0 g of *water R* and heat on a water-bath for 30 min. Allow to cool and make up to the initial mass with *water R*. Allow to stand and filter or centrifuge until a clear liquid is obtained. To 10 mL of this liquid add 0.1 mL of *phenolphthalein solution R*. Not more than 1.0 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Water-soluble salts

Maximum 1.5 per cent.

In a platinum dish, evaporate to dryness on a water-bath 20.0 mL of the liquid obtained in the test for alkalinity. The residue, ignited to constant mass at 900 ± 50 °C, weighs a maximum of 30 mg.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dilute 0.5 mL of solution S to 15 mL with *water R*. Prepare the standard using a mixture of 5 mL of *chloride standard solution (5 ppm Cl) R* and 10 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 0.5 per cent.

Dilute 0.3 mL of solution S to 15 mL with *distilled water R*.

Arsenic (*2.4.2, method A*)

Maximum 4 ppm, determined on 2.5 mL of solution S.

Loss on ignition

17 per cent to 34 per cent, determined on 0.5 g by ignition to constant mass at 900 ± 50 °C in a platinum crucible.

Acid-absorbing capacity

Suspend 0.25 g in *0.1 M hydrochloric acid*, dilute to 100.0 mL with the same acid and allow to stand for 2 h in a water-bath at 37 ± 0.5 °C, with frequent shaking. Allow to cool. To 20.0 mL of the supernatant add 0.1 mL of *bromophenol blue solution R* and titrate with *0.1 M*

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sodium hydroxide until a blue colour is obtained. The acid-absorbing capacity is not less than 100.0 mL of *0.1 M hydrochloric acid* per gram.

ASSAY

Magnesium oxide

To 1.000 g in a 200 mL conical flask, add 35 mL of *hydrochloric acid R* and 60 mL of *water R* and heat in a water-bath for 15 min. Allow to cool, filter, wash the conical flask and the residue with *water R* and dilute the combined filtrate and washings to 250.0 mL with *water R*. Neutralise 50.0 mL of the solution with *strong sodium hydroxide solution R* (about 8 mL). Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 4.030 mg of MgO.

Silicon dioxide

To 0.700 g add 10 mL of *dilute sulfuric acid R* and 10 mL of *water R*. Heat for 90 min on a water-bath with frequent shaking, replacing the evaporated water. Allow to cool and decant onto an ashless filter paper (diameter 7 cm). Wash the precipitate by decantation with 3 quantities, each of 5 mL, of hot *water R*, transfer it to the filter and wash it with hot *water R* until 1 mL of the filtrate remains clear after the addition of 0.05 mL of *dilute hydrochloric acid R* and 2 mL of *barium chloride solution R1*. Incinerate the filter and its contents in a platinum crucible, then ignite the residue (SiO_2) at 900 ± 50 °C to constant mass.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for magnesium trisilicate used as a lubricant in tablets and capsules.

Particle-size distribution (*2.9.31*)

Specific surface area (*2.9.26, Method I*)

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Magnesium Trisilicate Mixture

General Notices

Magnesium Trisilicate Oral Suspension; Compound Magnesium Trisilicate Mixture

DEFINITION

Magnesium Trisilicate Mixture is an *oral suspension* containing 5% w/v each of Magnesium Trisilicate, Light Magnesium Carbonate and Sodium Bicarbonate in a suitable vehicle with a peppermint flavour.

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of magnesium, Mg

1.70 to 2.20% w/v.

Content of sodium bicarbonate, $NaHCO_3$

4.60 to 5.40% w/v.

IDENTIFICATION

A. Filter 50 mL of the mixture using a Buchner funnel, reserving the filtrate, wash the filter with 50 mL of *water* and dry the residue at 100° to 105° for 1 hour. The filtrate yields reaction B characteristic of *sodium salts* and reaction A characteristic of *bicarbonates*, Appendix VI.

B. Shake 0.5 g of the residue obtained in test A with 5 mL of 1M *hydrochloric acid* for 5 minutes, add 5 mL of 1M *sodium hydroxide* and centrifuge. The supernatant liquid yields reaction B characteristic of *magnesium salts*, Appendix VI.

C. The residue obtained in test A yields reaction A characteristic of *carbonates*, Appendix VI.

D. 30 mg of the residue obtained in test A yields the reaction characteristic of *silicates*, Appendix VI.

Neutralising capacity

To 5 g add 100 mL of *water* and heat to 37°. Add 100 mL of *0.1M hydrochloric acid VS* previously heated to 37° and stir continuously using a suitable paddle stirrer rotating at a rate of about 200 revolutions per minute, maintaining the temperature at 37°. The pH of the suspension at 37° after 10 and 20 minutes is not less than 2.0 and not less than 2.4 respectively and at no time is it more than 4.0. Add 10 mL of *0.5M hydrochloric acid VS* previously heated to 37°, stir continuously for 1 hour, maintaining the temperature at 37°, and titrate with *0.1M sodium hydroxide VS* to pH 3.5. Subtract the volume of *0.1M sodium hydroxide VS* from 150 to obtain the number of mL of *0.1M hydrochloric acid VS* required for the neutralisation. Determine the *weight per mL* of the mixture, Appendix V G, and hence the volume of *0.1M hydrochloric acid VS* required to neutralise 5 mL of the mixture. Not less than 100 mL of *0.1M hydrochloric acid VS* is required.

ASSAY

For magnesium

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To 5 g add 7 mL of *hydrochloric acid* and 7 mL of *water*, stir and heat on a water bath for 15 minutes. Add 30 mL of hot *water*, mix, filter while still hot and wash the filter with hot *water*. Cool the combined filtrate and washings and dilute to 100 mL with *water*. To 25 mL of the resulting solution add 150 mL of *water* and 5 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 1.215 mg of Mg. Using the *weight per mL* of the mixture calculate the percentage of Mg, weight in volume.

For sodium bicarbonate

Boil 20 g with 100 mL of *water* for 5 minutes, filter, boil the residue with 100 mL of *water* for 5 minutes and filter. Combine the filtrates, cool and titrate with *0.5M hydrochloric acid VS* using *methyl orange–xylene cyanol FF solution* as indicator. Add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. After subtracting one-fifth of the volume of 0.05M *disodium edetate VS*, each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$. Using the *weight per mL* of the mixture calculate the percentage of $NaHCO_3$, weight in volume.

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Maize Starch[1]

General Notices

(Ph. Eur. monograph 0344)

Action and use

Excipient.

When Starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch or, in tropical countries where these are not available, Tapioca Starch may be supplied or used.

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DEFINITION

Maize starch is obtained from the caryopsis of *Zea mays* L.

♦ CHARACTERS

Appearance

Matt, white to slightly yellowish, very fine powder that creaks when pressed between the fingers.

Solubility

Practically insoluble in cold water and in ethanol (96 per cent).

The presence of granules with cracks or irregularities on the edge is exceptional.♦

IDENTIFICATION

A. Microscopic examination (2.8.23), using a 50 per cent *V/V* solution of *glycerol R*. It appears as either angular polyhedral granules of irregular sizes with diameters ranging from about 2 µm to about 23 µm or as rounded or spheroidal granules of irregular sizes with diameters ranging from about 25 µm to about 35 µm (Figure 0344.-1). The central hilum consists of a distinct cavity or 2- to 5-rayed cleft and there are no concentric striations. Between orthogonally orientated polarising plates or prisms, the starch granules show a distinct black cross intersecting at the hilum.

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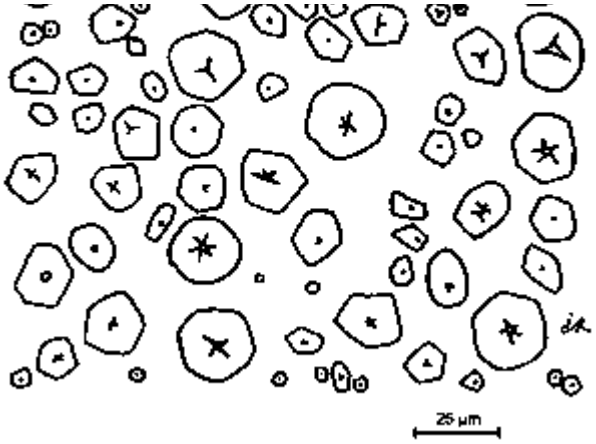

Figure 0344.-1. – *Illustration for identification test A of maize starch*

B. Suspend 1 g in 50 mL of *water R*, boil for 1 min and cool. A thin, cloudy mucilage is formed.

C. To 1 mL of the mucilage obtained in identification test B add 0.05 mL of *iodine solution R1*. An orange-red to dark blue colour is produced, which disappears on heating.

TESTS

pH (*2.2.3*)

4.0 to 7.0.

To 5.0 g add 25.0 mL of *carbon dioxide-free water R*. Agitate continuously at a moderate rate for 60 s. Stop the agitation and allow to stand for 15 min.

◊ Foreign matter

Examined under a microscope using a 50 per cent *V/V* solution of *glycerol R*, not more than traces of matter other than starch granules are present. No starch granules of any other origin are present.◊

Oxidising substances (*2.5.30*)

Maximum 20 ppm, calculated as H_2O_2.

Sulfur dioxide (*2.5.29*)

Maximum 50 ppm.

Iron (*2.4.9*)

Maximum 10 ppm.

Shake 1.5 g with 15 mL of *dilute hydrochloric acid R*. Filter. The filtrate complies with the test.

Loss on drying (*2.2.32*)

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Maximum 15.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 90 min.

Sulfated ash (*2.4.14*)

Maximum 0.6 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

◊ Absence of *Salmonella* (*2.6.13*).◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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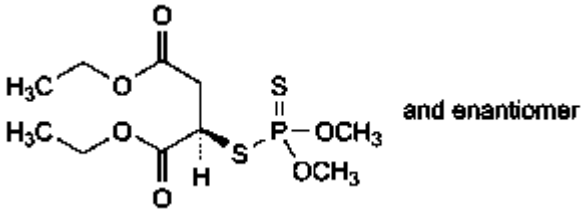
Malathion

General Notices

(Ph. Eur. monograph 1343)



$C_{10}H_{19}O_6PS_2$ 330.4 *121-75-5*

Action and use

Organophosphorus insecticide.

Preparations

Malathion Lotion

Malathion Shampoo

Ph Eur

DEFINITION

Diethyl (2*RS*)-2-(dimethoxyphosphinodithioyl)butanedioate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless or slightly yellowish liquid.

Solubility

Slightly soluble in water, miscible with acetone, with cyclohexane, with ethanol (96 per cent) and with vegetable oils.

It solidifies at about 3 °C.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *malathion CRS*.

TESTS

Relative density (2.2.5)

1.220 to 1.240.

Optical rotation (2.2.7)

-0.1° to + 0.1°.

Dissolve 2.50 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *acetonitrile R* (1:3 *V/V*).

Test solution (a) Dissolve 0.10 g of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 0.100 g of *malathion CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 0.5 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of *malathion impurity A CRS* and 5.0 mg of *malathion impurity B CRS* in the solvent mixture, then dilute 50.0 mL with the solvent mixture.

Reference solution (d) Dilute 2.0 mL of reference solution (c) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm);

— *temperature*: 35 °C.

Mobile phase *acetonitrile R*, *water R* (45:55 *V/V*).

Flow rate 1 mL/min.

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Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c) and (d).

Retention time Impurity B = about 3.5 min; impurity A = about 5 min; malathion = about 16 min.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurities B and A.

Limits:

— *impurity A*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *sum of impurities other than A and B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.1 per cent, determined on 2.000 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{10}H_{19}O_6PS_2$ from the declared content of *malathion CRS*.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B.*

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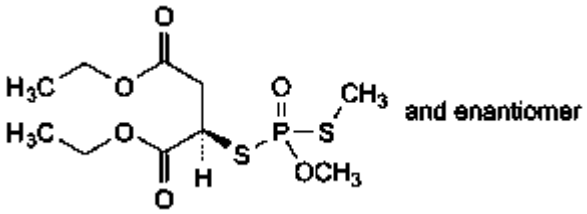
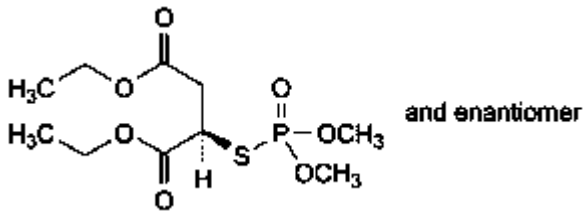
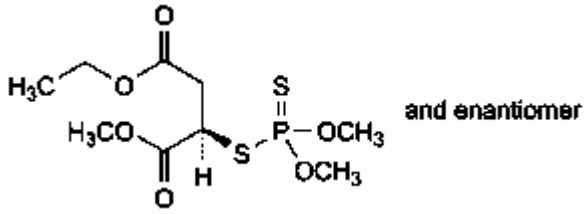
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. diethyl (2*RS*)-2-[(methoxy)(methylsulfanyl)-*S*-phosphinothioyl]butanedioate (isomalathion),



B. diethyl (2*RS*)-2-(dimethoxy-*S*-phosphinothioyl)butanedioate (maloxon),



C. ethyl and methyl (2*RS*)-2-(dimethoxyphosphinodithioyl)butanedioate (methyl analogue).

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Malathion Shampoo

General Notices

Action and use

Organophosphorus insecticide.

DEFINITION

Malathion Shampoo contains Malathion in a suitable vehicle.

The shampoo complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of malathion, $C_{10}H_{19}O_6PS_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *water* and 3 volumes of *acetonitrile* (solvent A).

(1) Dilute a quantity of the preparation being examined with sufficient solvent A to produce a solution containing 0.2% w/v of Malathion.
(2) Dilute 1 volume of solution (1) to 500 volumes.
(3) 0.0002% w/v each of *malathion impurity A EPCRS* and *malathion impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature 35°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

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MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to Malathion (retention time = about 16 minutes) are: impurity B = about 0.2 and impurity A = about 0.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity A and impurity B is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to malathion impurity A is not greater than three times the area of the corresponding peak in the chromatogram obtained with solution (3) (0.3%);

the area of any peak corresponding to malathion impurity B is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *water* and 3 volumes of *acetonitrile* (solvent B).

(1) Dilute a quantity of the preparation being examined with sufficient solvent B to produce a solution containing 0.2% w/v of Malathion.
(2) 0.2% w/v of *malathion EPCRS*.
(3) 0.0002% w/v each of *malathion impurity A EPCRS* and *malathion impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity A and impurity B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{19}O_6PS_2$ using the declared content of $C_{10}H_{19}O_6PS_2$ in *malathion EPCRS*.

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STORAGE

Malathion Shampoo should be stored in an airtight container, protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Malathion.

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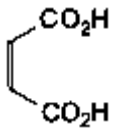
Maleic Acid

General Notices

(Ph. Eur. monograph 0365)



$C_4H_4O_4$ 116.1 *110-16-7*

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DEFINITION

Maleic acid contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (*Z*)-butenedioic acid, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Dilute 5 mL of solution S (see Tests) to 10 mL with *water R*. The pH of the dilution is less than 2.

B. Examine the chromatograms obtained in the test for fumaric acid. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.1 g in 10 mL of *water R* (solution a). To 0.3 mL of solution (a) add a solution of 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min; no colour develops. To 3 mL of solution (a) add 1 mL of *bromine water R*. Heat on a water-bath to remove the bromine (15 min), heat to boiling and cool. To 0.2 mL of this solution add a solution of 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min. A violet-pink colour develops.

TESTS

Solution S

Dissolve 5.0 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

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Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, Method II).

Fumaric acid

Examine by thin-layer chromatography (2.2.27), using silica gel GF_{254} R as the coating substance.

Test solution (a) Dissolve 0.5 g of the substance to be examined in acetone R and dilute to 5 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 50 mL with acetone R.

Reference solution (a) Dissolve 20 mg of maleic acid CRS in acetone R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 15 mg of fumaric acid CRS in acetone R and dilute to 10 mL with the same solvent.

Reference solution (c) Mix 5 mL of reference solution (a) and 5 mL of reference solution (b).

Apply separately to the plate 5 µL of test solutions (a) and (b), 5 µL of reference solutions (a) and (b) and 10 µL of reference solution (c). Develop in an unsaturated tank over a path of 10 cm using a mixture of 12 volumes of anhydrous formic acid R, 16 volumes of chloroform R, 32 volumes of butanol R and 44 volumes of heptane R. Dry the plate at 100 °C for 15 min and examine in ultraviolet light at 254 nm. Any spot corresponding to fumaric acid in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (b) (1.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated spots.

Iron

To 10 mL of solution S add 2 mL of dilute hydrochloric acid R and 0.05 mL of bromine water R. After 5 min, remove the excess of bromine by passing a current of air and add 3 mL of potassium thiocyanate solution R. Shake. Prepare a standard at the same time and in the same manner, using a mixture of 5 mL of iron standard solution (1 ppm Fe) R, 1 mL of dilute hydrochloric acid R, 6 mL of water R and 0.05 mL of bromine water R. Allow both solutions to stand for 5 min. Any red colour in the test solution is not more intense than that in the standard (5 ppm).

Water (2.5.12)

Not more than 2.0 per cent, determined on 1.00 g by the semi-micro determination of water.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 50 mL of water R. Titrate with 1 M sodium hydroxide using 0.5 mL of phenolphthalein solution R as indicator.

1 mL of 1 M sodium hydroxide is equivalent to 58.04 mg of $C_4H_4O_4$.

STORAGE

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Store in a glass container, protected from light.

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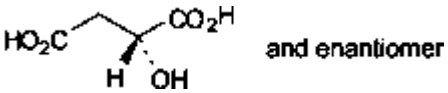
Malic Acid

General Notices

(Ph. Eur. monograph 2080)



and enantiomer

$C_4H_6O_5$ 134.1 *6915-15-7*

Action and use

Excipient.

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DEFINITION

(2*RS*)-2-Hydroxybutanedioic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), sparingly soluble in acetone.

IDENTIFICATION

A. Melting point (*2.2.14*): 128 °C to 132 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of malic acid*.

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TESTS

Solution S

Dissolve 5.00 g in *water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Water-insoluble substances

Maximum 0.1 per cent.

Dissolve 25.0 g in 100 mL of *water R*, filter the solution through a tared sintered-glass filter (16) (*2.1.2*), wash the filter with hot *water R* and dry at 100-105 °C to constant weight. The residue weighs a maximum of 25 mg.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 100.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 10.0 mg of *fumaric acid R* and 4.0 mg of *maleic acid R* in 25 mL of the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 2.5 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 20.0 mg of the substance to be examined in the mobile phase, add 1.0 mL of reference solution (a) and dilute to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm,

— *stationary phase*: *ion-exclusion resin for chromatography R* (9 µm),

— *temperature*: 37 °C.

Mobile phase *0.005 M sulfuric acid*.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

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Run time Twice the retention time of the principal peak in the chromatogram obtained with the test solution.

Relative retention With reference to malic acid (retention time = about 10 min): impurity B = about 0.8; impurity A = about 1.5.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurity B and malic acid.

Limits:

— *impurity A*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (b) (1.0 per cent),

— *impurity B*: not more than 0.25 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.05 per cent),

— *any other impurity*: for each impurity, not more than 0.5 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total of other impurities*: not more than 2.5 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *disregard limit*: 0.1 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.02 per cent).

Water (2.5.12)

Maximum 2.0 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 50 mL of *carbon dioxide-free water R*. Titrate with *1 M sodium hydroxide* determining the end-point potentiometrically (2.2.20).

1 mL of *1 M sodium hydroxide* is equivalent to 67.05 mg of $C_4H_6O_5$.

IMPURITIES

Specified impurities *A, B.*

A. (*E*)-butenedioic acid (fumaric acid),

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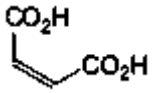

B. (*Z*)-butenedioic acid (maleic acid).

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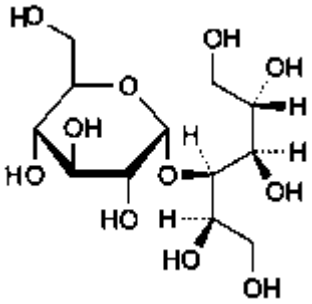
Maltitol

General Notices

(Ph. Eur. monograph 1235)



$C_{12}H_{24}O_{11}$ 344.3 *585-88-6*

Action and use

Sweetening agent.

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DEFINITION

4-*O*-α-D-Glucopyranosyl-D-glucitol (D-maltitol).

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, practically insoluble in anhydrous ethanol.

IDENTIFICATION

First identification: A.

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Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *maltitol CRS*.

B. Melting point (2.2.14): 148 °C to 151 °C.

C. Specific optical rotation (2.2.7): + 105.5 to + 108.5 (anhydrous substance).

Dissolve 5.00 g in *water R* and dilute to 100.0 mL with the same solvent.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *maltitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 25 mg of *maltitol CRS* and 25 mg of *sorbitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *ethyl acetate R*, *propanol R* (10:20:70 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with *4-aminobenzoic acid solution R*. Dry in a current of cold air until the acetone is removed. Heat at 100-105 °C for 15 min. Allow to cool and spray with a 2 g/L solution of *sodium periodate R*. Dry in a current of cold air. Heat at 100 °C for 15 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 5.0 g in *water R* and dilute to 50 mL with the same solvent.

Conductivity (2.2.38)

Maximum 20 µS·cm^{-1}.

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Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution, while gently stirring with a magnetic stirrer.

Reducing sugars

Maximum 0.2 per cent, expressed as glucose equivalent.

Dissolve 5.0 g in 6 mL of *water R* with the aid of gentle heat. Cool and add 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 5.0 g of the substance to be examined in 20 mL of *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 0.50 g of *maltitol CRS* in 2.0 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c) Dilute 10.0 mL of reference solution (b) to 100.0 mL with *water R*.

Reference solution (d) Dissolve 0.5 g of *maltitol R* and 0.5 g of *sorbitol R* in 5 mL of *water R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 85 ± 1 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 3 times the retention time of maltitol.

Relative retention With reference to maltitol (retention time = about 16 min): impurity B = about 0.8; impurity A = about 1.8.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to maltitol and impurity A.

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Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g.

Microbial contamination

If intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion: 10^2 CFU/g (2.6.12).

If not intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^3 CFU/g (2.6.12);

— TYMC: acceptance criterion 10^2 CFU/g (2.6.12);

— absence of *Escherichia coli* (2.6.13);

— absence of *Salmonella* (2.6.13).

Bacterial endotoxins (2.6.14)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins:

— less than 4 IU/g for parenteral preparations having a concentration of less than 100 g/L of maltitol;

— less than 2.5 IU/g for parenteral preparations having a concentration of 100 g/L or more of maltitol.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{12}H_{24}O_{11}$ taking into account the assigned content of *maltitol CRS*.

LABELLING

The label states:

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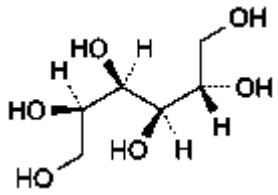
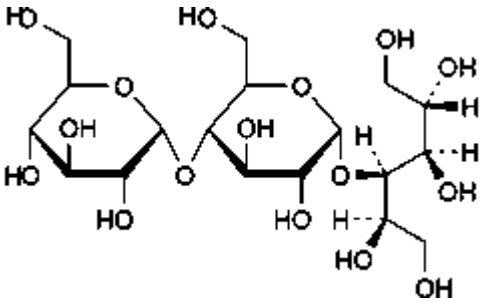
— where applicable, the maximum concentration of bacterial endotoxins;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES



A. D-glucitol (D-sorbitol),



B. α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucitol (maltotriitol).

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Maltodextrin

General Notices

(Ph. Eur. monograph 1542)

Action and use

Excipient.

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DEFINITION

Mixture of glucose, disaccharides and polysaccharides, obtained by the partial hydrolysis of starch.

The degree of hydrolysis, expressed as dextrose equivalent (DE), is less than 20 (nominal value).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder or granules.

Solubility

Freely soluble in water.

IDENTIFICATION

A. Dissolve 0.1 g in 2.5 mL of *water R* and heat with 2.5 mL of *cupri-tartaric solution R*. A red precipitate is formed.

B. Dip, for 1 s, a suitable stick with a reactive pad containing glucose-oxidase, peroxidase and a hydrogen-donating substance, such as tetramethylbenzidine, in a 100 g/L solution of the substance to be examined. Observe the colour of the reactive pad; within 60 s a colour change is observed, characteristic of the hydrogen-donating substance used (from yellow to green or blue if tetramethylbenzidine is used).

C. It is a powder or granules.

D. Dextrose equivalent (see Tests).

TESTS

Solution S

Dissolve 12.5 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

pH (*2.2.3*)

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4.0 to 7.0.

Mix 1 mL of a 223.6 g/L solution of *potassium chloride R* and 30 mL of solution S.

Sulfur dioxide (2.5.29)

Maximum 20 ppm.

Loss on drying (2.2.32)

Maximum 6.0 per cent, determined on 10.00 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

Dextrose equivalent

(DE): within 2 DE units of the nominal value.

Weigh an amount of the substance to be examined equivalent to 2.85-3.15 g of reducing carbohydrates, calculated as dextrose equivalent, into a 500 mL volumetric flask. Dissolve in *water R* and dilute to 500.0 mL with the same solvent. Transfer the solution to a 50 mL burette.

Pipette 25.0 mL of *cupri-tartaric solution R* into a 250 mL flask and add 18.5 mL of the test solution from the burette, mix and add a few glass beads. Place the flask on a hot plate, previously adjusted so that the solution begins to boil within 2 min ± 15 s. Allow to boil for exactly 120 s, add 1 mL of a 1 g/L solution of *methylene blue R* and titrate with the test solution (V_1) until the blue colour disappears. Maintain the solution at boiling throughout the titration.

Standardise the cupri-tartaric solution using a 6.00 g/L solution of *glucose R* (V_0).

Calculate the dextrose equivalent using the following expression:

$$\frac{300 \times V_0 \times 100}{V_1 \times M \times D}$$

V_0	=	total volume of glucose standard solution, in millilitres;
V_1	=	total volume of test solution, in millilitres;
M	=	sample mass, in grams;
D	=	percentage content of dry matter in the substance.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

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Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

LABELLING

The label states the dextrose equivalent (DE) (= nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for maltodextrin used as filler and binder in tablets and capsules.

Dextrose equivalent

(see Tests).

Particle-size distribution (2.9.31 or 2.9.38)

Powder flow (2.9.36)

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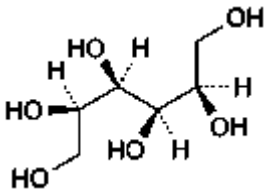
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Mannitol[1]

General Notices

(Ph. Eur. monograph 0559)



$C_6H_{14}O_6$ 182.2 *69-65-8*

Action and use

Diuretic.

Preparation

Mannitol Infusion

Ph Eur

DEFINITION

D-Mannitol.

Content

97.0 per cent to 102.0 per cent (dried substance).

♦ CHARACTERS

Appearance

White or almost white crystals or powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

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It shows polymorphism (5.9). ♦

IDENTIFICATION

First identification: C.

◊ *Second identification: A, B, D.*

A. Specific optical rotation (2.2.7): + 23 to + 25 (dried substance).
Dissolve 2.00 g of the substance to be examined and 2.6 g of *disodium tetraborate R* in about 20 mL of *water R* at 30 °C; shake continuously for 15-30 min without further heating. Dilute the resulting clear solution to 25.0 mL with *water R*.

B. Melting point (see Tests). ◊

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *mannitol CRS*.

If the spectra obtained in the solid state show differences, dissolve separately in 2 glass vials 25 mg of the substance to be examined and 25 mg of the reference substance in 0.25 mL of *distilled water R* without heating. The solutions obtained are clear. Evaporate to dryness by heating in a microwave oven with a power range of 600-700 W for 20 min or by heating in an oven at 100 °C for 1 h then gradually applying vacuum until a dry residue is obtained. Non-sticky, white or slightly yellowish powders are obtained. Record new spectra using the residues.

◊ D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *mannitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 25 mg of *mannitol R* and 25 mg of *sorbitol R* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *ethyl acetate R*, *propanol R* (10:20:70 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *4-aminobenzoic acid solution R* and dry in a current of cold air until the acetone is removed; heat at 100 °C for 15 min, allow to cool then spray with a 2 g/L solution of *sodium periodate R*; dry in a current of cold air and heat at 100 °C for 15 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

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Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a). ◊

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 5.0 g in *water R* and dilute to 50 mL with the same solvent.

Conductivity (*2.2.38*)

Maximum 20 $\mu S \cdot cm^{-1}$.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* by heating at 40-50 °C and dilute to 100.0 mL with the same solvent. After cooling, measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Melting point (*2.2.14*)

165 °C to 170 °C.

Reducing sugars

Maximum 0.1 per cent (calculated as glucose equivalent).

To 7.0 g add 13 mL of *water R*. Boil gently with 40 mL of *cupri-tartaric solution R* for 3 min, and allow to stand for 2 min. A precipitate is formed. Filter through a sintered-glass filter (16) (*2.1.2*) coated with *diatomaceous earth R* or a sintered-glass filter (10) (*2.1.2*). Wash the precipitate with hot *water R* (about 50-60 °C) until the washing is no longer alkaline, and filter the washings through the same sintered-glass filter. Discard the filtrate. Immediately dissolve the precipitate in 20 mL of *ferric sulfate solution R*, filter through the same sintered-glass filter, and wash the filter with 15-20 mL of *water R*. Combine the washings and the filtrate, heat to 80 °C, and titrate with *0.02 M potassium permanganate*. Not more than 3.2 mL is required to change the colour of the solution from green to pink so that the colour persists for at least 10 s.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.50 g of the substance to be examined in 2.5 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.50 g of *mannitol CRS* in 2.5 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c) Dilute 0.5 mL of reference solution (b) to 20.0 mL with *water R*.

Reference solution (d) Dissolve 0.25 g of *mannitol R* and 0.25 g of *sorbitol R* (impurity A) in 5 mL of *water R* and dilute to 10 mL with the same solvent.

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Reference solution (e) Dissolve 0.5 g of *maltitol R* (impurity B) and 0.5 g of *isomalt R* (impurity C) in 5 mL of *water R* and dilute to 100 mL with the same solvent. Dilute 2 mL of the solution to 10 mL with *water R*.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 85 ± 2 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 40 °C).

Injection 20 µL of the test solution and reference solutions (b), (c), (d) and (e).

Run time 1.5 times the retention time of mannitol.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities B and C.

Relative retention With reference to mannitol (retention time = about 20 min): impurity C (1^{st} peak) = about 0.6; impurity B = about 0.7; impurity C (2^{nd} peak) = about 0.73; impurity A = about 1.2. Impurity C elutes in 2 peaks. Coelution of impurity B and the 2^{nd} peak due to impurity C may be observed.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to mannitol and impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *sum of impurities B and C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

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Microbial contamination

If intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

If not intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^3 CFU/g (2.6.12);

— TYMC: acceptance criterion 10^2 CFU/g (2.6.12);

— absence of *Escherichia coli* (2.6.13);

— ◊ absence of *Salmonella* (2.6.13). ◊

Bacterial endotoxins (2.6.14)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins:

— less than 4 IU/g for parenteral preparations having a concentration of 100 g/L or less of mannitol;

— less than 2.5 IU/g for parenteral preparations having a concentration of more than 100 g/L of mannitol.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_6H_{14}O_6$ taking into account the assigned content of *mannitol CRS*.

LABELLING

The label states:

— where applicable, the maximum concentration of bacterial endotoxins;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, B, C.*

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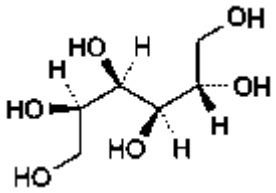
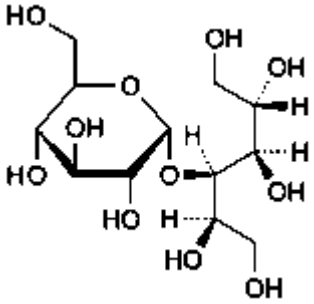
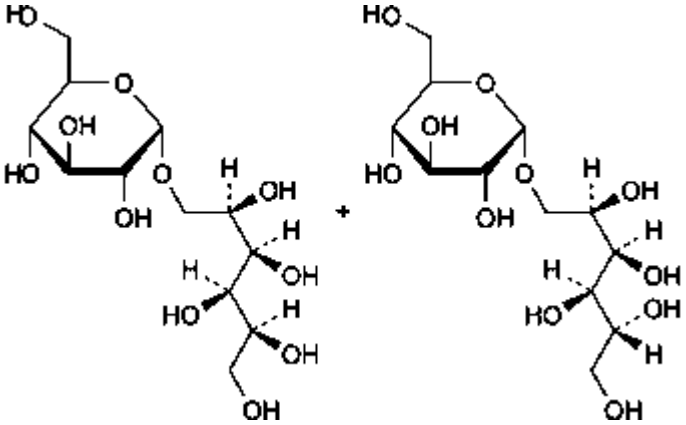


A. D-glucitol (D-sorbitol),



B. 4-*O*-α-D-glucopyranosyl-D-glucitol (D-maltitol),



C. mixture of 6-*O*-α-D-glucopyranosyl-D-glucitol and 1-*O*-α-D-glucopyranosyl-D-mannitol (isomalt).

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for mannitol used as filler in tablets and capsules.

Particle-size distribution (2.9.31 or 2.9.38)

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Powder flow (*2.9.36*) ◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Mannitol Infusion

General Notices

Mannitol Intravenous Infusion

DEFINITION

Mannitol Infusion is a sterile solution containing Mannitol. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of mannitol, $C_6H_{14}O_6$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Evaporate to dryness on a water bath a volume containing 0.2 g of Mannitol. The *melting point* of the residue, Appendix V A, is about 167°.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the infusion with *water* to contain 0.25% w/v of Mannitol.

(2) 0.25% w/v of *mannitol EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 17 cm.

(e) After removal of the plate, dry in air and spray with a 0.2% w/v solution of *sodium periodate*. Allow the plate to dry in air for 15 minutes and spray with a 2% w/v solution of *4,4′-methylenebis*-N,N-*dimethylaniline* in a mixture of 1 volume of *glacial acetic acid* and 4 volumes of *acetone*.

MOBILE PHASE

10 volumes of *water*, 20 volumes of *ethyl acetate* and 70 volumes of *propan-1-ol*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

C. Add 0.3 mL of a solution containing 10% w/v of Mannitol to 3 mL of a cooled mixture prepared by adding 6 mL of *sulfuric acid* to 3 mL of a freshly prepared 10% w/v solution of *catechol* while cooling in ice. Heat gently over a naked flame for about 30 seconds. A pink colour develops.

TESTS

Acidity or alkalinity

pH, 4.5 to 7.0, Appendix V L, when determined on solutions diluted, if necessary, with *water for injections* to contain 10% w/v of Mannitol and to which 0.30 mL of a saturated solution of *potassium chloride* has been added for each 100 mL of solution.

Reducing sugars

Add 20 mL of *cupri-citric solution* and a few glass beads to a volume of the infusion containing 5 g of Mannitol. Heat so that boiling begins after 4 minutes and continue boiling for 3 minutes. Cool rapidly and add 100 mL of a 2.4% v/v solution of *glacial acetic acid* and 20 mL of *0.025M iodine VS*. With continuous shaking add 25 mL of a mixture of 6 volumes of *hydrochloric acid* and 94 volumes of *water* and, when the precipitate has dissolved, titrate the excess of iodine with 0.05M *sodium thiosulfate VS* using 1 mL of *starch solution*, added towards the end of the titration, as indicator. Not less than 12.8 mL of 0.05M *sodium thiosulfate VS* is required.

Bacterial endotoxins

The endotoxin limit concentration is 0.5 IU per mL, Appendix XIV C. Dilute infusions containing more than 10% w/v (100 g/L) of Mannitol with *water BET* to contain 10% w/v.

ASSAY

Dilute a quantity containing 0.4 g of Mannitol to 100 mL with *water*, transfer 10 mL to a stoppered flask, add 20 mL of 0.1M *sodium periodate* and 2 mL of 1M *sulfuric acid* and heat on a water bath for 15 minutes. Cool, add 3 g of *sodium hydrogen carbonate* and 25 mL of 0.1M *sodium arsenite VS*, mix, add 5 mL of a 20% w/v solution of *potassium iodide*, allow to stand for 15 minutes and titrate with *0.05M iodine VS* until the first trace of yellow colour appears. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of iodine required. Each mL of *0.05M iodine VS* is equivalent to 1.822 mg of $C_6H_{14}O_6$.

STORAGE

Mannitol Infusion should be stored at a temperature of 20° to 30°. Exposure to lower temperatures may cause the deposition of crystals, which should be dissolved by warming before use.

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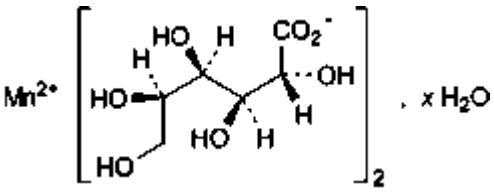
Manganese Gluconate

General Notices

(Ph. Eur. monograph 2162)



$C_{12}H_{22}MnO_{14},xH_2O$ 445.2 (anhydrous substance)

Ph Eur

DEFINITION

Anhydrous or hydrated manganese(II) bis[(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate] (anhydrous or hydrated manganese(II) di(D-gluconate)).

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale pink, slightly hygroscopic, crystalline powder.

Solubility

Soluble in water, practically insoluble in anhydrous ethanol, insoluble in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *water R*.

Reference solution Dissolve 20 mg of *calcium gluconate CRS* in 1 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Plate *TLC silica gel plate R* (5-40 µm) [or *TLC silica gel plate R* (2-10 µm)].

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Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *water R*, *ethanol (96 per cent) R* (10:10:30:50 *V/V/V/V*).

Application 1 µL.

Development Over 3/4 of the plate.

Drying At 105 °C for 20 min, then allow to cool to room temperature.

Detection Spray with a solution containing 25 g/L of *ammonium molybdate R* and 10 g/L of *cerium sulfate R* in *dilute sulfuric acid R*, and heat at 105 °C for about 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve 50 mg in 5 mL of *water R*. Add 0.5 mL of *ammonium sulfide solution R*. A pale pink precipitate is formed that dissolves upon the addition of 1 mL of *glacial acetic acid R*.

TESTS

Solution S

Dissolve 1.0 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Sucrose and reducing sugars

Dissolve 0.5 g in a mixture of 2 mL of *hydrochloric acid R1* and 10 mL of *water R*. Boil for 5 min, allow to cool, add 10 mL of *sodium carbonate solution R* and allow to stand for 10 min. Dilute to 25 mL with *water R* and filter. To 5 mL of the filtrate add 2 mL of *cupri-tartaric solution R* and boil for 1 min. Allow to stand for 2 min. No red precipitate is formed.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

Dissolve 2.0 g in a mixture of 10 mL of *acetic acid R* and 90 mL of *distilled water R*.

Zinc

Maximum 50 ppm.

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To 10 mL of solution S add 1 mL of *sulfuric acid R* and 0.1 mL of *potassium ferrocyanide solution R*. After 30 s, any opalescence in the solution is not more intense than that in a mixture of 1.0 mL of *zinc standard solution (10 ppm Zn) R*, 9 mL of *water R*, 1 mL of *sulfuric acid R* and 0.1 mL of *potassium ferrocyanide solution R*.

Water (*2.5.32*)

Maximum 9.0 per cent, determined on 80 mg.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

ASSAY

Dissolve 0.400 g in 50 mL of *water R*. Add 10 mg of *ascorbic acid R*, 20 mL of *ammonium chloride buffer solution pH 10.0 R* and 0.2 mL of a 2 g/L solution of *mordant black 11 R* in *triethanolamine R*. Titrate with *0.1 M sodium edetate* until the colour changes from violet to pure blue.

1 mL of *0.1 M sodium edetate* is equivalent to 44.52 mg of $C_{12}H_{22}MnO_{14}$.

STORAGE

In a non-metallic, airtight container.

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Manganese Sulfate

General Notices

Manganese Sulphate

$MnSO_4,4H_2O$ 223.1 *7785-87-7*

DEFINITION

Manganese Sulfate is manganese(II) sulfate tetrahydrate. It contains not less than 98.0% and not more than 100.5% of $MnSO_4$, calculated with reference to the substance ignited at 450° to 500°.

CHARACTERISTICS

Pale pink crystals or crystalline powder.

Freely soluble in *water*; practically insoluble in *ethanol (96%)*.

IDENTIFICATION

A. Dissolve 0.5 g in 10 mL of *water* and add 1 mL of *sodium sulfide solution*. A pink precipitate is produced which is soluble in 6M *acetic acid*.

B. To 0.1 g add 2 g of *lead(IV) oxide* and 5 mL of *nitric acid*, boil gently for a few minutes, add 100 mL of *water* and filter. A purple solution is produced.

C. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Arsenic

0.25 g complies with the *limit test for arsenic*, Appendix VII (4 ppm).

Heavy metals

Dissolve 0.50 g in 50 mL of *water*, add 1 mL of 1M *acetic acid* and pass *hydrogen sulfide* through the solution for 20 seconds. The colour produced within 2 minutes is not more intense than that obtained by treating 10 mL of *lead standard solution (2 ppm Pb)* diluted to 50 mL in the same manner (40 ppm).

Iron

Dissolve 1.0 g in 10 mL of *water* and add 2 mL of 1M *hydrochloric acid* and, dropwise, 0.05M *potassium permanganate* until a permanent pink colour is produced. Add 5 mL of a 10% w/v solution of *ammonium thiocyanate* and 20 mL of a mixture of equal volumes of *isoamyl*

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alcohol and *amyl acetate*, shake well and allow to separate. Any colour in the upper layer is not more intense than that obtained by treating 2 mL of *iron standard solution (20 ppm Fe)* diluted to 10 mL in the same manner (40 ppm).

Zinc

Dissolve 2.0 g in 10 mL of *water*, add 3 mL of 1M *hydrochloric acid* and 0.3 mL of a freshly prepared 3% w/v solution of *potassium hexacyanoferrate(II)*, mix and allow to stand for 15 minutes. Any turbidity produced is not more intense than that obtained by treating 10 mL of *zinc standard solution (100 ppm Zn)* in the same manner (500 ppm).

Chloride

15 mL of a 1.0% w/v solution complies with the *limit test for chlorides*, Appendix VII (330 ppm).

Loss on ignition

When ignited to constant weight at 450° to 500°, loses 31.0 to 34.0% of its weight. Use 1 g.

ASSAY

Dissolve 0.15 g in 40 mL of *water*, add 8 mL of freshly boiled and cooled *nitric acid*, cool, add 1.5 g of *sodium bismuthate* and shake for 2 minutes. Add 25 mL of a mixture of 3 volumes of *nitric acid* and 97 volumes of *water*, filter, wash the residue with 40 mL of the mixture, collecting the filtrate and washings in 50 mL of 0.1M *ammonium iron(II) sulfate VS*, and titrate immediately with 0.02M *potassium permanganate VS*. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of ammonium iron(II) sulfate required. Each mL of 0.1M *ammonium iron(II) sulfate VS* is equivalent to 3.020 mg of $MnSO_4$.

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Manganese Sulfate Monohydrate

General Notices

Manganese Sulphate Monohydrate

(Ph. Eur. monograph 1543)

$MnSO_4,H_2O$ 169.0 *10034-96-5*

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent (ignited substance).

CHARACTERS

Appearance

Pale pink crystalline powder, slightly hygroscopic.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of sulfates (*2.3.1*).

B. Dissolve 50 mg in 5 mL of *water R*. Add 0.5 mL of *sodium sulfide solution R*. A pale pink precipitate is formed which dissolves on the addition of 1 mL of *anhydrous acetic acid R*.

C. Loss on ignition (see Tests).

TESTS

Solution S

Dissolve 10.0 g in *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*).

Chloride (*2.4.4*)

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Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Iron	10
Zinc	50

Loss on ignition

10.0 per cent to 12.0 per cent, determined on 1.00 g at 500 ± 50 °C.

ASSAY

Dissolve 0.150 g in 50 mL of *water R*. Add 10 mg of *ascorbic acid R*, 20 mL of *ammonium chloride buffer solution pH 10.0 R* and 0.2 mL of a 2 g/L solution of *mordant black 11 R* in *triethanolamine R*. Titrate with *0.1 M sodium edetate* until the colour changes from violet to pure blue.

1 mL of *0.1 M sodium edetate* is equivalent to 15.10 mg of $MnSO_4$.

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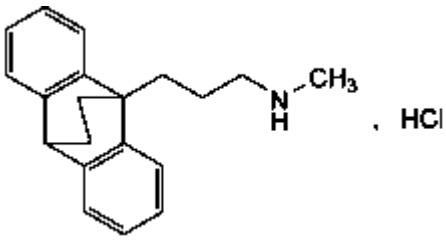
Maprotiline Hydrochloride

General Notices

(Ph. Eur. monograph 1237)



$C_{20}H_{24}ClN$ 313.9 *10347-81-6*

Action and use

Antidepressant.

Ph Eur

DEFINITION

3-(9,10-Ethanoanthracen-9(10*H*)-yl)-*N*-methylpropan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), sparingly soluble in methylene chloride, very slightly soluble in acetone.

It shows polymorphism (*5.9*).

IDENTIFICATION

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First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 10 mg in *1 M hydrochloric acid* and dilute to 100 mL with the same acid.

Spectral range 250-300 nm.

Absorption maxima At 265 nm and 272 nm.

Absorption minimum At 268 nm.

Absorbance ratio A_{272}/A_{265} = 1.1 to 1.3.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *maprotiline hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *maprotiline hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *maprotiline impurity D CRS* in reference solution (a) and dilute to 2 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ethyl acetate R*, *dilute ammonia R1*, *2-butanol R1* (4:5:14 *V/V/V*).

Application 5 µL.

Development Over half of the plate.

Drying In a current of warm air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

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D. Dilute 0.5 mL of solution S (see Tests) to 2 mL with *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 1.0 mg of *maprotiline impurity D CRS* in the test solution and dilute to 10.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm).

Mobile phase Dissolve about 0.580 g of *ammonium acetate R* in 200 mL of *water R* and add 2 mL of a 70 g/L solution of *concentrated ammonia R*; add 150 mL of *2-propanol R* and 650 mL of *methanol R*; the resulting apparent pH value is between 8.2 and 8.4.

Flow rate 1 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL.

Run time 1.5 times the retention time of maprotiline.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to maprotiline (retention time = about 10 min): impurity A = about 0.3; impurity B = about 0.5; impurity C = about 0.7; impurity D = about 0.8; impurity E = about 1.3.

System suitability Reference solution (b):

— *resolution*: 1.8 to 3.2 between the peaks due to impurity D and maprotiline; if necessary, adjust the pH of the mobile phase, in steps of 0.1 pH unit, by adding a 50 per cent *V/V* solution of *acetic acid R* if the resolution is less than 1.8, or by adding a 70 g/L solution of

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concentrated ammonia R if the resolution is greater than 3.2.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 80 °C at a pressure not exceeding 2.5 kPa for 6 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

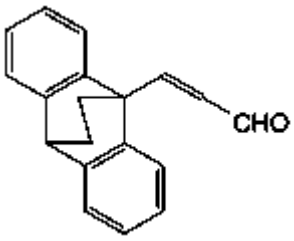
ASSAY

Dissolve 0.250 g in a mixture of 5 mL of *0.1 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.39 mg of $C_{20}H_{24}ClN$.

IMPURITIES

Specified impurities *A, B, C, D, E.*



A. 3-(9,10-ethanoanthracen-9(10*H*)-yl)prop-2-enal,

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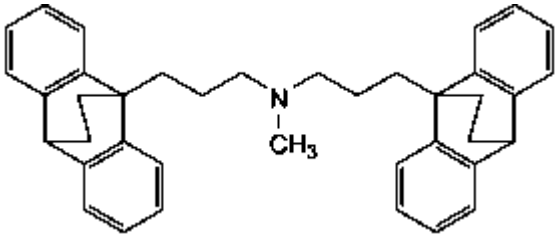
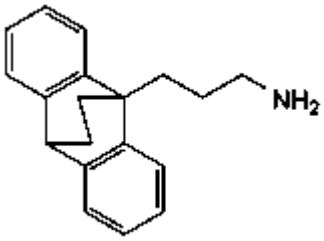
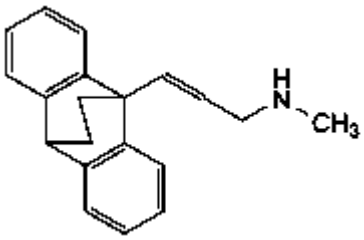


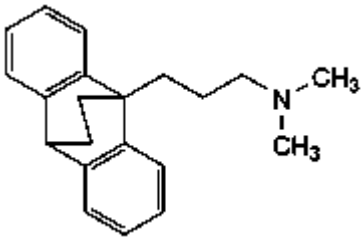
B. 3-(9,10-ethanoanthracen-9(10*H*)-yl)-*N*-[3-(9,10-ethanoanthracen-9(10*H*)-yl)propyl]-*N*-methylpropan-1-amine,



C. 3-(9,10-ethanoanthracen-9(10*H*)-yl)propan-1-amine,



D. 3-(9,10-ethanoanthracen-9(10*H*)-yl)-*N*-methylprop-2-en-1-amine (dehydromaprotiline),



E. 3-(9,10-ethanoanthracen-9(10*H*)-yl)-*N,N*-dimethylpropan-1-amine.

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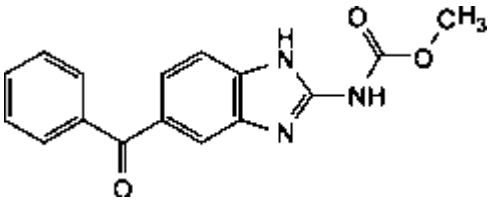
Mebendazole

General Notices

(Ph. Eur. monograph 0845)



$C_{16}H_{13}N_3O_3$ 295.3 *31431-39-7*

Action and use

Benzimadazole antihelminthic.

Preparations

Mebendazole Chewable Tablets

Mebendazole Oral Suspension

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DEFINITION

Methyl (5-benzoyl-1*H*-benzimidazol-2-yl)carbamate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*). The acceptable crystalline form corresponds to *mebendazole CRS*.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Preparation Examine the substances without prior treatment.

Comparison *mebendazole CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in *dimethylformamide R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *mebendazole for system suitability CRS* (containing impurities A, B, C, D, E, F and G) in *dimethylformamide R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *dimethylformamide R*. Dilute 5.0 mL of this solution to 20.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 7.5 g/L solution of *ammonium acetate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	80 → 70	20 → 30
15 - 20	70 → 10	30 → 90
20 - 25	10	90

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 250 nm.

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Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *mebendazole for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, F and G.

Relative retention With reference to mebendazole (retention time = about 12 min): impurity A = about 0.4; impurity B = about 0.5; impurity C = about 0.7; impurity D = about 1.1; impurity E = about 1.3; impurity F = about 1.4; impurity G = about 1.6.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to mebendazole.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 1.4;

— *impurity G*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 3 mL of *anhydrous formic acid R* and add 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 29.53 mg of $C_{16}H_{13}N_3O_3$.

STORAGE

Protected from light.

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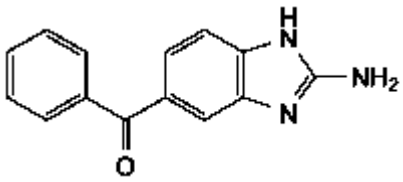
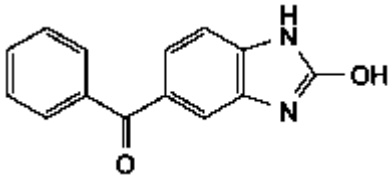
IMPURITIES

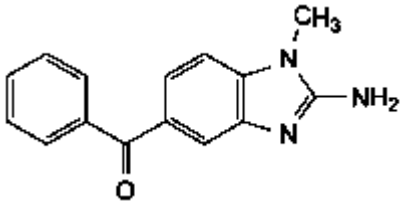
Specified impurities *A, B, C, D, E, F, G.*



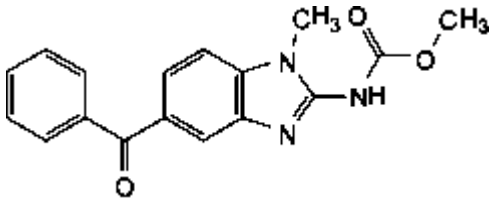
A. (2-amino-1*H*-benzimidazol-5-yl)phenylmethanone,



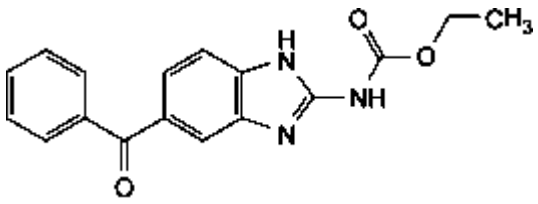
B. (2-hydroxy-1*H*-benzimidazol-5-yl)phenylmethanone,



C. (2-amino-1-methyl-1*H*-benzimidazol-5-yl)phenylmethanone,



D. methyl (5-benzoyl-1-methyl-1*H*-benzimidazol-2-yl)carbamate,



E. ethyl (5-benzoyl-1*H*-benzimidazol-2-yl)carbamate,

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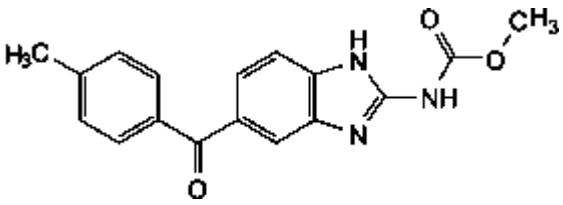
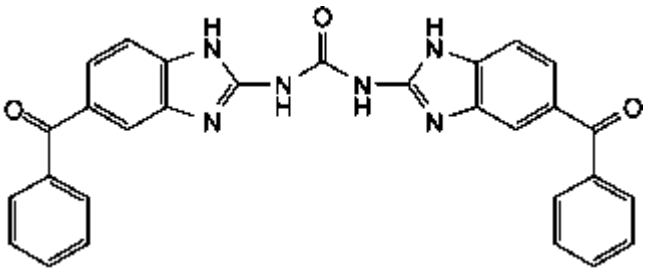


F. methyl [5-(4-methylbenzoyl)-1*H*-benzimidazol-2-yl]carbamate,



G. *N*,*N*′-bis(5-benzoyl-1*H*,-benzimidazol-2-yl)urea.

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Mebendazole Chewable Tablets

General Notices

Action and use

Benzimidazole antihelminthic.

DEFINITION

Mebendazole Chewable Tablets contain Mebendazole.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

The formulation and production of Mebendazole chewable tablets are designed to control and minimise the conversion of the polymorphic form of mebendazole from C to A. They ensure that, at any stage of the life cycle of the product, when tested by a suitable method the mebendazole in the tablets is predominantly in the form of polymorph C. The acceptable crystalline form corresponds to *mebendazole EPCRS*.

Content of mebendazole, $C_{16}H_{13}N_3O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Mebendazole with 20 mL of *water*. Filter, retain the residue and wash with three 10-mL quantities of *water* and dry overnight under vacuum at room temperature. The *infrared absorption spectrum* of the residue, Appendix II A at 3405 cm^{-1} and 1720 cm^{-1} is concordant with the Mebendazole polymorph C (*RS 503*). The presence of different polymorphic forms is indicated by differences in the spectra at 3405 cm^{-1} and 1720 cm^{-1}.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, containing 1.0% w/v *sodium lauryl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 120 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with dissolution medium, if necessary, to produce a solution expected to contain 0.011% w/v of Mebendazole.

(2) 0.011% w/v of *mebendazole BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 250 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a 0.75% w/v of *ammonium acetate*.

DETERMINATION OF CONTENT

Calculate the total content of mebendazole, $C_{16}H_{13}N_3O_3$, in the medium using the declared content of $C_{16}H_{13}N_3O_3$, in *mebendazole BPCRS*.

LIMITS

The amount of Mebendazole released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Mebendazole in 30 mL of *anhydrous formic acid*. Dilute with *methanol (60%)* to produce 100 mL, mix, and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (60%)*. Dilute 1 volume of the resulting solution to 4 volumes with *methanol (60%)*.

(3) To 10 mg of *mebendazole BPCRS* add 5 mL of *methanol* and 1 mL of 1M *sodium hydroxide*. Heat in a water bath at 60 ° for 1 hour, cool to room temperature, and adjust to pH 7 with 1M *hydrochloric acid*. Dilute to 10 mL with *methanol* and mix (generation of impurity A).

(4) 0.1% w/v of *mebendazole for system suitability EPCRS* in *dimethylformamide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 40°.

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(e) Use a detection wavelength of 250 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.75% w/v of *ammonium acetate* in *water*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	80→70	20→30	isocratic
15-20	70→10	30→90	linear gradient
20-25	10	90	isocratic
25-26	10→80	90→20	linear gradient
26-36	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mebendazole (retention time, about 12 min) are: impurity A, about 0.4; impurity B, about 0.5; impurity C, about 0.7; impurity D, about 1.1; impurity E, about 1.3; impurity F, about 1.4; impurity G, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and mebendazole is at least 10.

LIMITS

Identify any peak in solution (1) corresponding to impurity G using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity G is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Mebendazole in 30 mL of *anhydrous formic acid*. Dilute with *methanol (60%)* to produce 100 mL, mix, and filter. Dilute 1 volume of the filtrate to 20 volumes with *methanol (60%)* .

(2) Dissolve with the aid of ultrasound 25 mg of *mebendazole BPCRS* in 10 mL of *anhydrous formic acid*. Dilute with *methanol (60%)* to produce 25 mL. Dilute 1 volume of the solution to 20 volumes with *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of mebendazole, $C_{16}H_{13}N_3O_3$, in the tablets, using the declared content of $C_{16}H_{13}N_3O_3$, in *mebendazole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mebendazole.

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Mebendazole Oral Suspension

General Notices

Action and use

Benzimidazole antihelminthic.

DEFINITION

Mebendazole Oral Suspension is a suspension of Mebendazole in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

PRODUCTION

The formulation and production of Mebendazole Oral Suspension are designed to control and minimise the conversion of the polymorphic form of Mebendazole from C to A. They ensure that, at any stage of the life cycle of the product, when tested by a suitable method the Mebendazole in the oral suspension is predominantly in the form of polymorph C. The acceptable crystalline form corresponds to *mebendazole EPCRS*

Content of mebendazole, $C_{16}H_{13}N_3O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the suspension containing 50 mg of Mebendazole with 20 mL of *water*. Filter, retain the residue and wash with three 10-mL quantities of *water* and dry overnight under vacuum at room temperature. The *infrared absorption spectrum* of the residue, Appendix II A, at 3405 cm^{-1} and 1720 cm^{-1} is concordant with the mebendazole polymorph C (*RS 503*). The presence of different polymorphic forms is indicated by differences in the spectra at 3405 cm^{-1} and 1720 cm^{-1}.

TESTS

Acidity

pH, 4.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Shake a quantity of the oral suspension containing 50 mg of Mebendazole with 30 mL of *formic acid* and 30 mL of *methanol* (60%). Add sufficient *methanol* (60%) to produce 100 mL, filter (Acrodisc 0.45-µm GxF glass fiber PVDF is suitable), and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol* (60%). Dilute 1 volume of the resulting solution to 4 volumes with *methanol* (60%).

(3) To 5 mg of *mebendazole BPCRS* add 5 mL of *methanol* and 1 mL of 1M *sodium hydroxide*. Heat in a water bath at 60° for 1 hour, cool to room temperature, and adjust to pH 7 with 1M *hydrochloric acid*. Dilute to 100 mL with *methanol* and mix (generation of impurity A). To 1 volume of this solution, add 1 mL of 0.1% w/v of *methyl parahydroxybenzoate* in *methanol* and dilute to 100 volumes of *methanol (60%)*.

(4) 0.1% w/v of *mebendazole for system suitability EPCRS* in *dimethylformamide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable)

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 250 nm.

(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.025% v/v of *trifluoroacetic acid* in *water*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	90→70	10→30	linear gradient
20-29	70→30	30→70	linear gradient
29-30	30→90	70→10	linear gradient
30-35	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to mebendazole (retention time about 17 minutes) are: methyl parahydroxybenzoate, about 0.66; impurity A, about 0.69; impurity C, about 0.74; impurity B, about 0.9; impurity D, about 1.1; impurity E, about 1.20; impurity F, about 1.23; impurity G, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methyl parahydroxybenzoate and mebendazole impurity A is at least 2.0;

in the chromatogram obtained with solution (2), the *signal-to-noise ratio* of the peak due to mebendazole is at least 25.

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LIMITS

Identify any peak in solution (1) corresponding to impurity G using the chromatogram obtained with solution (3) and multiply the area of this peak by a correction factor of 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity G is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak due to methyl parahydroxybenzoate and any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a weighed quantity of the oral suspension containing 50 mg of Mebendazole with 30 mL of *formic acid* and 30 mL of *methanol* (60%). Add sufficient *methanol* (60%) to produce 100 mL. Dilute 1 volume of the resulting solution to 5 volumes with *methanol* (60%). Filter (Acrodisc 0.45-µm GxF glass fiber PVDF is suitable) and use the filtrate.
(2) 0.01% w/v of *mebendazole BPCRS* in *dimethylformamide*.
(3) 0.01% w/v each of *mebendazole for system suitability EPCRS* and *methyl parahydroxybenzoate* in *dimethylformamide*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methyl parahydroxybenzoate and mebendazole impurity A is at least 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{16}H_{13}N_3O_3$, weight in volume, using the declared content of $C_{16}H_{13}N_3O_3$ in *mebendazole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mebendazole.

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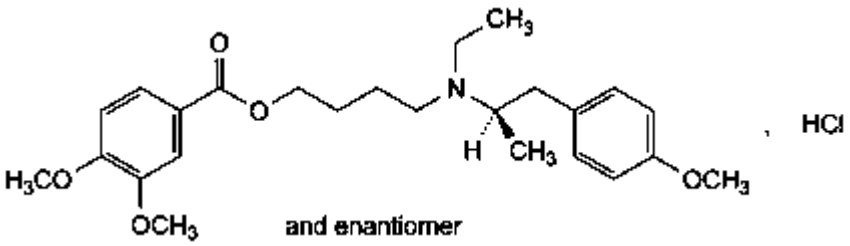
Mebeverine Hydrochloride

General Notices

(Ph. Eur. monograph 2097)



$C_{25}H_{36}ClNO_5$ 466.0 *2753-45-9*

Action and use

Smooth muscle relaxant; antispasmodic.

Preparations

Mebeverine Tablets

Mebeverine Prolonged-release Capsules

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DEFINITION

4-[Ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butyl 3,4-dimethoxybenzoate hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water and in methylene chloride, freely soluble in ethanol (96 per cent).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mebeverine hydrochloride CRS*.

B. Dissolve 50 mg in 4 mL of *water R*, acidify with 0.6 mL of *dilute nitric acid R* and centrifuge at 1800 g for 15 min. The supernatant gives reaction (a) of chlorides (2.3.1) starting from 'add 0.4 mL of *silver nitrate solution R1*'.

TESTS

pH (2.2.3)

4.5 to 6.5.

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *mebeverine for system suitability CRS* (containing impurity J) in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 1 volume of *triethylamine R* and 100 volumes of *water for chromatography R* and adjust to pH 5.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	75	25
6 - 20	75 → 30	25 → 70

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
20 - 40	30	70

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 2 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity J.

Relative retention With reference to mebeverine (retention time = about 15 min): impurity J = about 0.82.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurity J and mebeverine in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 70 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity J by 3.5;

— for each impurity, use the concentration of mebeverine hydrochloride in reference solution (a).

Limits:

— *impurity J*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous ethanol R* and add 5.0 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

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1 mL of *0.1 M sodium hydroxide* is equivalent to 46.60 mg of $C_{25}H_{36}ClNO_5$.

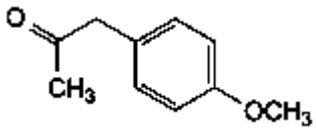
STORAGE

Protected from light.

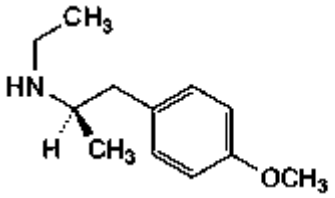
IMPURITIES

Specified impurities J.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I, K, N, O.

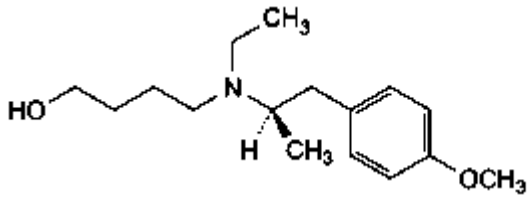


A. 1-(4-methoxyphenyl)propan-2-one,



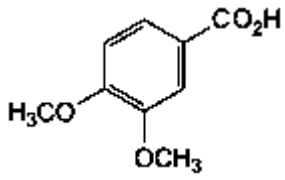
and enantiomer

B. (2*RS*)-*N*-ethyl-1-(4-methoxyphenyl)propan-2-amine,



and enantiomer

C. 4-[ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butan-1-ol,



D. 3,4-dimethoxybenzoic acid,

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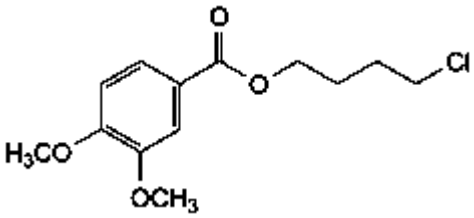
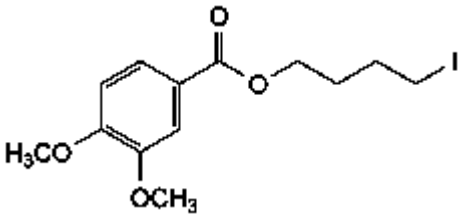
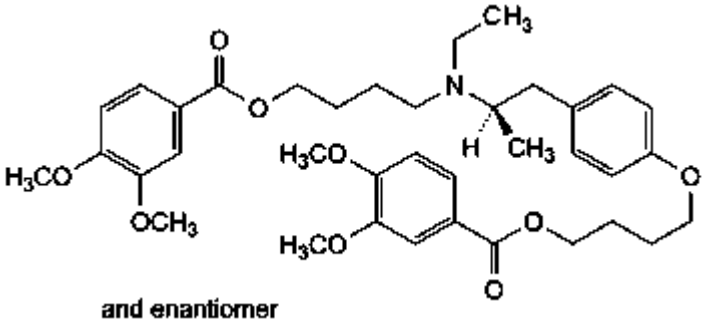


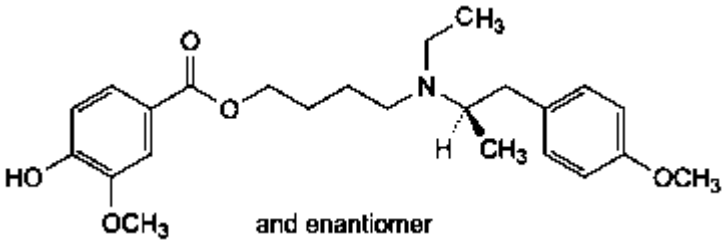
E. 4-chlorobutyl 3,4-dimethoxybenzoate,



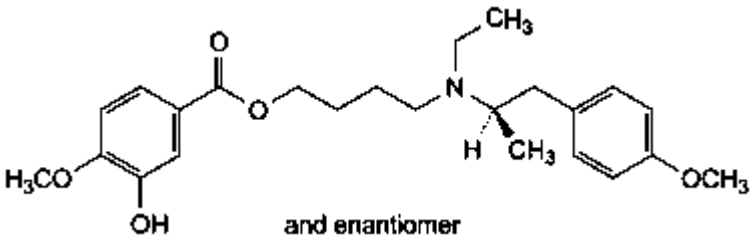
F. 4-iodobutyl 3,4-dimethoxybenzoate,



G. 4-[[(2*RS*)-1-[4-[4-[(3,4-dimethoxybenzoyl)oxy]butoxy]phenyl]propan-2-yl](ethyl)amino]butyl 3,4-dimethoxybenzoate,



H. 4-[ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butyl 4-hydroxy-3-methoxybenzoate,



I. 4-[ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butyl 3-hydroxy-4-methoxybenzoate,

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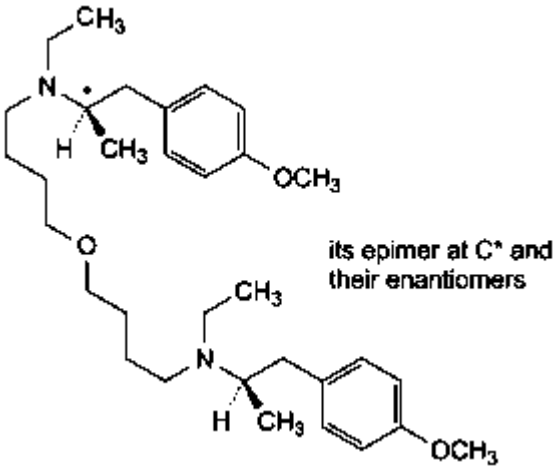
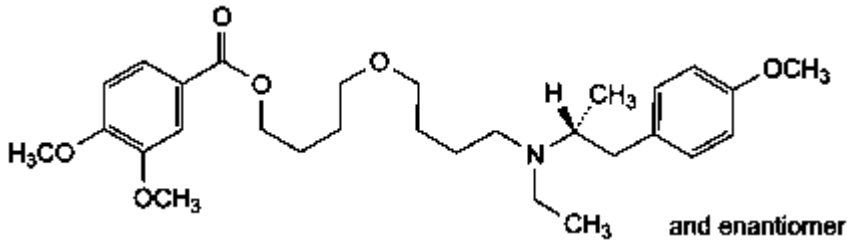
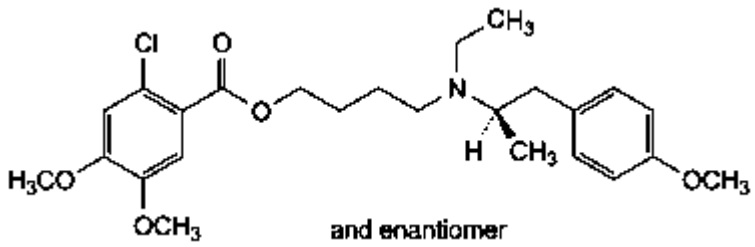


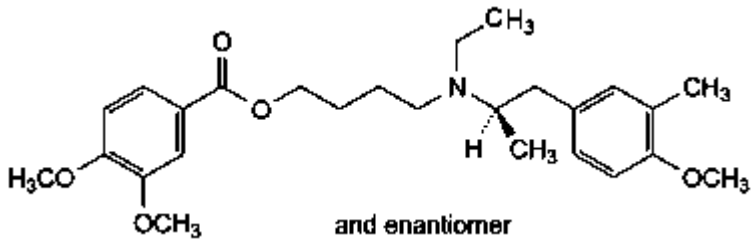
J. mixture of *N*-ethyl-4-[4-[ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butoxy]-*N*-[(2*R*)-1-(4-methoxyphenyl)propan-2-yl]butan-1-amine and *N*-ethyl-4-[4-[ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butoxy]-*N*-[(2*S*)-1-(4-methoxyphenyl)propan-2-yl]butan-1-amine,



K. 4-[4-[ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butoxy]butyl 3,4-dimethoxybenzoate,



N. 4-[ethyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]butyl 2-chloro-4,5-dimethoxybenzoate,



O. 4-[ethyl[(2*RS*)-1-(4-methoxy-3-methylphenyl)propan-2-yl]amino]butyl 3,4-dimethoxybenzoate.

Ph Eur

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Mebeverine Prolonged-release Capsules

General Notices

Mebeverine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Smooth muscle relaxant; antispasmodic.

DEFINITION

Mebeverine Prolonged-release Capsules contain Mebeverine Hydrochloride. They are formulated so that the Mebeverine Hydrochloride is released over a period of several hours.

The capsules comply with the requirements stated under Capsules and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Mebeverine Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

Content of mebeverine hydrochloride, $C_{25}H_{35}NO_5$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of powdered capsule contents containing 0.2 g of Mebeverine Hydrochloride in 20 mL of *water*, add 5 mL of 5M *sodium hydroxide* and extract with two 25-mL quantities of *dichloromethane*. Dry the combined extracts over *anhydrous sodium sulfate* and evaporate the solvent. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of mebeverine *(RS 208)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 3 volumes of *acetonitrile* and 7 volumes of mobile phase A.

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(1) Shake a quantity of powdered capsule contents containing 50 mg of Mebeverine Hydrochloride with 50 mL of solution A, mix with the aid of ultrasound and shake intermittently. Dilute to 100 mL, mix and filter (a 0.45-µm nylon filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.05% w/v of *mebeverine impurity standard BPCRS*.

(4) 0.0001% w/v of *mebeverine impurity C BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *triethylamine* and 1000 volumes of 0.38% w/v *ammonium acetate*, adjusted to pH 3.0 with *orthophosphoric acid*.

Mobile phase B *Acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	70	30	isocratic
5-15	70→30	30→70	linear gradient
15-25	30	70	isocratic
25-27	30→70	70→30	linear gradient
27-35	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mebeverine (retention time about 12 minutes) are: impurity C, about 0.3 and impurity D, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and D is at least 15;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of the peak due to impurity C is at least 10.

LIMITS

Identify any peaks corresponding to impurities C and D in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of the peak corresponding to impurity D by a correction factor of 0.4.

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

The total impurity content is not greater than 1.0%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound and intermittent shaking, a quantity of powdered capsule contents containing 25 mg of Mebeverine Hydrochloride in 70 mL of *methanol*. Dilute to 100 mL with *methanol* and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume to 5 volumes with the mobile phase.

(2) 0.025% w/v of *mebeverine hydrochloride BPCRS* in *methanol*. Dilute 1 volume of the solution to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

380 volumes of *acetonitrile* and 620 volumes of 0.38% w/v *ammonium acetate*, previously adjusted to pH 5.2 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of mebeverine is about 10 minutes.

DETERMINATION OF CONTENT

Calculate the content of mebeverine hydrochloride, $C_{25}H_{35}NO_5$,HCl, in the capsules from the chromatograms obtained and using the declared content of $C_{25}H_{35}NO_5$,HCl in *mebeverine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and D listed under Mebeverine Hydrochloride.

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Mebeverine Tablets

General Notices

Action and use

Smooth muscle relaxant; antispasmodic.

DEFINITION

Mebeverine Tablets contain Mebeverine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mebeverine hydrochloride, $C_{25}H_{35}NO_5$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of powdered tablets containing 0.2 g of Mebeverine Hydrochloride in 20 mL of *water*, add 5 mL of 5M *sodium hydroxide* and extract with two 25 -mL quantities of *dichloromethane*. Dry the combined extracts over *anhydrous sodium sulfate* and evaporate the solvent. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of mebeverine *(RS 208)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 3 volumes of *acetonitrile* and 7 volumes of mobile phase A.

(1) Shake a quantity of powdered tablets containing 50 mg of Mebeverine Hydrochloride with 50 mL of solution A, mix with the aid of ultrasound and shake intermittently. Dilute to 100 mL, mix and filter (a 0.45-µm nylon filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.
(3) 0.05% w/v of *mebeverine impurity standard BPCRS*.
(4) 0.0001% w/v of *mebeverine impurity C BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Intertsil ODS-3 is suitable).
(b) Use gradient elution and the mobile phase described below.

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(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *triethylamine* and 1000 volumes of 0.38% w/v *ammonium acetate*, adjusted to pH 3.0 with *orthophosphoric acid*.

Mobile phase B *Acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	70	30	isocratic
5-15	70→30	30→70	linear gradient
15-25	30	70	isocratic
25-27	30→70	70→30	linear gradient
27-35	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mebeverine (retention time about 12 minutes) are: impurity C, about 0.3 and impurity D, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and D is at least 15;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of the peak due to impurity C is at least 10.

LIMITS

Identify any peaks corresponding to impurities C and D in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of the peak corresponding to impurity D by a correction factor of 0.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

The total impurity content is not greater than 1.0%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

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ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound and intermittent shaking, a quantity of powdered tablets containing 25 mg of Mebeverine Hydrochloride in 20 mL of *methanol*. Dilute to 100 mL with the mobile phase and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume to 5 volumes with the mobile phase.

(2) 0.025% w/v solution, prepared by dissolving 25 mg *mebeverine hydrochloride BPCRS* in 20 mL *methanol* then diluting to 100 mL with the mobile phase. Further dilute 1 volume of the solution to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

380 volumes of *acetonitrile* and 620 volumes of 0.38% w/v *ammonium acetate*, previously adjusted to pH 5.2 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of mebeverine is about 10 minutes.

DETERMINATION OF CONTENT

Calculate the content of mebeverine hydrochloride, $C_{25}H_{35}NO_5$,HCl, in the tablets from the chromatograms obtained and using the declared content of $C_{25}H_{35}NO_5$,HCl in *mebeverine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and D listed under Mebeverine Hydrochloride.

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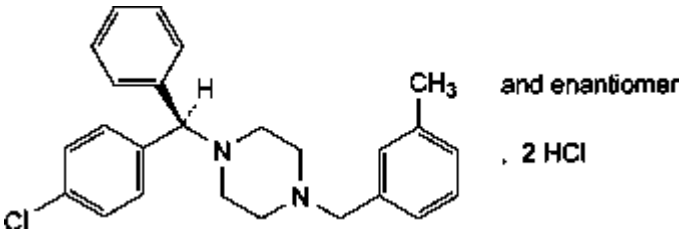
Meclozine Hydrochloride

General Notices

(Meclozine Dihydrochloride, Ph. Eur. monograph 0622)



$C_{25}H_{29}Cl_3N_2$ 463.9 *1104-22-9*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

1-[(*RS*)-(4-Chlorophenyl)phenylmethyl]-4-[(3-methylphenyl)methyl]piperazine dihydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white, slightly hygroscopic, crystalline powder.

Solubility

Slightly soluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 15.0 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of this solution to 100.0 mL with *0.1 M hydrochloric acid*.

Spectral range 220-350 nm.

Absorption maximum At 232 nm.

Specific absorbance at the absorption maximum 345 to 380 (anhydrous substance).

The solution also shows a weak absorbance without a defined maximum between 260 nm and 300 nm.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *meclozine dihydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *meclozine dihydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *diethylamine R*, *toluene R*, *cyclohexane R* (10:15:75 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air for 5 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 15 mg in 2 mL of *ethanol (96 per cent) R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Acidity or alkalinity

Calculate the acidity or alkalinity from the titration volumes obtained in the assay using the following equation:

$$A = V_2 - 2V_1$$

V_1 = volume of *0.1 M sodium hydroxide* added at the 1st point of inflexion;

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V_2 = volume of *0.1 M sodium hydroxide* added at the 2nd point of inflexion.

A is not less than -0.3 mL and not more than 0.3 mL for 0.350 g of the substance to be examined.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 7.5 mg of *meclozine impurity B CRS* and 7.5 mg of *meclozine impurity H CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *concentrated ammonia R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	60	40
3 - 13	60 → 15	40 → 85
13 - 23	15 → 5	85 → 95
23 - 33	5	95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

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Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and H.

Relative retention With reference to meclozine (retention time = about 18 min): impurity B = about 0.45; impurity H = about 0.49.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and H.

Limits:

— *impurity B*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 5.0 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 46.39 mg of $C_{25}H_{29}Cl_3N_2$.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, H.*

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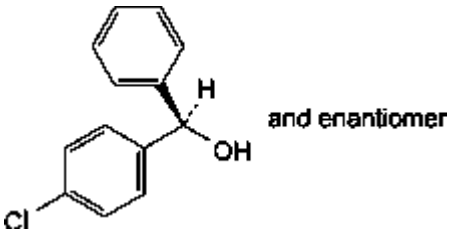
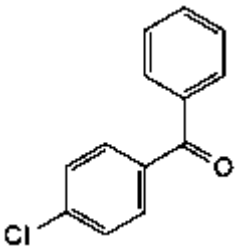
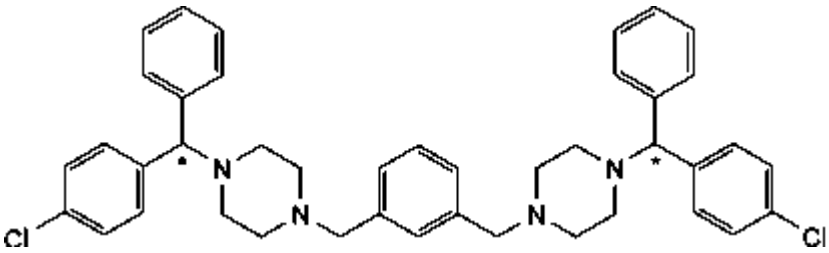


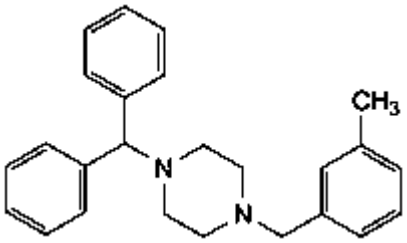
B. (*RS*)-(4-chlorophenyl)phenylmethanol,



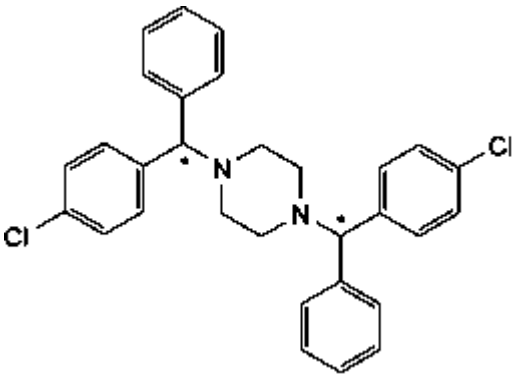
C. (4-chlorophenyl)phenylmethanone (4-chlorobenzophenone),



D. 1,1′-(1,3-phenylenebismethylene)bis[4-[(4-chlorophenyl)phenylmethyl]piperazine],



E. 1-(diphenylmethyl)-4-[(3-methylphenyl)methyl]piperazine,



F. 1,4-bis[(4-chlorophenyl)phenylmethyl]piperazine,

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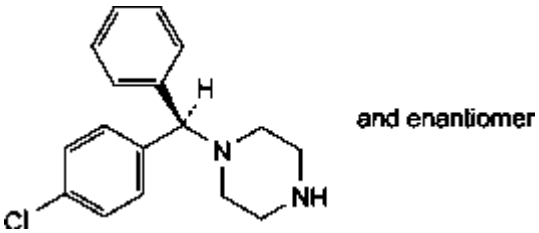

H. 1-[(*RS*)-(4-chlorophenyl)phenylmethyl]piperazine.

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Medical Air

General Notices

(Medicinal Air, Ph. Eur. monograph 1238)

When Medical Air is intended for use in a room in which magnetic resonance imaging (MRI) is being performed, the cylinder and fittings should be made from suitable non-ferromagnetic materials and labelled accordingly.

Ph Eur

DEFINITION

Compressed ambient air.

Content

20.4 per cent *V/V* to 21.4 per cent *V/V* of oxygen (O_2).

CHARACTERS

Appearance

Colourless gas.

Solubility

At 20 °C at a pressure of 101 kPa, 1 volume dissolves in about 50 volumes of water.

PRODUCTION

Carbon dioxide

Maximum 500 ppm *V/V*, determined using an infrared analyser (*2.5.24*).

Gas to be examined Filter the substance to be examined to avoid stray light phenomena.

Reference gas (a) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing less than 1 ppm *V/V* of *carbon dioxide R1*.

Reference gas (b) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing 500 ppm *V/V* of *carbon dioxide R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon dioxide in the gas to be examined.

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Carbon monoxide

Maximum 5 ppm *V/V*, determined using an infrared analyser (2.5.25).

Gas to be examined Filter the substance to be examined to avoid stray light phenomena.

Reference gas (a) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing less than 1 ppm *V/V* of *carbon monoxide R*.

Reference gas (b) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing 5 ppm *V/V* of *carbon monoxide R*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

Sulfur dioxide

Maximum 1 ppm *V/V*, determined using an ultraviolet fluorescence analyser (Figure 1238.-1).

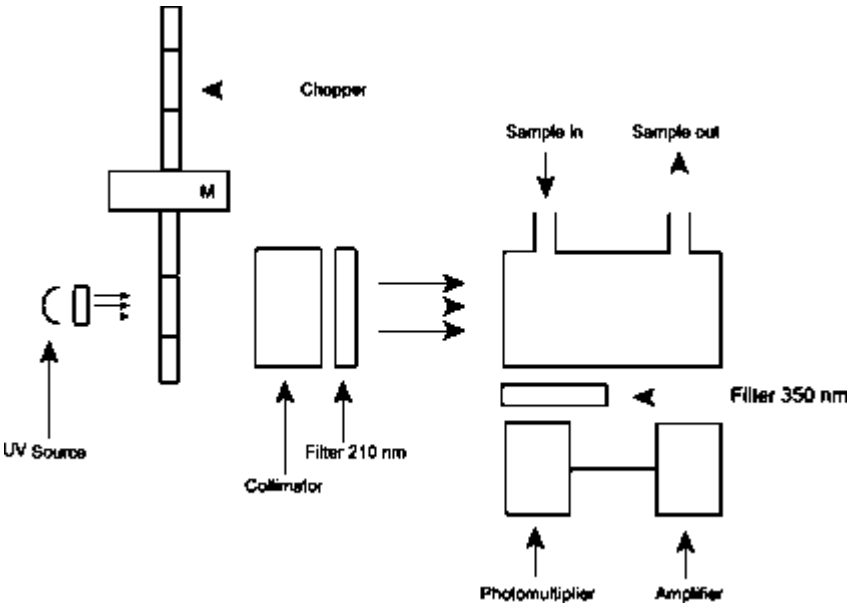

Figure 1238.-1. – *UV fluorescence analyser*

The apparatus consists of the following:

— a system generating ultraviolet radiation with a wavelength of 210 nm, made up of an ultraviolet lamp, a collimator, and a selective filter; the beam is blocked periodically by a chopper rotating at high speeds;

— a reaction chamber, through which flows the gas to be examined;

— a system that detects radiation emitted at a wavelength of 350 nm, made up of a selective filter, a photomultiplier tube and an amplifier.

Gas to be examined Filter the substance to be examined.

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Reference gas (a) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*.

Reference gas (b) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing 0.5 ppm *V/V* to 2 ppm *V/V* of *sulfur dioxide R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of sulfur dioxide in the gas to be examined.

Oil

Maximum 0.1 mg/m^3, determined using an oil detector tube (2.1.6), when an oil-lubricated compressor is used for the production.

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V* in total, determined using a chemiluminescence analyser (2.5.26).

Gas to be examined The substance to be examined.

Reference gas (a) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing less than 0.05 ppm *V/V* of nitrogen monoxide and nitrogen dioxide.

Reference gas (b) Use a mixture of 21 per cent *V/V* of *oxygen R* and 79 per cent *V/V* of *nitrogen R1*, containing 2 ppm *V/V* of *nitrogen dioxide R*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of nitrogen monoxide and nitrogen dioxide in the gas to be examined.

Water

Maximum 67 ppm *V/V*, determined using an electrolytic hygrometer (2.5.28), except where the competent authority decides that the following limit applies to medicinal air generated on-site and distributed in pipe-line systems operating at a pressure not greater than 10 bar and a temperature not less than 5 °C: maximum 870 ppm *V/V*, determined using an electrolytic hygrometer (2.5.28).

Assay

Determine the concentration of oxygen in air using a paramagnetic analyser (2.5.27).

IDENTIFICATION

First identification: C.

Second identification: A, B.

A. In a conical flask containing the substance to be examined, place a glowing wood splinter. The splinter remains glowing.

B. Use a gas burette (Figure 1238.-2) of 25 mL capacity in the form of a chamber in the middle of which is a tube graduated in 0.2 per cent between 19.0 per cent and 23.0 per cent, and isolated at each end by a tap with a conical barrel. The lower tap is joined to a tube with an olive-shaped nozzle and is used to introduce the gas into the apparatus. A cylindrical funnel above the upper tap is used to introduce the absorbent solution. Wash the burette with *water R* and dry. Open the 2 taps. Connect the nozzle to the source of the gas to be examined

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and set the flow rate to 1 L/min. Flush the burette by passing the gas to be examined through it for 1 min. Close the lower tap of the burette and immediately afterwards the upper tap. Rapidly disconnect the burette from the source of the gas to be examined. Rapidly give a half turn to the upper tap to eliminate any excess pressure in the burette. Keeping the burette vertical, fill the funnel with a freshly prepared mixture of 21 mL of a 560 g/L solution of *potassium hydroxide R* and 130 mL of a 200 g/L solution of *sodium dithionite R*. Open the upper tap slowly. The solution absorbs the oxygen and enters the burette. Allow to stand for 10 min without shaking. Read the level of the liquid meniscus on the graduated part of the burette. This figure represents the percentage *V/V* of oxygen. The value read is 20.4 to 21.4.

C. It complies with the limits of the assay.

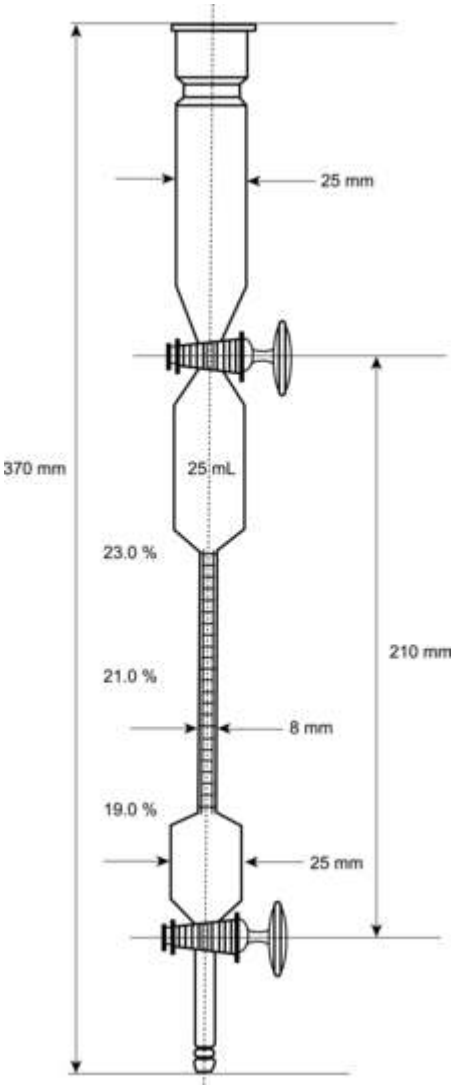

Figure 1238.-2. – *Gas burette*

TESTS

Carbon dioxide

Maximum 500 ppm *V/V*, determined using a carbon dioxide detector tube (*2.1.6*).

Sulfur dioxide

Maximum 1 ppm *V/V*, determined using a sulfur dioxide detector tube (*2.1.6*).

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Oil

Maximum 0.1 mg/m^3, determined using an oil detector tube (*2.1.6*), when an oil-lubricated compressor is used for the production.

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V*, determined using a nitrogen monoxide and nitrogen dioxide detector tube (*2.1.6*).

Carbon monoxide

Maximum 5 ppm *V/V*, determined using a carbon monoxide detector tube (*2.1.6*).

Water vapour

Maximum 67 ppm *V/V*, determined using a water vapour detector tube (*2.1.6*), except where the competent authority decides that the following limit applies to medicinal air generated on-site and distributed in pipe-line systems operating at a pressure not greater than 10 bar and a temperature not less than 5 °C: maximum 870 ppm *V/V*, determined using a water vapour detector tube (*2.1.6*).

STORAGE

As a gas, in suitable containers complying with the legal regulations or as a gas supplied by a pipe network.

LABELLING

Where applicable, the label states the production method and any use of an oil-lubricated compressor.

IMPURITIES

A. CO_2: carbon dioxide,

B. SO_2: sulfur dioxide,

C. NO: nitrogen monoxide,

D. NO_2: nitrogen dioxide,

E. oil,

F. CO: carbon monoxide,

G. H_2O: water.

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Medium-chain Triglycerides

General Notices

Fractionated Coconut Oil

(Ph. Eur. monograph 0868)

Action and use

Excipient.

When Medium-chain Triglycerides are prepared from the endosperm of Cocos nucifera L the title fractionated coconut oil may be used.

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DEFINITION

Mixture of triglycerides of saturated fatty acids, mainly of caprylic (octanoic) acid and of capric (decanoic) acid. The fatty acids are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineensis* Jacq.

Content

Minimum 95.0 per cent of saturated fatty acids with 8 and 10 carbon atoms.

CHARACTERS

Appearance

Colourless or slightly yellowish, oily liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent), with methylene chloride, with light petroleum and with fatty oils.

Relative density

About 0.95.

Refractive index

About 1.446.

IDENTIFICATION

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First identification: C, D.

Second identification: A, B, D.

A. Iodine value (2.5.4): maximum 1.0.

B. Saponification value (2.5.6): 310 to 360.

C. Composition of fatty acids (see Tests).

D. Viscosity (see Tests).

TESTS

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution Y_3 (2.2.2, Method I).

Alkaline impurities

Dissolve 2.00 g in a mixture of 1.5 mL of ethanol (96 per cent) R and 3.0 mL of ether R. Add 0.05 mL of bromophenol blue solution R. Not more than 0.15 mL of 0.01 M hydrochloric acid is required to change the colour of the indicator to yellow.

Viscosity (2.2.9)

25 mPa·s to 33 mPa·s.

Acid value (2.5.1)

Maximum 0.2.

Hydroxyl value (2.5.3, Method A)

Maximum 10.

Peroxide value (2.5.5, Method A)

Maximum 1.0.

Composition of fatty acids

Gas chromatography (2.4.22, Method C) with the following modifications. Use the mixture of calibrating substances in Table 2.4.22.-2.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: macrogol 20 000 R (film thickness 0.5 µm).

Carrier gas helium for chromatography R.

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Flow rate 1.3 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	70
	1 - 35	70 → 240
	35 - 50	240
Injection port		250
Detector		250

Detection Flame ionisation.

Split ratio 1:100.

Composition of the fatty-acid fraction of the substance:

— *caproic acid*: maximum 2.0 per cent;

— *caprylic acid*: 50.0 per cent to 80.0 per cent;

— *capric acid*: 20.0 per cent to 50.0 per cent;

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 1.0 per cent;

— *fatty acids of chain length greater than or equal to* C_{16}: maximum 1.0 per cent.

Water (*2.5.32*)

Maximum 0.2 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

STORAGE

In a well-filled container, protected from light.

LABELLING

The label states, where applicable, that the substance is intended for use in parenteral nutrition.

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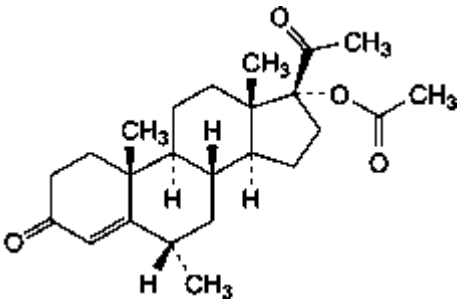
Medroxyprogesterone Acetate

General Notices

(Ph. Eur. monograph 0673)



$C_{24}H_{34}O_4$ 386.5 *71-58-9*

Action and use

Progestogen.

Preparations

Medroxyprogesterone Injection

Medroxyprogesterone Tablets

Ph Eur

DEFINITION

6α-Methyl-3,20-dioxopregn-4-en-17-yl acetate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, sparingly soluble in ethanol (96 per cent).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *medroxyprogesterone acetate CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 47 to + 53 (dried substance).

Dissolve 0.250 g in *acetone R* and dilute to 25.0 mL with the same solvent.

Impurity F

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in 5.0 mL of *acetonitrile R1* and dilute to 10.0 mL with *water for chromatography R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *medroxyprogesterone acetate for peak identification CRS* (containing impurity F) in 3.0 mL of *acetonitrile R1* and dilute to 5.0 mL with *water for chromatography R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *water for chromatography R*, *acetonitrile R1* (44:56 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 25 µL.

Identification of impurities Use the chromatogram supplied with *medroxyprogesterone acetate for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity F.

Relative retention With reference to medroxyprogesterone acetate (retention time = about 8 min): impurity F = about 1.8.

Limit:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 1.8;

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— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 4 mg of medroxyprogesterone acetate for system suitability CRS (containing impurities A, B, C, D, E, G and I) in the solvent mixture and dilute to 2.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 60 °C.

Mobile phase tetrahydrofuran R, acetonitrile R, water R (12:23:65 *V/V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time Twice the retention time of medroxyprogesterone acetate.

Identification of impurities Use the chromatogram supplied with medroxyprogesterone acetate for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, G and I.

Relative retention With reference to medroxyprogesterone acetate (retention time = about 20 min): impurity A = about 0.3; impurity I = about 0.5; impurity H = about 0.65; impurity B = about 0.7; impurity C = about 0.8; impurity G = about 0.85; impurity D = about 0.9; impurity E = about 0.95.

System suitability Reference solution (a):

— peak-to-valley ratio: minimum 2.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to medroxyprogesterone acetate.

Limits:

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— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.5; impurity G = 2.6;

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity B*: not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities C, E, G, I*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 241 nm.

Calculate the content of $C_{24}H_{34}O_4$ taking the specific absorbance to be 420.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H.*

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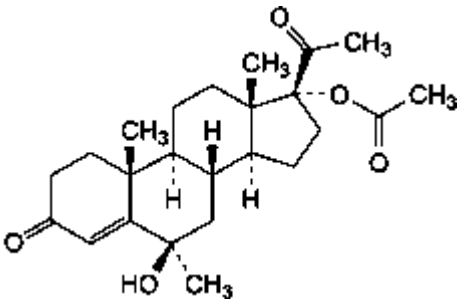
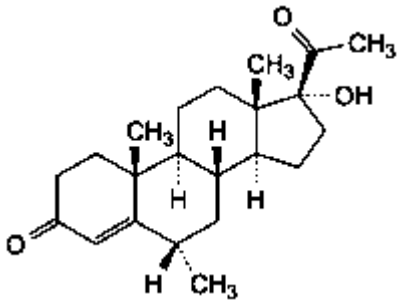
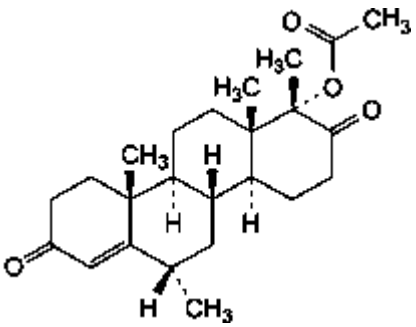


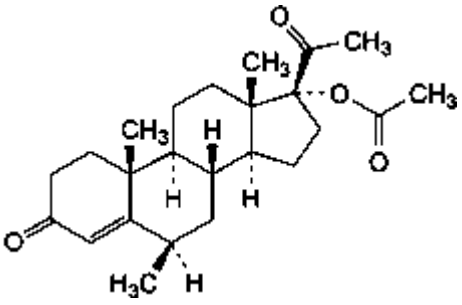
A. 6β-hydroxy-6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-hydroxymedroxyprogesterone acetate),



B. 17-hydroxy-6α-methylpregn-4-ene-3,20-dione (medroxyprogesterone),



C. 6α,17a-dimethyl-3,17-dioxo-*D*-homoandrost-4-en-17aα-yl acetate,



D. 6β-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-epimedroxyprogesterone acetate),

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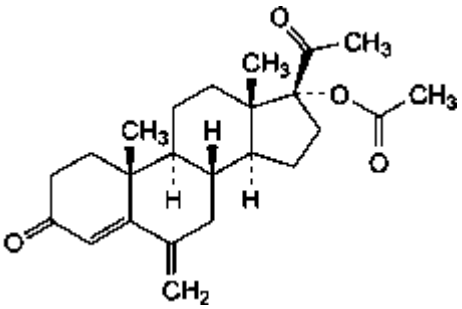
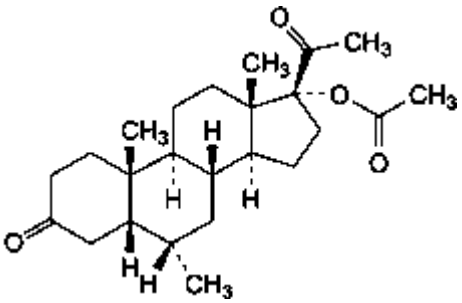
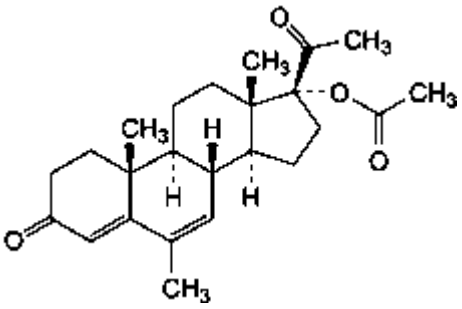


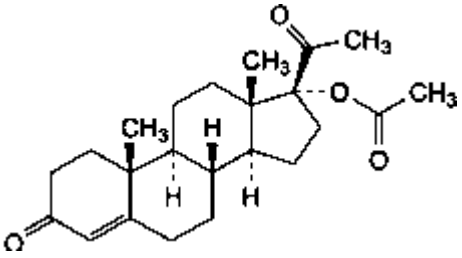
E. 6-methylidene-3,20-dioxopregn-4-en-17-yl acetate (6-methylenehydroxyprogesterone acetate),



F. 6α-methyl-3,20-dioxo-5β-pregnan-17-yl acetate (4,5-dihydromedroxyprogesterone acetate),



G. 6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate (megestrol acetate),



H. 3,20-dioxopregn-4-en-17-yl acetate (hydroxyprogesterone acetate),

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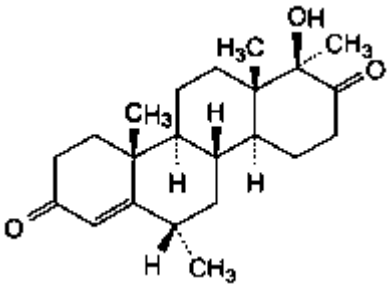

I. 17aβ-hydroxy-6,17a-dimethyl-*D*-homoandrost-4-ene-3,17-dione.

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Medroxyprogesterone Injection

General Notices

Action and use

Progestogen.

DEFINITION

Medroxyprogesterone Injection is a sterile suspension of Medroxyprogesterone Acetate in a suitable vehicle

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of medroxyprogesterone acetate, $C_{24}H_{34}O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Dissolve a volume of the injection containing 50 mg of Medroxyprogesterone Acetate in 8 mL of *petroleum spirit* (*boiling range, 40° to 60°*) and extract with three 8-mL quantities of a mixture of 7 volumes of *glacial acetic acid* and 3 volumes of *water*. Wash the combined extracts with 10 mL of *petroleum spirit* (*boiling range, 40° to 60°*), dilute with *water* until the solution becomes turbid, allow to stand in ice for 2 hours and filter. Wash the precipitate with *water* and dry at 105°. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of medroxyprogesterone acetate (*RS 421*).

TESTS

Impurity F (6a-methyl-3,20-dioxo-5b-pregnan-17-yl acetate)

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) The injection, diluted with *dichloromethane* if necessary, to contain 2.0% w/v of Medroxyprogesterone Acetate.

(2) 2.0% w/v of *medroxyprogesterone acetate for performance test EPCRS* (containing 0.5% of impurity F) in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable)

(b) 10 volumes of *tetrahydrofuran*, 45 volumes of *1,1-dimethylethyl methyl ether* and 45 volumes of *hexane* as the mobile phase.

(c) Apply to the plate 10 µL of each of solutions (1) and (2).

(d) After removal of the plate, allow it to dry in air and carry out a second development in the same direction using a freshly prepared mobile phase.

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(e) Dry the plate at 100° to 105° and allow to cool, spray with a 200 g/L solution of *toluenesulfonic acid* in *ethanol (96 %)*. Heat at 120 °C for 10 min, allow to cool and examine the plate in *ultraviolet light 365 nm*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (2) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1) any blue fluorescent spot with an Rf value higher than the principal spot is not more intense than the corresponding blue fluorescent spot due to impurity F in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection containing 40 mg of Medroxyprogesterone Acetate with sufficient of the mobile phase to produce 100 mL.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) 0.002% w/v of *medroxyprogesterone acetate BPCRS* and 0.005% w/v of *megestrol acetate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Prodigy ODS3 is suitable).
(b) Isocratic elution using the mobile phase described below.
(c) Flow rate of 2 mL per minute.
(d) Maintain the temperature of the column at 40°.
(e) Detection wavelength of 241 nm.
(f) Injection volume of 20 µL for each solution.

MOBILE PHASE

A mixture of 100 volumes of *tetrahydrofuran*, 350 volumes of *acetonitrile*, 500 volumes of *water* and allowed to equilibrate and the volume adjusted to 1000 volumes with *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the two principal peaks is at least 3.3;

the *symmetry factor* of the peak due to medroxyprogesterone acetate is not more than 1.3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

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the sum of the areas of any such peaks is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

disregard any peaks with an area not greater than 0.05 times the area of the principal peak in solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) The injection, diluted if necessary with the mobile phase, to contain 0.004% w/v of Medroxyprogesterone Acetate.

(2) 0.004% w/v of *medroxyprogesterone acetate BPCRS* in the mobile phase.

(3) 0.002% w/v of *medroxyprogesterone acetate BPCRS* and 0.005% w/v of *megestrol acetate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the two principal peaks is at least 3.3;

the *symmetry factor* of the peak due to medroxyprogesterone acetate is not more than 1.3.

DETERMINATION OF CONTENT

Calculate the content of medroxyprogesterone acetate, $C_{24}H_{34}O_4$, in the injection using the declared content of $C_{24}H_{34}O_4$ in *medroxyprogesterone acetate BPCRS*.

STORAGE

Medroxyprogesterone Injection should be protected from light. On standing, solid matter may separate; it should be redissolved by heating before use.

IMPURITIES

A. 6-hydroxy-6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-hydroxymedroxyprogesterone acetate),

B. 17-hydroxy-6-methylpregn-4-ene-3,20-dione (medroxyprogesterone),

C. 6,17a-dimethyl-3,17-dioxo-*D*-homoandrost-4-en-17a-yl acetate,

D. 6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-epimedroxyprogesterone acetate),

E. 6-methylidene-3,20-dioxopregn-4-en-17-yl acetate (6-methylenehydroxyprogesterone acetate),

F. 6-methyl-3,20-dioxo-5-pregnan-17-yl acetate (4,5-dihydromedroxyprogesterone acetate),

G. 6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate (megestrol acetate).

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Medroxyprogesterone Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Medroxyprogesterone Tablets contain Medroxyprogesterone Acetate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of medroxyprogesterone acetate, $C_{24}H_{34}O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Disperse a quantity of the powdered tablets containing 50 mg of Medroxyprogesterone Acetate in 8 mL of *petroleum spirit* (*boiling range, 40° to 60°*) and extract with three 8-mL quantities of a mixture of 7 volumes of *glacial acetic acid* and 3 volumes of *water*. Wash the combined extracts with 10 mL of *petroleum spirit* (*boiling range, 40° to 60°*), dilute with *water* until the solution becomes turbid, allow to stand in ice for 2 hours and filter. Wash the precipitate with water and dry at 105°. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of medroxyprogesterone acetate *(RS 421)*.

TESTS

Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1, using apparatus 2. Use as the medium 900 mL of 0.5% w/v *sodium lauryl sulfate* and rotate the paddle at 50 revolutions per minute. Withdraw a sample of the medium and filter.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the filtrate add sufficient of a solution of 0.5% w/v *sodium lauryl sulfate* to produce a solution expected to contain 0.0028% w/v of Medroxyprogesterone Acetate.
(2) 0.0028% w/v of *medroxyprogesterone acetate BPCRS* in a solution of 0.5% w/v *sodium lauryl sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) Stainless steel column (8 cm × 4 mm) packed with *octylsilyl silica gel for chromatography R1* (10 µm) (Zorbax C8 is suitable)
(b) Isocratic elution using the mobile phase described below.
(c) Flow rate of 1.5 mL per minute.

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(d) Ambient column temperature.

(e) Detection wavelength of 254 nm.

(f) Injection volume of 20 µL for each solution.

MOBILE PHASE

40 volumes of *water* and 60 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of medroxyprogesterone acetate, $C_{24}H_{34}O_4$, in the medium using the declared content of $C_{24}H_{34}O_4$ in *medroxyprogesterone acetate BPCRS*.

Impurity F (6a-methyl-3,20-dioxo-5b-pregnan-17-yl acetate)

Carry out the method for *thin-layer chromatography*, Appendix III A using the following solutions.

(1) Shake a quantity of powdered tablets containing 0.2 g of Medroxyprogesterone Acetate with *dichloromethane*, add sufficient *dichloromethane* to produce 10 mL, centrifuge and use the supernatant liquid.

(2) 2.0% w/v of *medroxyprogesterone acetate for performance test EPCRS* (containing 0.5% of impurity F) in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) 10 volumes of *tetrahydrofuran*, 45 volumes of *1,1-dimethylethyl methyl ether* and 45 volumes of *hexane* as the mobile phase.

(c) Apply to the plate 10 µL of each of solutions (1) and (2).

(d) After removal of the plate, allow the plate to dry in air and carry out a second development in the same direction using a freshly prepared mobile phase.

(e) Dry the plate at 100° to 105° and allow to cool, spray with a 200 g/L solution of *toluenesulfonic acid* in *ethanol (96 %)*. Heat at 120 °C for 10 min, allow to cool and examine the plate in *ultraviolet light 365 nm*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (2) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1) any blue fluorescent spot with an Rf value higher than that of the principal spot is not more intense than the corresponding blue fluorescent spot due to impurity F in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 40 mg of Medroxyprogesterone Acetate with 50 mL of the mobile phase for 15 minutes, add sufficient of the mobile phase to produce 100 mL, mix, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.002% w/v of *medroxyprogesterone acetate BPCRS* and 0.005% w/v of *megestrol acetate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Prodigy ODS3 is suitable).

(b) Isocratic elution using the mobile phase described below.

(c) Flow rate of 2 mL per minute.

(d) Maintain the temperature of the column at 40°.

(e) Detection wavelength of 241 nm.

(f) Injection volume of 20 µL for each solution.

MOBILE PHASE

A mixture of 100 volumes of *tetrahydrofuran*, 350 volumes of *acetonitrile*, 500 volumes of *water* and allowed to equilibrate and the volume adjusted to 1000 volumes with *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the two principal peaks is at least 3.3;

the *symmetry factor* of the peak due to medroxyprogesterone acetate is not more than 1.3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peaks with an area not greater than 0.05 times the area of the principal peak in solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 40 mg of Medroxyprogesterone Acetate with 50 mL of the mobile phase for 15 minutes, add sufficient of the mobile phase to produce 100 mL, mix and filter. To 5mL of the filtrate add sufficient of the mobile phase to produce 50 mL.

(2) 0.004% w/v of *medroxyprogesterone acetate BPCRS* in the mobile phase.

(3) 0.002% w/v of *medroxyprogesterone acetate BPCRS* and 0.005% w/v of *megestrol acetate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

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the *resolution factor* between the two principal peaks is at least 3.3;

the *symmetry factor* of the peak due to medroxyprogesterone acetate is not more than 1.3.

DETERMINATION OF CONTENT

Calculate the content of medroxyprogesterone acetate, $C_{24}H_{34}O_4$, in the tablets using the declared content of $C_{24}H_{34}O_4$ in *medroxyprogesterone acetate BPCRS*.

IMPURITIES

A. 6-hydroxy-6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-hydroxymedroxyprogesterone acetate),

B. 17-hydroxy-6-methylpregn-4-ene-3,20-dione (medroxyprogesterone),

C. 6,17a-dimethyl-3,17-dioxo-*D*-homoandrost-4-en-17a-yl acetate,

D. 6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-epimedroxyprogesterone acetate),

E. 6-methylidene-3,20-dioxopregn-4-en-17-yl acetate (6-methylenehydroxyprogesterone acetate),

F. 6-methyl-3,20-dioxo-5-pregnan-17-yl acetate (4,5-dihydromedroxyprogesterone acetate),

G. 6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate (megestrol acetate).

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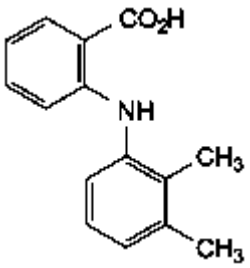
Mefenamic Acid

General Notices

(Ph. Eur. monograph 1240)



$C_{15}H_{15}NO_2$ 241.3 *61-68-7*

Action and use

Cyao-oxygenase Inhibitor, anargeric anti-inflammatory.

Preparations

Mefenamic Acid Capsules

Mefenamic Acid Tablets

Ph Eur

DEFINITION

2-(2,3-Dimethylanilino)benzoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, microcrystalline powder.

Solubility

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Practically insoluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *mefenamic acid CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *ethanol (96 per cent) R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50 mg of *2-chlorobenzoic acid R* (impurity C) and 50 mg of *benzoic acid R* (impurity D) in the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 mL of the solution to 100 mL with the mobile phase.

Reference solution (c) Dissolve 10.0 mg of *mefenamic acid impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve 20.0 mg of *benzoic acid R* in the mobile phase and dilute to 1000.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 14 volumes of *tetrahydrofuran R*, 40 volumes of a 5.75 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 5.0 with *dilute ammonia R2*, and 46 volumes of *acetonitrile R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

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Run time 4 times the retention time of mefenamic acid.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and D.

Relative retention With reference to mefenamic acid (retention time = about 8 min): impurity C = about 0.3; impurity D = about 0.35; impurity A = about 0.5.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to impurities C and D in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (d).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 5.9; impurity D = 4.0;

— *impurities C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (100 ppm);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to impurity A.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve with the aid of ultrasound 0.200 g in 100 mL of warm *anhydrous ethanol R*, previously neutralised to *phenol red solution R*. Add 0.1 mL of *phenol red solution R* and titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 24.13 mg of $C_{15}H_{15}NO_2$.

IMPURITIES

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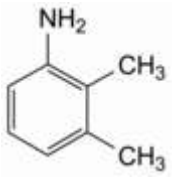
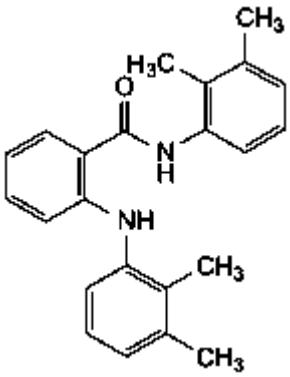
Specified impurities A, C, D.

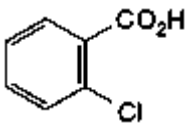
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, E.



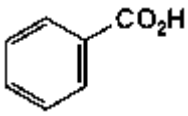
A. 2,3-dimethylaniline,



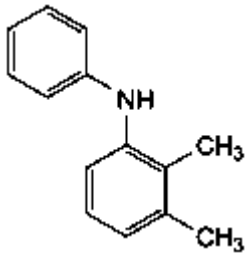
B. 2-(2,3-dimethylanilino)-*N*-(2,3-dimethylphenyl)benzamide,



C. 2-chlorobenzoic acid,



D. benzoic acid,



E. 2,3-dimethyl-*N*-phenylaniline.

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Mefenamic Acid Capsules

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Mefenamic Acid Capsules contain Mefenamic Acid.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of mefenamic acid, $C_{15}H_{15}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the contents of the capsules containing 0.25 g of Mefenamic Acid with two 30-mL quantities of *ether*. Wash the combined extracts with *water*, evaporate to dryness on a water bath and dry the residue at 105°. Dissolve a sufficient quantity in the minimum volume of *absolute ethanol* and evaporate to dryness on a water bath. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of mefenamic acid *(RS 210)*.

TESTS

Disintegration

Maximum time, 15 minutes, Appendix XII A1.

2,3-Dimethylaniline

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel G plate* and a mixture of 1 volume of 18M *ammonia*, 25 volumes of *1,4-dioxan* and 90 volumes of *toluene* as the mobile phase. Apply separately to the plate 40 µL of each of the following solutions. For solution (1) shake a quantity of the contents of the capsules containing 0.25 g of Mefenamic Acid with a mixture of 7.5 mL of *dichloromethane* and 2.5 mL of *methanol*, allow the insoluble matter to settle and use the supernatant liquid. Solution (2) contains 0.00025% w/v of *2,3-dimethylaniline* in a mixture of 3 volumes of *dichloromethane* and 1 volume of *methanol*. After removal of the plate, dry it in a current of warm air and visualise by *Method I*. Any spot corresponding to 2,3-dimethylaniline in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (100 ppm).

Related substances

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Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel GF_{254} plate* and a mixture of 1 volume of *glacial acetic acid*, 25 volumes of *1,4-dioxan* and 90 volumes of *toluene* as the mobile phase. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) use the supernatant liquid obtained in the test for 2,3-Dimethylaniline. For solution (2) dilute 1 volume of solution (1) to 500 volumes with a mixture of 3 volumes of *dichloromethane* and 1 volume of *methanol*. After removal of the plate, allow it to dry in air, expose to iodine vapour for 5 minutes and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%).

ASSAY

Dissolve a quantity of the mixed contents of 20 capsules containing 0.5 g of Mefenamic Acid in 100 mL of warm *absolute ethanol* previously neutralised to *phenol red solution* and titrate with *0.1M sodium hydroxide VS* using *phenol red solution* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 24.13 mg of $C_{15}H_{15}NO_2$.

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Mefenamic Acid Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Mefenamic Acid Tablets contain Mefenamic Acid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mefenamic acid, $C_{15}H_{15}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.25 g of Mefenamic Acid with two 30-mL quantities of *ether*. Wash the combined extracts with *water*, evaporate to dryness on a water bath and dry the residue at 105°. Dissolve a sufficient quantity in the minimum volume of *absolute ethanol* and evaporate to dryness on a water bath. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of mefenamic acid *(RS 210)*.

TESTS

2,3-Dimethylaniline

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel G plate* and a mixture of 1 volume of 18M *ammonia*, 25 volumes of *1,4-dioxan* and 90 volumes of *toluene* as the mobile phase. Apply separately to the plate 40 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.25 g of Mefenamic Acid with a mixture of 7.5 mL of *dichloromethane* and 2.5 mL of *methanol* for 10 minutes, centrifuge and use the supernatant liquid. Solution (2) contains 0.00025% w/v of *2,3-dimethyl-aniline* in a mixture of 3 volumes of *dichloromethane* and 1 volume of *methanol*. After removal of the plate, dry it in a current of warm air and visualise by *Method I*. Any spot corresponding to 2,3-dimethylaniline in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (100 ppm).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel GF_{254} plate* and a mixture of 1 volume of *glacial acetic acid*, 25 volumes of *1,4-dioxan* and 90 volumes of *toluene* as the mobile phase. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) use the supernatant liquid obtained in the test for 2,3-Dimethylaniline. For solution (2) dilute 1 volume of

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solution (1) to 500 volumes with a mixture of 3 volumes of *dichloromethane* and 1 volume of *methanol*. After removal of the plate, allow it to dry in air, expose to iodine vapour for 5 minutes and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%). Disregard any spot with an Rf value of 0.04 or less.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powdered tablets containing 0.5 g of Mefenamic Acid in about 80 mL of warm *absolute ethanol* previously neutralised to *phenol red solution* alternating between heating and ultrasound to aid dissolution. Cool, add sufficient of the neutralised absolute ethanol to produce 100 mL, mix well and titrate with *0.1M sodium hydroxide VS* using *phenol red solution* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 24.13 mg of $C_{15}H_{15}NO_2$.

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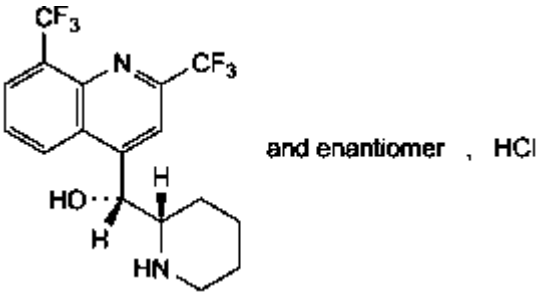
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Mefloquine Hydrochloride

General Notices

(Ph. Eur. monograph 1241)



$C_{17}H_{17}ClF_6N_2O$ 414.8 *51773-92-3*

Action and use

Antiprotozoal (malaria).

Ph Eur

DEFINITION

(*RS*)-[2,8-Bis(trifluoromethyl)quinolin-4-yl][(2*SR*)-piperidin-2-yl]methanol hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

mp

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m.p.

About 260 °C, with decomposition.

IDENTIFICATION

First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mefloquine hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 8 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 8 mg of *mefloquine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dilute 2.5 mL of the test solution to 100 mL with *methanol R*.

Reference solution (c) To 1 mL of reference solution (b) add 1 mL of a 0.016 g/L solution of *quinidine sulfate R* in *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Pretreatment Develop the plate with a mixture of 20 volumes of *methanol R* and 80 volumes of *methylene chloride R*, and dry at 100-105 °C for 15 min before use.

Mobile phase *anhydrous acetic acid R*, *methanol R*, *methylene chloride R* (10:10:80 *V/V/V*).

Application 20 µL.

Development Over a path of 10 cm.

Drying In a current of warm air for 15 min.

Detection Examine in ultraviolet light at 254 nm; lightly spray with a mixture prepared immediately before use of 1 volume of *sulfuric acid R* and 40 volumes of *iodoplatinate reagent R*; spray with *strong hydrogen peroxide solution R*.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

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C. Mix about 10 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until a practically white residue is obtained. Allow to cool, then add 2 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to make the solution colourless. Filter. To the filtrate add a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with a blank prepared in the same manner. The test solution is yellow and the blank is red.

D. To about 20 mg add 0.2 mL of *sulfuric acid R*. Blue fluorescence appears in ultraviolet light at 365 nm.

E. Dissolve about 23 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*); use *methanol R* instead of *water R* to wash the precipitate.

TESTS

Solution S

Dissolve 2.50 g in *methanol R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method I*).

Optical rotation (*2.2.7*)

-0.2° to + 0.2°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 8 mg of *mefloquine hydrochloride CRS* and 8 mg of *quinidine sulfate R* in the mobile phase and dilute to 50 mL with the mobile phase. Dilute 5 mL of the solution to 100 mL with the mobile phase.

Precolumn:

— *size*: *l* = 0.025 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

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Mobile phase Dissolve 1 g of *tetraheptylammonium bromide R* in a mixture of 200 volumes of *methanol R*, 400 volumes of *acetonitrile R* and 400 volumes of a 1.5 g/L solution of *sodium hydrogen sulfate R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 280 nm.

Equilibration With the mobile phase at a flow rate of 2 mL/min for about 30 min.

Injection 20 µL.

Run time 10 times the retention time of mefloquine.

Retention time Quinidine = about 2 min; mefloquine = about 4 min; impurity B = about 15 min; impurity A = about 36 min.

System suitability Reference solution (b):

— *resolution*: minimum 8.5 between the peaks due to quinidine and mefloquine.

Limits:

— *impurity with a relative retention with reference to mefloquine of about 0.7*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than the impurity with a relative retention with reference to mefloquine of about 0.7*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.350 g in 15 mL of *formic acid R* and add 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 41.48 mg of $C_{17}H_{17}ClF_6N_2O$.

STORAGE

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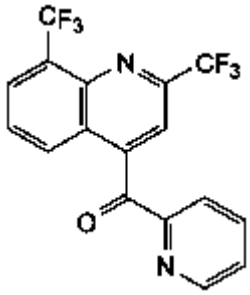
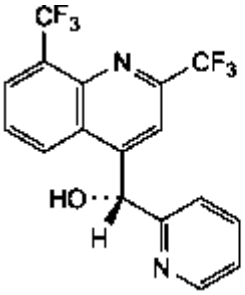
IMPURITIES

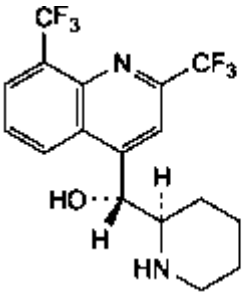


A. [2,8-bis(trifluoromethyl)quinolin-4-yl](pyridin-2-yl)methanone,



and enantiomer

B. (*RS*)-[2,8-bis(trifluoromethyl)quinolin-4-yl](pyridin-2-yl)methanol,



and enantiomer

C. (*RS*)-[2,8-bis(trifluoromethyl)quinolin-4-yl][(2*RS*)-piperidin-2-yl]methanol.

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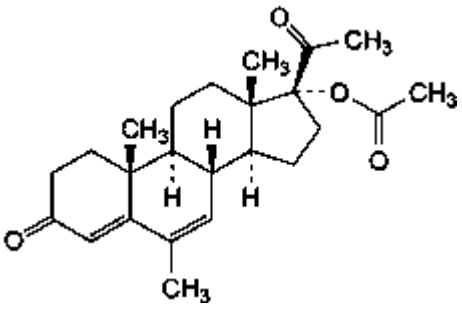
Megestrol Acetate

General Notices

(Ph. Eur. monograph 1593)



$C_{24}H_{32}O_4$ 384.5 *595-33-5*

Action and use

Progestogen.

Preparation

Megestrol Tablets

Ph Eur

DEFINITION

6-Methyl-3,20-dioxopregna-4,6-dien-17-yl acetate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent).

mp

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About 217 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *megestrol acetate CRS*.

TESTS

Specific optical rotation (*2.2.7*)

+ 14.0 to + 17.0 (dried substance).

Dissolve 2.50 g in *methylene chloride R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetic acid R*, *water R*, *acetonitrile R1* (0.1:20:80 *V/V/V*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *megestrol acetate for system suitability CRS* (containing impurities A, D, G, H, I, J and L) in 1.0 mL of the solvent mixture.

Reference solution (c) Dissolve 10 mg of *megestrol acetate for peak identification CRS* (containing impurities B, C and E) in 1.0 mL of the solvent mixture.

Reference solution (d) Dissolve 50.0 mg of *megestrol acetate CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (e) Dissolve the contents of a vial of *megestrol acetate for impurity K identification CRS* in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m; Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

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— *mobile phase A*: tetrahydrofuran R, acetonitrile R1, water R (7.5:12.5:80 *V/V/V*);

— *mobile phase B*: water R, tetrahydrofuran R, acetonitrile R1 (20:30:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 16	70	30
16 - 42	70 → 30	30 → 70
42 - 49	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 245 nm and, for impurity J, at 210 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b), (c) and (e).

Identification of impurities Use the chromatogram supplied with megestrol acetate for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, D, G, H, I, J and L; use the chromatogram supplied with megestrol acetate for peak identification CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C and E; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity K.

Relative retention With reference to megestrol acetate (retention time = about 22 min): impurity B = about 0.75; impurity E = about 0.80; impurity K = about 0.83; impurity C = about 0.9; impurity D = about 1.11; impurity A = about 1.14; impurity I = about 1.2; impurity G = about 1.3; impurity J = about 1.4; impurity H = about 1.5; impurity L = about 1.9.

System suitability Reference solution (b):

— peak-to-valley ratio: minimum 5.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.2; impurity D = 0.4; impurity E = 0.4; impurity I = 0.5; impurity K = 0.2; impurity L = 0.6;

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities D, H*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity J at 210 nm*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) at 210 nm (0.3 per cent);

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— *impurity G*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities B, C, E, I, K, L*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than J*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{24}H_{32}O_4$ taking into account the assigned content of *megestrol acetate CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, G, H, I, J, K, L.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F.*

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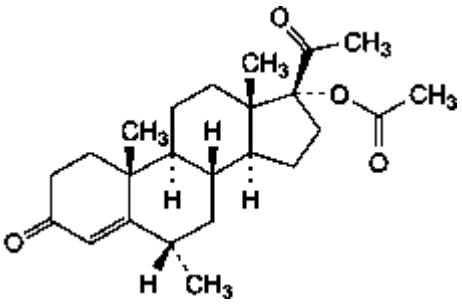
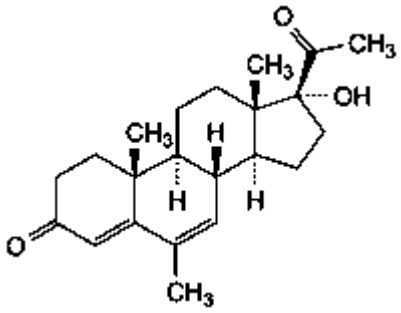
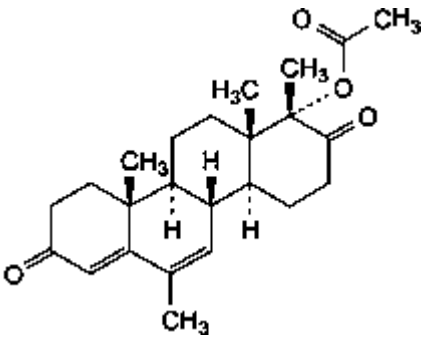


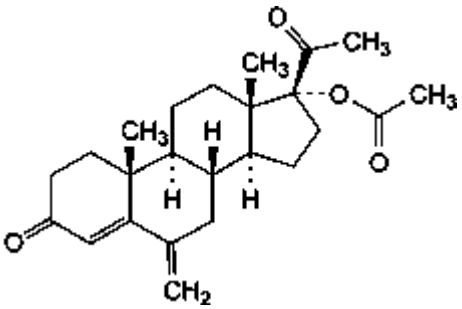
A. 6α-methyl-3,20-dioxopregn-4-en-17-yl acetate (medroxyprogesterone acetate),



B. 6-methyl-17-hydroxypregna-4,6-diene-3,20-dione (megestrol),



C. 6,17a-dimethyl-3,17-dioxo-*D*-homoandrosta-4,6-dien-17aα-yl acetate (*D-homo* megestrol acetate),



D. 6-methylene-3,20-dioxopregn-4-en-17-yl acetate (6-methylene hydroxyprogesterone acetate),

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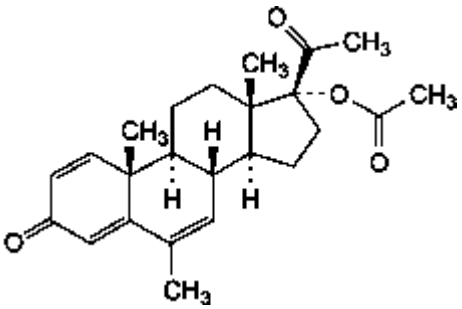
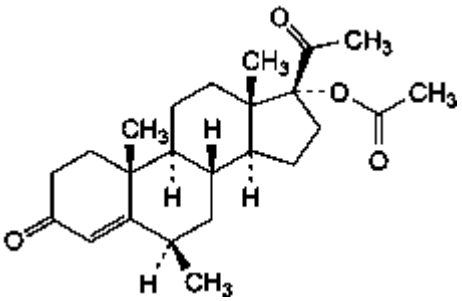
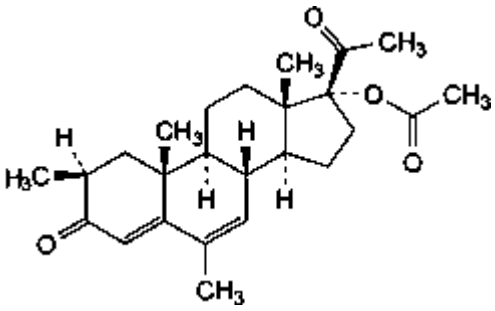


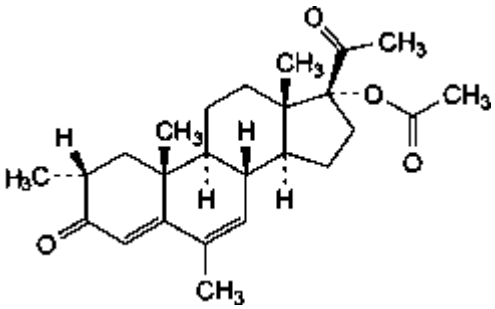
E. 6-methyl-3,20-dioxopregna-1,4,6-trien-17-yl acetate,



F. 6β-methyl-3,20-dioxopregn-4-en-17-yl acetate,



G. 2β,6-dimethyl-3,20-dioxopregna-4,6-dien-17-yl acetate,



H. 2α,6-dimethyl-3,20-dioxopregna-4,6-dien-17-yl acetate,

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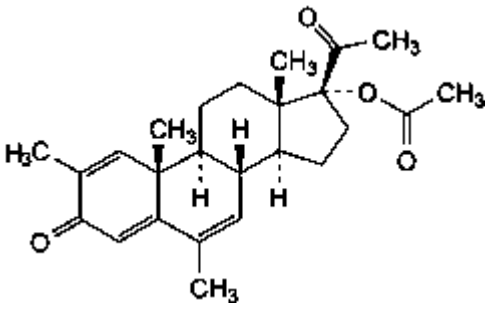
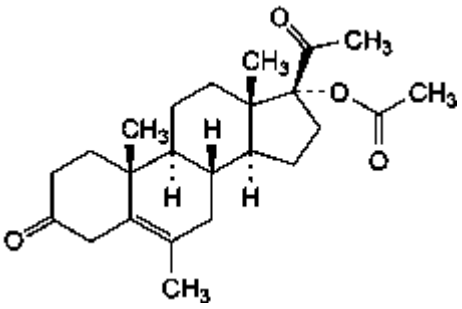
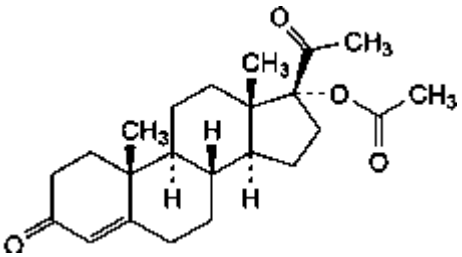


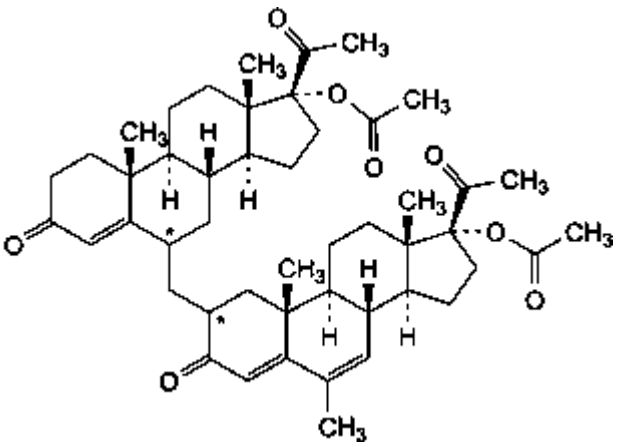
I. 2,6-dimethyl-3,20-dioxopregna-1,4,6-trien-17-yl acetate,



J. 6-methyl-3,20-dioxopregn-5-en-17-yl acetate,



K. 3,20-dioxopregn-4-en-17-yl acetate,



L. 2ξ-[[17-(acetyloxy)-3,20-dioxopregn-4-en-6ξ-yl]methyl]-6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate (megestrol acetate dimer).

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Megestrol Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Megestrol Tablets contain Megestrol Acetate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of megestrol acetate, $C_{24}H_{32}O_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 40 mg of Megestrol Acetate with 250 mL of *chloroform* for 30 minutes, filter into a separating funnel, wash the filtrate with 20 mL of *water* and evaporate the chloroform. The residue, after drying at 60° at a pressure not exceeding 0.7 kPa for 2 hours, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of megestrol acetate *(RS 211)*.

B. Complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent II* and *mobile phase D*.

TESTS

Disintegration

Maximum time, 30 minutes, Appendix XII A1.

Related foreign steroids

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 100 mg of Megestrol Acetate with 10 mL of a mixture of 1 volume of *methanol* and 9 volumes of *chloroform* for 10 minutes, centrifuge and use the clear supernatant liquid.

(2) 0.005% w/v of *megestrol BPCRS* in a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

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(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with spray with *ethanolic sulfuric acid (20%)*, heat at 110° for 10 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

0.5 volume of *water*, 8 volumes of *methanol* and 92 volumes of *1,2-dichloroethane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Prepare a 0.016% w/v solution of *propyl 4-hydroxybenzoate* (internal standard) in *acetonitrile* (solution A).

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 80 mg of Megestrol Acetate with 10 mL of *water* for 10 minutes, add 75 mL of *acetonitrile*, shake for 30 minutes, dilute to 100 mL with *acetonitrile*, centrifuge and dilute 10 mL of the clear supernatant liquid to 50 mL with a 40% v/v solution of *acetonitrile*; to 5 mL of this solution add 10 mL of *acetonitrile* and dilute to 50 mL with a 40% v/v solution of *acetonitrile*.

(2) Mix 4 mL of a 0.02% w/v solution of *megestrol acetate BPCRS* in *acetonitrile* with 10 mL of solution A and dilute to 50 mL with a 40% v/v solution of *acetonitrile*.

(3) Prepare solution (3) in the same manner as solution (1) but adding 10 mL of solution A in place of the 10 mL of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

32 volumes of *water* and 68 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to propyl 4-hydroxybenzoate and megestrol acetate is at least 8.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{24}H_{32}O_4$ in the tablets using the declared content of $C_{24}H_{32}O_4$ in *megestrol acetate BPCRS*.

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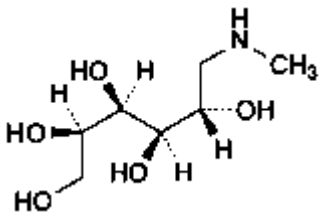
Meglumine

General Notices

(Ph. Eur. monograph 2055)



$C_7H_{17}NO_5$ 195.2 *6284-40-8*

Action and use

Organic base used in the preparation of organic acids.

Ph Eur

DEFINITION

1-Deoxy-1-(methylamino)-D-glucitol.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

mp

About 128 °C.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *meglumine CRS*.

TESTS

Solution S

Dissolve 20.0 g in *distilled water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 420 nm is not greater than 0.03.

Dissolve the residue obtained in the test for loss on drying in *water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

-17.0 to -16.0 (dried substance).

Dilute 12.5 mL of solution S to 25.0 mL with *water R*.

Reducing substances

Maximum 0.2 per cent, expressed as glucose.

Dilute 1.25 mL of solution S to 2.5 mL with *water R*, add 2 mL of *cupri-tartaric solution R* and heat on a water-bath for 10 min. Cool under running water for 1 min, then sonicate for 20 s. Immediately filter through a membrane filter 25 mm in diameter (nominal pore size 0.5 µm). Rinse with 10 mL of *water R*. Prepare a standard in the same manner using 2.5 mL of a solution obtained by dissolving 20 mg of *glucose R* in *water R* and diluting to 100 mL with the same solvent. Any precipitate on the membrane filter obtained with the test solution is not more intensely coloured than the precipitate obtained with the standard.

Chlorides (2.4.4)

Maximum 100 ppm.

To 2.5 mL of solution S add 12.5 mL of *water R*.

Sulfates (2.4.13)

Maximum 150 ppm.

To 5 mL of solution S add 10 mL of *distilled water R*.

Aluminium

Maximum 5 ppm.

Inductively coupled plasma-atomic emission spectrometry (ICP-AES) (2.2.57).

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Test solution Dissolve 5.00 g in 30 mL of *water R*, add 10.0 mL of *lead-free hydrochloric acid R* and dilute to 50.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *aluminium standard solution (10 ppm Al) R*, diluted as necessary with *water R*.

Wavelength 396.153 nm.

Iron

Maximum 10 ppm.

To 10 mL of solution S add about 0.8 mL of *hydrochloric acid R* and 0.05 mL of *bromine water R*. Allow to stand for 5 min, evaporate the excess of bromine in a current of air and add 3 mL of *potassium thiocyanate solution R*. Prepare a reference solution at the same time and in the same manner using 10 mL of *iron standard solution (2 ppm Fe) R*, to which 2 mL of *hydrochloric acid R* has been added. After 5 min, any red colour in the test solution is not more intense than that in the reference solution.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 1.5 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.180 g in 30 mL of *water R*. Titrate with *0.05 M sulfuric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.05 M sulfuric acid* is equivalent to 19.52 mg of $C_7H_{17}NO_5$.

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Meglumine Amidotrizoate Injection

General Notices

Action and use

Organic base used in the preparation of organic acids.

DEFINITION

Meglumine Amidotrizoate Injection is a sterile solution of the Meglumine salt of Amidotrizoic Acid Dihydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of meglumine amidotrizoate, $C_{11}H_9I_3N_2O_4,C_7H_{17}NO_5$

97.0 to 103.0% of the stated amount.

CHARACTERISTICS

A colourless to pale yellow, slightly viscous liquid.

IDENTIFICATION

A. Evaporate 2 mL of the injection to dryness and heat 50 mg of the residue. Violet vapours of iodine are evolved.

B. To 20 mg of the residue obtained by evaporating the injection to dryness add 5 mL of 1M *sodium hydroxide* and boil gently under a reflux condenser for 10 minutes. Cool, add 5 mL of 2M *hydrochloric acid* and cool in ice for 5 minutes. Add 4 mL of a 1% w/v solution of *sodium nitrite*, cool in ice for 5 minutes, add 0.3 g of *sulfamic acid*, swirl gently until effervescence ceases and add 2 mL of a 0.4% w/v solution of N-*(1-naphthyl)ethylenediamine dihydrochloride*. An orange-red colour is produced.

C. To a quantity containing 1 g of meglumine amidotrizoate add 50 mL of *water* and a slight excess of 2M *hydrochloric acid* and filter. Evaporate the filtrate to dryness on a water bath, dissolve the residue in a small quantity of boiling *ethanol (90%)*, filter and cool the filtrate in ice. The *melting point* of the dried precipitate is about 146°, Appendix V A.

TESTS

Acidity or alkalinity

pH, 6.0 to 7.0, Appendix V L.

Meglumine

22.9 to 25.3% of the stated content of meglumine amidotrizoate when determined by the following method. Measure the *optical rotation* of the injection, Appendix V F, using a 2-dm tube. Calculate the percentage content of meglumine using the expression 2.104*R* where *R* is the

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numerical value of the rotation.

Free amine

To a quantity containing 1 g of meglumine amidotrizoate in a 50 mL glass-stoppered graduated flask add sufficient *water* to produce 5 mL, 10 mL of 0.1M *sodium hydroxide* and 25 mL of *dimethyl sulfoxide*. Stopper the flask, mix the contents by gentle swirling and cool in ice, protected from light. After 5 minutes add slowly 2 mL of *hydrochloric acid*, mix and allow to stand for 5 minutes. Add 2 mL of a 2% w/v solution of *sodium nitrite*, mix and allow to stand for 5 minutes. Add 1 mL of an 8% w/v solution of *sulfamic acid*, mix and allow to stand for 5 minutes. Add 2 mL of a 0.1% w/v solution of N-*(1-naphthyl)ethylenediamine dihydrochloride* in a 70% v/v solution of *propane-1,2-diol* and mix. Remove the flask from the ice and allow to stand in water at 22° to 25° for 10 minutes, occasionally shaking gently. Add sufficient *dimethyl sulfoxide* to produce 50 mL and mix. Within 5 minutes of diluting to 50 mL measure the *absorbance* of the resulting solution at the maximum at 470 nm, Appendix II B, using in the reference cell a solution prepared by treating 5 mL of *water* in the same manner. The absorbance is not more than 0.40.

Inorganic iodide

Dilute a quantity containing 0.80 g of meglumine amidotrizoate to 10 mL with *water*, add sufficient 2M *nitric acid* dropwise to ensure complete precipitation of the iodinated acid and add 3 mL in excess. Filter, wash the precipitate with 5 mL of *water*, add to the filtrate 1 mL of *hydrogen peroxide solution (100 vol)* and 1 mL of *chloroform* and shake. Any purple colour in the chloroform layer is not more intense than that obtained by adding 2 mL of *iodide standard solution (20 ppm I)* to a mixture of 3 mL of 2M *nitric acid* and sufficient *water* to equal the volume of the test solution, adding 1 mL of *hydrogen peroxide solution (100 vol)* and 1 mL of *chloroform* and shaking (50 ppm).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 1.0 IU per mL of Meglumine Amidotrizoate Injection.

ASSAY

Mix a quantity containing 0.5 g of meglumine amidotrizoate with 12 mL of 5M *sodium hydroxide* and 20 mL of *water*, add 1 g of *zinc powder* and boil under a reflux condenser for 30 minutes. Cool, rinse the condenser with 30 mL of *water*, filter through absorbent cotton and wash the flask and filter with two 20 mL quantities of *water*. To the combined filtrate and washings add 80 mL of *hydrochloric acid*, cool and titrate with *0.05M potassium iodate VS* until the dark brown solution becomes light brown. Add 5 mL of *chloroform* and continue the titration, shaking well after each addition, until the chloroform becomes colourless. Each mL of *0.05M potassium iodate VS* is equivalent to 26.97 mg of $C_{11}H_9I_3N_2O_4,C_7H_{17}NO_5$. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of $C_{11}H_9I_3N_2O_4,C_7H_{17}NO_5$.

STORAGE

Meglumine Amidotrizoate Injection should be protected from light.

LABELLING

The strength is stated as the percentage w/v of meglumine amidotrizoate.

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Meglumine Iodipamide Injection

General Notices

Action and use

Organic base used in the preparation of organic acids.

DEFINITION

Meglumine Iodipamide Injection is a sterile solution of the Meglumine salt of 3,3′-adipoyldiamino-bis(2,4,6-tri-iodobenzoic acid) (2:1) in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of meglumine iodipamide, $C_{20}H_{14}I_6N_2O_6,2C_7H_{17}NO_5$

97.0 to 103.0% of the stated amount.

CHARACTERISTICS

A colourless to pale yellow solution.

IDENTIFICATION

A. To a volume of the injection containing 0.6 g of meglumine iodipamide add 1 mL of 1M *hydrochloric acid*, stir until the precipitate becomes crystalline, add 5 mL of 1M *hydrochloric acid*, stir, filter and reserve the filtrate for test C. Wash the residue with 1M *hydrochloric acid* and then with *water* and dry at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of iodipamide *(RS 191)*.

B. Heat 50 mg of the residue obtained in test A. Violet vapours of iodine are evolved.

C. Evaporate the filtrate reserved in test A to dryness on a water bath, dissolve the residue in a small quantity of boiling *ethanol (90%)*, filter and cool the filtrate in ice. The *melting point* of the dried precipitate is about 146°, Appendix V A.

TESTS

Acidity or alkalinity

pH, 6.0 to 7.1, Appendix V L.

Meglumine

11.8 to 13.7% of the stated content of meglumine iodipamide when determined by the following method. Measure the *optical rotation* of the injection, Appendix V G, using a 2-dm tube. Calculate the percentage content of meglumine using the expression 2.104*R* where *R* is the

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numerical value of the rotation.

Free amine

To a quantity containing 0.25 g of meglumine iodipamide add 25 mL of *water*, 8 mL of 1M *hydrochloric acid* and 4 mL of a 1.0% w/v solution of *sodium nitrite* and shake for 2 minutes. Add 6 mL of a 2% w/v solution of *ammonium sulfamate* and swirl gently until effervescence ceases. Add 0.4 mL of a 10% w/v solution of *1-naphthol* in *ethanol (96%)*, shake and add 3 mL of 5M *sodium hydroxide*. Dilute the solution to 50 mL with *water* and measure the *absorbance* at the maximum at 485 nm, Appendix II B, using in the reference cell a solution prepared in the same manner but omitting the injection. The absorbance is not more than 0.17.

Inorganic iodide

Dilute a quantity containing 0.80 g of meglumine iodipamide to 10 mL with *water*, add sufficient 2M *nitric acid* dropwise to ensure complete precipitation of the iodinated acid and add 3 mL in excess. Filter, wash the precipitate with 5 mL of *water*, add to the filtrate 1 mL of *hydrogen peroxide solution (100 vol)* and 1 mL of *chloroform* and shake. Any purple colour in the chloroform layer is not more intense than that obtained by adding 2 mL of *iodide standard solution (20 ppm I)* to a mixture of 3 mL of 2M *nitric acid* and sufficient *water* to equal the volume of the test solution, adding 1 mL of *hydrogen peroxide solution (100 vol)* and 1 mL of *chloroform* and shaking (50 ppm).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is not more than 3.6 IU per mL of Meglumine Iodipamide Injection.

ASSAY

Mix 0.4 g with 12 mL of 5M *sodium hydroxide* and 20 mL of *water*, add 1 g of *zinc powder* and boil under a reflux condenser for 30 minutes. Cool, rinse the condenser with 30 mL of *water*, filter through absorbent cotton and wash the flask and filter with two 20-mL quantities of *water*. To the combined filtrate and washings add 80 mL of *hydrochloric acid*, cool and titrate with *0.05M potassium iodate VS* until the dark brown solution becomes light brown. Add 5 mL of *chloroform* and continue the titration, shaking well after each addition, until the chloroform becomes colourless. Each mL of *0.05M potassium iodate VS* is equivalent to 25.50 mg of $C_{20}H_{14}I_6N_2O_6,2C_7H_{17}NO_5$. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of $C_{20}H_{14}I_6N_2O_6,2C_7H_{17}NO_5$.

LABELLING

The strength is stated as the percentage w/v of meglumine iodipamide.

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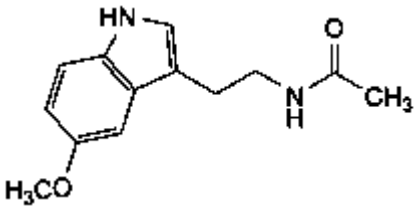
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Melatonin

General Notices

(Ph. Eur. monograph 3059)



$C_{13}H_{16}N_2O_2$ 232.3 *73-31-4*

Action and use

Treatment of sleep onset insomnia

Preparation

Melatonin Capsules

Ph Eur

DEFINITION

N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]acetamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White to slightly yellowish powder.

Solubility

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Slightly soluble in water, soluble in ethanol (96 per cent), sparingly soluble in ethyl acetate and practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison melatonin CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture A acetonitrile R, water R (20:80 *V/V*).

Solvent mixture B Mobile phase B, mobile phase A (20:80 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in solvent mixture A and dilute to 100.0 mL with solvent mixture A.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in solvent mixture B and dilute to 100.0 mL with solvent mixture B. Dilute 1.0 mL of the solution to 10.0 mL with solvent mixture B.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with solvent mixture A. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture A.

Reference solution (b) Dissolve the contents of a vial of melatonin for system suitability CRS (containing impurity D) in 1 mL of solvent mixture A.

Reference solution (c) Dissolve 50.0 mg of melatonin CRS in solvent mixture B and dilute to 100.0 mL with solvent mixture B. Dilute 1.0 mL of the solution to 10.0 mL with solvent mixture B.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (1.8 µm).

Mobile phase:

— *mobile phase A*: a 2.45 g/L solution of potassium dihydrogen phosphate R, previously adjusted to pH 3.0 with a 235 g/L solution of phosphoric acid R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	90 → 70	10 → 30

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
20 - 36	70 → 30	30 → 70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *melatonin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to melatonin (retention time = about 7 min): impurity D = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 5.0 between the peaks due to melatonin and impurity D.

Calculation of percentage contents:

— for each impurity, use the concentration of melatonin in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 0.3 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (20:80 *V/V*).

Injection 5 µL of test solution (b) and reference solution (c).

Run time Twice the retention time of melatonin (retention time = about 2 min).

Calculate the percentage contents of $C_{13}H_{16}N_2O_2$ taking into account the assigned content of *melatonin CRS*.

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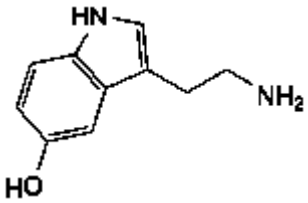
STORAGE

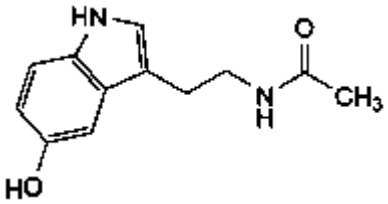
Protected from light.

IMPURITIES

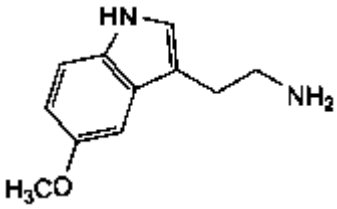
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



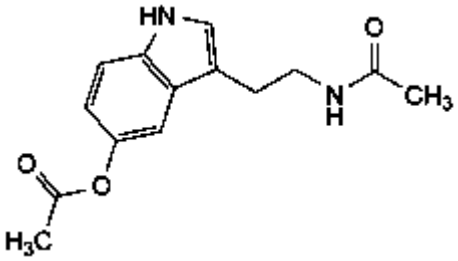
A. 3-(2-aminoethyl)-1*H*-indol-5-ol,



B. *N*-[2-(5-hydroxy-1*H*-indol-3-yl)ethyl]acetamide,



C. 2-(5-methoxy-1*H*-indol-3-yl)ethan-1-amine,



D. 3-(2-acetamidoethyl)-1*H*-indol-5-yl acetate.

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Melatonin Capsules

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Treatment of sleep onset insomnia.

DEFINITION

Melatonin Capsules contain Melatonin.

The capsules comply with the requirements stated under Capsules and with the following requirements. Where appropriate, the capsules also comply with the requirements stated under Unlicensed Medicines.

Content of melatonin, $C_{13}H_{16}N_2O_2$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, of solution (1) obtained in the test for Dissolution, in the range 200 to 350 nm, exhibits a maximum at 278 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10-mL sample of the medium, filter and dilute the filtered solution, if necessary, with sufficient 0.1M *hydrochloric acid* to produce a solution expected to contain about 0.0001% w/v of Melatonin. Measure the *absorbance* of the filtered sample at the maximum at 278 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

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(2) Measure the *absorbance* of a 0.0001% w/v solution of *melatonin BPCRS* in 0.1M *hydrochloric acid* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of melatonin, $C_{13}H_{16}N_2O_2$, in the medium from the absorbances obtained and using the declared content of $C_{13}H_{16}N_2O_2$ in *melatonin BPCRS*.

LIMITS

The amount of melatonin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile* and 80 volumes of a 0.245% w/v solution of *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.0 with 20% v/v *orthophosphoric acid*.

(1) To a quantity of the contents of the capsules containing 25 mg of Melatonin add 15 mL, mix with the aid of ultrasound for 10 minutes and then shake vigorously for 60 minutes. Dilute to 25 mL, mix well, filter and dilute 1 volume of the filtrate to 2 volumes.
(2) 0.0005% w/v of *melatonin BPCRS*.
(3) Dilute a mixture of 10 volumes of solution (2) and 1 volume of a 0.025% w/v solution of *5-methoxytryptamine BPCRS* to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Agilent Eclipse XDB is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.25 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 278 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.245% w/v of *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with 20% v/v *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	90→70	10→30	linear gradient
20-36	70→30	30→70	linear gradient
36-40	30→90	70→10	linear gradient
40-45	90	10	re-equilibration

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When the chromatograms are recorded under the prescribed conditions, the retention time of melatonin is about 37.8 minutes and the retention of 5-methoxytryptamine relative to that of melatonin is about 0.63.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to melatonin and 5-methoxytryptamine is at least 12.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to 5-methoxytryptamine is not greater than the area of the peak due to 5-methoxytryptamine in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of total impurities is not more than 1.0%.

Disregard any peak with an area less than 0.5 times the area of the peak due to melatonin in the chromatogram obtained with solution (3) (0.05%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Melatonin comply with the requirements stated under Capsules using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of *methanol (30%)* to the contents and shell of one capsule, mix with the aid of ultrasound for 10 minutes and then shake for 60 minutes. Dilute 1 volume of the resulting solution to 2 volumes with *methanol (30%)*. Dilute the resulting solution, if necessary, with sufficient *methanol (30%)* to produce a solution containing 0.0025% w/v of Melatonin.
(2) Shake 25 mg of *melatonin BPCRS* with 15 mL of *methanol (30%)* for 10 minutes and add sufficient *methanol (30%)* to produce 25 mL. Dilute 1 volume of the resulting solution to 10 volumes with *methanol (30%)* and further dilute 1 volume to 4 volumes with *methanol (30%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Phenomenex Synergi-Hydro RP is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 285 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

400 volumes of *methanol* and 600 volumes of *water* containing 1 volume of *orthophosphoric acid*.

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DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{16}N_2O_2$ in each capsule using the declared content of $C_{13}H_{16}N_2O_2$ in *melatonin BPCRS*.

ASSAY

For capsules containing less than 2 mg and/or less than 2% w/w of Melatonin

Use the average of the individual results obtained in the test for Uniformity of content.

For capsules containing 2 mg or more and 2% w/w or more of Melatonin

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the mixed capsule contents containing 20 mg of Melatonin add 20 mL of *methanol (30%)*, mix with the aid of ultrasound for 10 minutes and then shake for 60 minutes. Dilute 1 volume of the resulting solution to 10 volumes with *methanol (30%)*.
(2) Shake 25 mg of *melatonin BPCRS* with 15 mL of *methanol (30%)* for 10 minutes; add sufficient *methanol (30%)* to produce 25 mL and dilute 1 volume to 10 volumes with *methanol (30%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{16}N_2O_2$ in the capsules using the declared content of $C_{13}H_{16}N_2O_2$ in *melatonin BPCRS*.

STORAGE

Melatonin Capsules should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include 5-methoxytryptamine.

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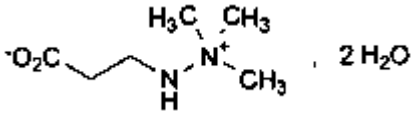
Meldonium Dihydrate

General Notices

(Ph. Eur. monograph 2624)



$C_6H_{14}N_2O_2,2H_2O$ 182.2 *86426-17-7*

Ph Eur

DEFINITION

3-(2,2,2-Trimethylhydrazin-2-ium-1-yl)propanoate dihydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white crystals or crystalline powder, deliquescent.

Solubility

Very soluble in water, freely soluble in methanol, practically insoluble in acetone.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *meldonium dihydrate CRS*.

TESTS

Solution S

Dissolve 10.0 g in 50 mL of *distilled water R*.

Appearance of solution

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Solution S is not more opalescent than reference suspension I (2.2.1) and not more intensely coloured than reference solution B_9 (2.2.2, Method II).

Related substances

Liquid chromatography (2.2.29) coupled with mass spectrometry (2.2.43).

Test solution Dissolve 10.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 10.0 mg of meldonium impurity A CRS, 10.0 mg of meldonium impurity B CRS, 10.0 mg of meldonium impurity C CRS, 10.0 mg of meldonium impurity D CRS, 10.0 mg of meldonium impurity E CRS and 10.0 mg of meldonium impurity F CRS in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.5 mL of reference solution (a) to 100.0 mL with mobile phase A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3.5 µm).

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of heptafluorobutyric acid R in water for chromatography R;

— *mobile phase B*: 0.1 per cent *V/V* solution of heptafluorobutyric acid R in methanol R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	90 → 65	10 → 35
7 - 12	65 → 40	35 → 60
12 - 18	40 → 25	60 → 75

Flow rate 0.2 mL/min.

Detection:

— triple-quadrupole mass spectrometer; the following settings have been found to be suitable and are given as examples; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criteria:

— *ionisation*: ESI-positive;

— *detection*:

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— multiple reaction monitoring (MRM) mode;

— scanning mode: 50 - 300 *m*/*z*;

— *ion source temperature*: 110 °C;

— *desolvation temperature*: 220 °C;

— *cone voltage*: 15 V;

— *capillary voltage (Vcap)*: 3 kV;

— *CID gas*: argon;

— *CID gas pressure*: 2.7×10^{-3} mbar.

— MRM mode parameters:

Substance	MRM channels	Collision energy (eV) for the interval 0-25 min
Meldonium	147.00 → 59.00	18.0
Impurity A	59.97 → 44.98	18.0
Impurity B	74.99 → 59.04	15.0
Impurity F	115.19 → 71.92	19.0
Impurity C	161.19 → 59.00	23.0
Impurity D	175.19 → 58.07	23.0
Impurity E	189.26 → 58.01	22.0

Injection 20 µL of the test solution and reference solutions (b) and (c).

Relative retention With reference to meldonium (retention time = about 9 min): impurity F = about 0.7; impurity B = about 0.8; impurity A = about 0.9; impurity C = about 1.5; impurity D = about 1.8; impurity E = about 2.0.

System suitability Reference solution (b):

— *signal-to-noise ratio*: impurity A = minimum 10; impurity B = minimum 50; impurity C = minimum 200; impurity D = minimum 1000; impurity E = minimum 1000; impurity F = minimum 50;

— *repeatability*: maximum relative standard deviation of 10 per cent after 6 injections.

Calculation of percentage contents:

— for impurities A, B, C, D, E and F (MRM mode), use the concentration of the corresponding impurity in reference solution (b);

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— for impurities other than A, B, C, D, E and F (complete spectrum mode), use the concentration of meldonium dihydrate in reference solution (c).

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 30 mL with *distilled water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm.

Dilute 10 mL of solution S to 20 mL with *distilled water R*.

Water (*2.5.12*)

19.7 per cent to 21.0 per cent, determined on 0.120 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 40 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 14.62 mg of $C_6H_{14}N_2O_2$.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*

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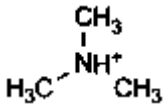
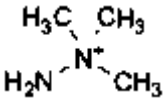
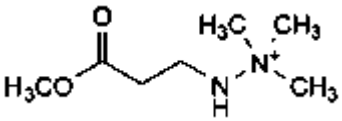


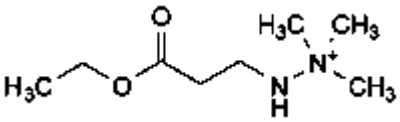
A. *N*,*N*-dimethylmethanaminium,



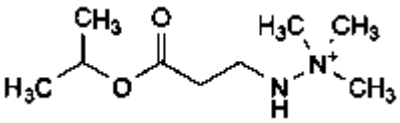
B. 1,1,1-trimethylhydrazin-1-ium,



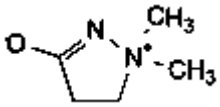
C. 2-(3-methoxy-3-oxopropyl)-1,1,1-trimethylhydrazin-1-ium,



D. 2-(3-ethoxy-3-oxopropyl)-1,1,1-trimethylhydrazin-1-ium,



E. 1,1,1-trimethyl-2-[3-(1-methylethoxy)-3-oxopropyl]hydrazin-1-ium,



F. 1,1-dimethyl-4,5-dihydro-1*H*-pyrazol-1-ium-3-olate.

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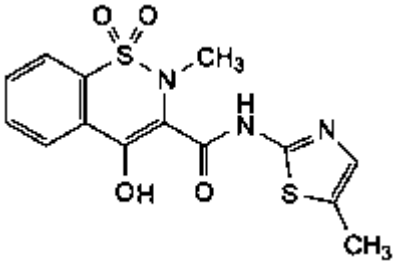
Meloxicam

General Notices

(Ph. Eur. monograph 2373)



$C_{14}H_{13}N_3O_4S_2$ 351.4 *71125-38-7*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Meloxicam Injection

Meloxicam Oral Suspension

Meloxicam Tablets

Ph Eur

DEFINITION

4-Hydroxy-2-methyl-*N*-(5-methylthiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow powder.

Solubility

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Practically insoluble in water, soluble in dimethylformamide, very slightly soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison meloxicam CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 40 mg of the substance to be examined in a mixture of 5 mL of methanol R and 0.3 mL of 1 M sodium hydroxide and dilute to 20.0 mL with methanol R.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with methanol R. Dilute 5.0 mL of this solution to 100.0 mL with methanol R.

Reference solution (b) Dissolve 2 mg of the substance to be examined, 2 mg of meloxicam impurity A CRS, 2 mg of meloxicam impurity B CRS, 2 mg of meloxicam impurity C CRS and 2 mg of meloxicam impurity D CRS in a mixture of 5 mL of methanol R and 0.3 mL of 1 M sodium hydroxide and dilute to 25 mL with methanol R. If complete dissolution cannot be achieved, filter the solution through a membrane filter (nominal pore size 0.45 µm) before injection.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: 1 g/L solution of potassium dihydrogen phosphate R adjusted to pH 6.0 with 1 M sodium hydroxide;

— *mobile phase B*: methanol R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	60	40

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
2 - 10	60 → 30	40 → 70
10 - 15	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm and 350 nm.

Injection 10 µL.

Relative retention With reference to meloxicam (retention time = about 7 min): impurity B = about 0.5; impurity A = about 1.4; impurity C = about 1.7; impurity D = about 1.9.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to meloxicam and impurity A at 350 nm; minimum 3.0 between the peaks due to impurity B and meloxicam at 260 nm.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 2.0;

— *impurity A at 350 nm*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) at 350 nm (0.1 per cent);

— *impurity B at 260 nm*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) at 350 nm (0.1 per cent);

— *impurities C, D at 350 nm*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) at 350 nm (0.05 per cent);

— *unspecified impurities*: for each impurity, at the wavelength giving the higher value for the impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) at the same wavelength (0.10 per cent);

— *total*: not more than 0.3 per cent;

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) at the same wavelength (0.03 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating during the titration, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.250 g in a mixture of 5 mL of *anhydrous formic acid R* and 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 35.14 mg of $C_{14}H_{13}N_3O_4S_2$.

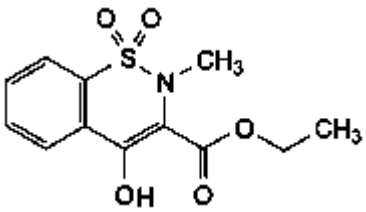
STORAGE

Protected from light.

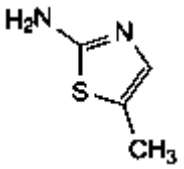
IMPURITIES

Specified impurities *A, B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F.*



A. ethyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,



B. 5-methylthiazol-2-amine,

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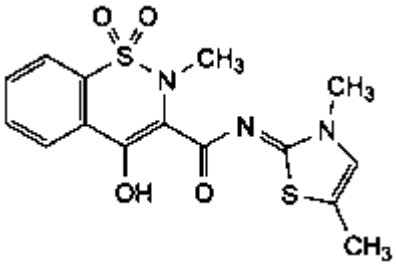
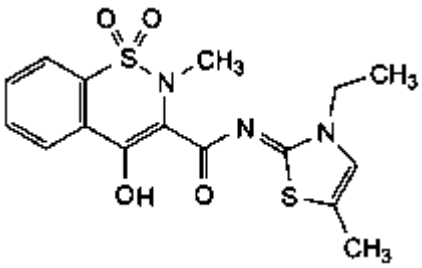
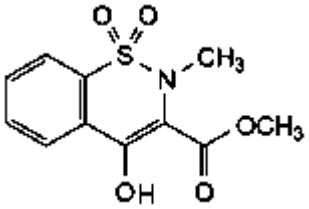


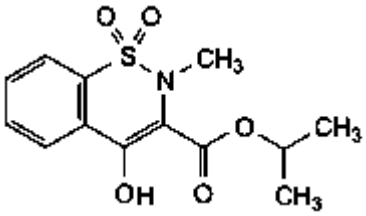
C. *N*-[(2*Z*)-3,5-dimethylthiazol-2(3*H*)-ylidene]-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide,



D. *N*-[(2*Z*)-3-ethyl-5-methylthiazol-2(3*H*)-ylidene]-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide,



E. methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,



F. isopropyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide.

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Meloxicam Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Meloxicam Tablets contain Meloxicam.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of meloxicam, $C_{14}H_{13}N_3O_4S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of Meloxicam, add 5 mL of 0.1M *methanolic sodium hydroxide* and 20 mL of *methanol*, stir for 15 minutes and filter.

(2) Dissolve 50 mg of *meloxicam BPCRS* in 5 mL of 0.1M *methanolic sodium hydroxide* and add sufficient *methanol* to produce 25 mL of solution.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel F_{254} plate* (Merck HPTLC plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a buffer prepared by dissolving 13.61 g of *potassium dihydrogen orthophosphate* in 800 mL of *water*, adjusting the pH to 7.5 with 0.5M *sodium hydroxide*, adding sufficient *water* to produce 1000 mL, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes, withdraw a sample of the medium and filter. Measure the absorbance of the filtrate, Appendix II B, diluted with the dissolution medium if necessary, at 362 nm using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a solution prepared by dissolving 30 mg of *meloxicam BPCRS* in 5 mL of *methanol*, adding 1 mL of 0.1M *sodium hydroxide* and adding sufficient dissolution medium to produce 100 mL. Dilute a volume of the resulting solution with sufficient dissolution medium to produce a solution containing 0.00075% w/v of Meloxicam.

DETERMINATION OF CONTENT

Calculate the total content of Meloxicam, $C_{14}H_{13}N_3O_4S_2$, in the medium from the absorbances obtained using the declared content of $C_{14}H_{13}N_3O_4S_2$ in *meloxicam BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Moisten a quantity of powdered tablets containing 30 mg of Meloxicam with 10 mL of 1M *sodium hydroxide*, add 40 mL of *methanol* and mix with the aid of ultrasound for 5 minutes. Add 40 mL of *methanol (40%)*, mix for 3 hours using a magnetic stirrer and then with the aid of ultrasound for 5 minutes. Cool, add sufficient *methanol (40%)* to produce 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (40%)*. Dilute 1 volume of the resulting solution to 10 volumes with *methanol (40%)*.

(3) Add 0.3 mL of 1M *sodium hydroxide* and 1 mL of *dimethylformamide* to 40 mg of *meloxicam impurity standard BPCRS* and dilute with *methanol (40%)* to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS 2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use detection wavelengths of 260 nm and 350 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

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Mobile phase A 0.1% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 6.0 with 2M *sodium hydroxide*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	60	40	isocratic
2.5-12	60→30	40→70	linear gradient
12-25	30	70	isocratic
25-26	30→60	70→40	linear gradient
26-30	60	40	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the chromatogram closely resembles the chromatogram supplied with *meloxicam impurity standard BPCRS* at 260 nm and 350 nm;

the *resolution* between the peaks due to meloxicam and impurity A at 350 nm is at least 3.0;

the *resolution* between the peaks due to impurity B and meloxicam at 260 nm is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity A at 350 nm and multiply the area of this peak by a correction factor of 2.0;

the area of any peak corresponding to impurity A at 350 nm is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any peak corresponding to impurity B at 260 nm is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%).

In both the chromatograms obtained with solution (1) at 350 nm and at 260 nm:

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) at that wavelength (0.2%).

The nominal total content of all such impurities is not greater than 0.5%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) at the same wavelength (0.1%).

ASSAY

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Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Moisten a quantity of the powdered tablets containing 30 mg of Meloxicam with 10 mL of 1M *sodium hydroxide*, add 40 mL of *methanol* and mix with the aid of ultrasound for 5 minutes. Add a further 40 mL of *methanol*, mix for 3 hours using a magnetic stirrer and then with the aid of ultrasound for 5 minutes. Cool, add sufficient *methanol* to produce 100 mL and filter.

(2) Dissolve 30 mg of *meloxicam BPCRS* in 10 mL of 1M *sodium hydroxide* and 40 mL of *methanol*, cool and add sufficient *methanol* to produce 100 mL.

(3) Add 0.3 mL of 0.4M *sodium hydroxide* to 40 mg of *meloxicam impurity standard BPCRS* and dilute with *methanol (40%)* to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a detection wavelength of 350 nm.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3):

the chromatogram closely resembles the chromatogram supplied with *meloxicam impurity standard BPCRS*;

the *resolution* between the peaks due to meloxicam and impurity A is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{13}N_3O_4S_2$ in the tablets using the declared content of $C_{14}H_{13}N_3O_4S_2$ in *meloxicam BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Meloxicam.

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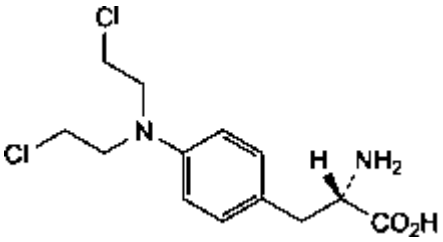
Melphalan

General Notices

(Ph. Eur. monograph 1698)



$C_{13}H_{18}Cl_2N_2O_2$ 305.2 *148-82-3*

Action and use

Cytotoxic alkylating agent.

Preparations

Melphalan Tablets

Melphalan for Injection

Ph Eur

DEFINITION

4-[Bis(2-chloroethyl)amino]-L-phenylalanine.

Content

94.0 per cent to 102.0 per cent (anhydrous and diethylamine-free substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Practically insoluble in water, slightly soluble in methanol. It dissolves in dilute mineral acids.

IDENTIFICATION

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of melphalan*.

TESTS

Appearance of solution

If intended for use in the manufacture of parenteral preparations, the solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.25 g in *dilute hydrochloric acid R* and dilute to 25 mL with the same acid.

Specific optical rotation (2.2.7)

-36.0 to -30.0 (anhydrous and diethylamine-free substance).

Dissolve 0.175 g at 45 °C for 10 min in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions and protect from light.*

Test solution (a) Dissolve 50.0 mg of the substance to be examined in *methanol R1* and dilute to 50.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methanol R1*.

Reference solution (a) Dissolve 50.0 mg of *melphalan hydrochloride CRS* in *methanol R1* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methanol R1*.

Reference solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with *methanol R1*.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 100.0 mL with *methanol R1*.

Reference solution (d) Dilute 5.0 mL of reference solution (b) to 100.0 mL with *methanol R1*.

Reference solution (e) In order to prepare impurity I *in situ*, dissolve 5 mg of *melphalan for system suitability CRS* (containing impurities B, D, G, H and J) in *methanol R1*, dilute to 5.0 mL with the same solvent and heat at 60 °C for 15 min.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mixture of 5 volumes of *acetonitrile for chromatography R* and 95 volumes of *water R* containing 0.01 per cent *V/V* of *triethylamine R*, 0.05 per cent *m/m* of *ammonium acetate R* and 0.05 per cent *V/V* of *glacial acetic acid R*;

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— *mobile phase B*: mixture of 40 volumes of *water R* containing 0.01 per cent *V/V* of *triethylamine R*, 0.05 per cent *m/m* of *ammonium acetate R* and 0.05 per cent *V/V* of *glacial acetic acid R*, and 60 volumes of *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100 → 0	0 → 100
20 - 25	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL of test solution (a) and reference solutions (c), (d) and (e).

Identification of impurities Use the chromatogram supplied with *melphalan for system suitability CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities B, D, G, H, I and J.

Relative retention With reference to melphalan (retention time = about 10 min): impurity B = about 0.3; impurity D = about 0.6; impurity I = about 0.8; impurity J = about 1.04; impurity G = about 1.4; impurity H = about 1.5.

System suitability Reference solution (e):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to melphalan.

Limits:

— *impurity D*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (d) (3.0 per cent);

— *impurity G*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (1.0 per cent);

— *impurities J, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurity I*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 11 times the area of the principal peak in the chromatogram obtained with reference solution (d) (5.5 per cent);

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— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Impurity K (diethylamine)

Gas chromatography (2.2.28).

Test solution Dissolve 0.125 g of substance to be examined in 0.15 mL of hydrochloric acid R and dilute to 5.0 mL with dimethyl sulfoxide R.

Reference solution Dilute 1 mL of methanol R and 0.125 g of diethylamine R1 (impurity K) to 10.0 mL with dimethyl sulfoxide R. Dilute 1.0 mL of the solution to 100.0 mL with dimethyl sulfoxide R.

Column:

— *material*: glass;

— *size*: *l* = 1.6 m, Ø = 4 mm;

— *stationary phase*: styrene-divinylbenzene copolymer R coated with potassium carbonate (149-177 µm).

Carrier gas nitrogen for chromatography R.

Flow rate 42.5 mL/min.

Temperature:

— *column*: 170 °C;

— *injection port*: 190 °C;

— *detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL.

Elution order Methanol, impurity K.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to methanol and impurity K.

Limit:

— *impurity K*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.5 per cent).

Water (2.5.12)

Maximum 5.0 per cent, determined on 0.200 g.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{13}H_{18}Cl_2N_2O_2$ taking into account the assigned content of *melphalan hydrochloride CRS* and a conversion factor of 0.8933.

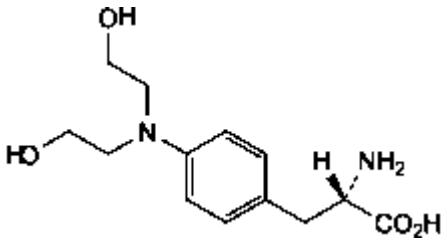
STORAGE

In an airtight container, protected from light.

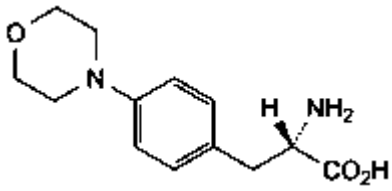
IMPURITIES

Specified impurities *B, D, G, H, I, J, K.*

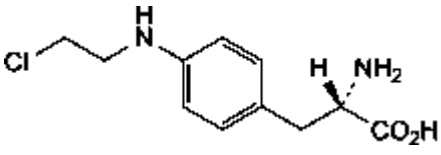
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, E, F.*



A. 4-[bis(2-hydroxyethyl)amino]-L-phenylalanine,



B. 4-morpholin-4-yl-L-phenylalanine,



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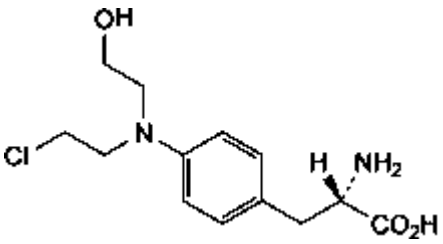
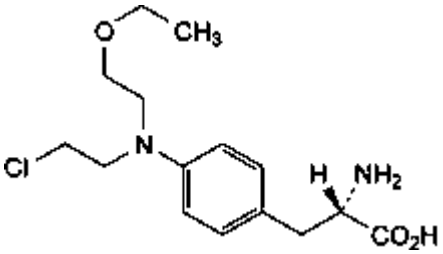
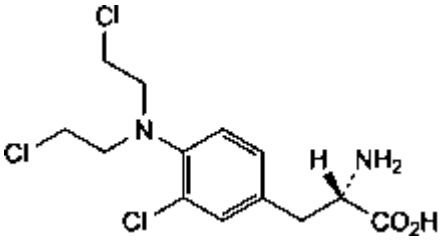
C. 4-[(2-chloroethyl)amino]-L-phenylalanine,



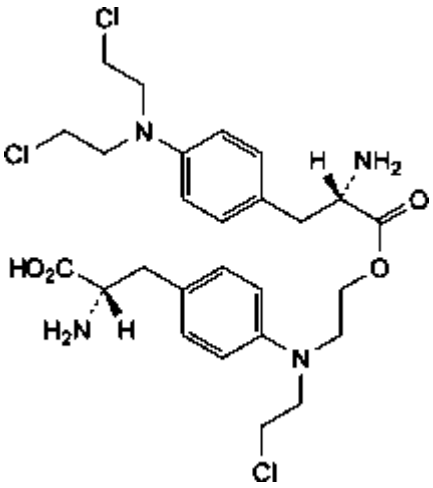
D. 4-[(2-chloroethyl)(2-hydroxyethyl)amino]-L-phenylalanine,



E. 4-[(2-chloroethyl)(2-ethoxyethyl)amino]-L-phenylalanine,



F. 4-[bis(2-chloroethyl)amino]-3-chloro-L-phenylalanine (3-chloromelphalan),



G. 4-[[2-[[4-[bis(2-chloroethyl)amino]-L-phenylalanyl]oxy]ethyl](2-chloroethyl)amino]-L-phenylalanine (melphalan dimer),

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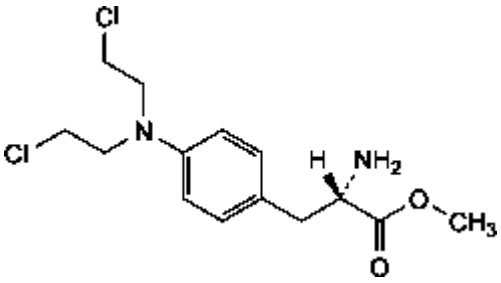
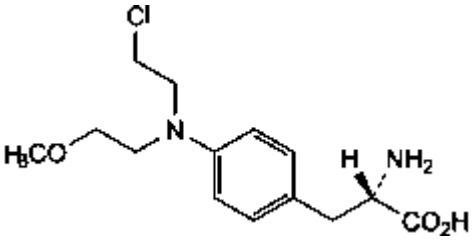
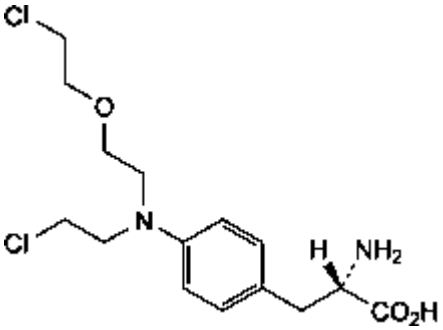


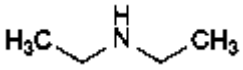
H. methyl 4-[bis(2-chloroethyl)amino]-L-phenylalaninate,



I. 4-[(2-chloroethyl)(2-methoxyethyl)amino]-L-phenylalanine,



J. 4-[[2-(2-chloroethoxy)ethyl](2-chloroethyl)amino]-L-phenylalanine,



K. *N*-ethylethanamine (diethylamine).

Ph Eur

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Melphalan for Injection

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Melphalan for Injection is a sterile material consisting of Melphalan with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of anhydrous melphalan, $C_{13}H_{18}Cl_2N_2O_2$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.001% w/v solution in *methanol* exhibits a maximum at 260 nm and a less well-defined maximum at 302 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Dissolve a quantity of the contents of a sealed container containing the equivalent of 20 mg of anhydrous melphalan in 50 mL of *methanol* with the aid of gentle heat, add 1 mL of a 5% w/v solution of *4-(4-nitrobenzyl)pyridine* in *acetone* and evaporate to dryness. Dissolve the residue in 1 mL of hot *methanol* and add 0.1 mL of 13.5M *ammonia*. A red colour is produced (identification of chloromethyl group).

TESTS

Dissolve the contents of one container in a suitable solvent, dilute with the requisite volume of a suitable diluent in accordance with the manufacturer's instructions to produce a final solution containing the equivalent of 0.5% w/v of anhydrous melphalan and allow to stand for 30 minutes (solution A).

Acidity or alkalinity

The pH of solution A is 6.0 to 7.0, Appendix V L.

Clarity of solution

Solution A is not more opalescent than *reference suspension II*, Appendix IV A.

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Related substances

Prepare a solution containing 4% v/v of *glacial acetic acid* in *methanol* (solvent A).

The total of all impurities from methods A and B, is not more than 10.0%.

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient of solvent A to produce 100 mL and dilute with sufficient of the same solvent mixture to produce a final solution containing the equivalent of 0.01% w/v of anhydrous melphalan.

(2) 0.0001% w/v of *melphalan BPCRS* in solvent A.

(3) 0.01% w/v of *melphalan for system suitability EPCRS* in solvent A.

(4) 0.000005% w/v of *melphalan BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Ultrasphere is suitable). A guard column is recommended (1.5 cm × 4.6 mm Brownlee RP-18 (7 µm) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 3 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.5 times the retention of melphalan.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to melphalan (retention time about 9 minutes) are: impurity D, about 0.2; impurity J, about 1.3.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 100 volumes of *methanol* and 200 volumes of a 0.25% w/v solution of *ammonium carbonate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and melphalan is at least 12.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (7.5%);

the area of any peak corresponding to impurity J is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

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the sum of the areas of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve the contents of a sealed container in solvent A to produce 100 mL and dilute with sufficient of the same solvent mixture to produce a final solution containing the equivalent of 0.01% w/v of anhydrous melphalan.

(2) 0.0001% w/v of *melphalan BPCRS* in solvent A.

(3) 0.01% w/v of *melphalan for system suitability EPCRS* in solvent A.

(4) 0.000005% w/v of *melphalan BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Ultrasphere is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention of melphalan.

When the chromatograms are recorded under the prescribed conditions the retention time of melphalan is about 5 minutes, the retention time of impurity H is about 8 minutes and the retention time of impurity G is about 12 minutes.

MOBILE PHASE

Equal volumes of a 0.136% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid* and *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *symmetry factor* of the peak corresponding to melphalan is between 0.8 and 1.2 and the peak is resolved from the peak corresponding to impurity G;

the peak corresponding to impurity G elutes within 15 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity G is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity H is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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the area of any other *secondary peaks* is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Uniformity of content

Sealed containers containing the equivalent of 100 mg or less of anhydrous melphalan comply with the requirements stated under Parenteral Preparations, Powders for Injections or Infusions. Use the individual results obtained in the Assay.

Water

Not more than 5.0% w/w, Appendix IX C, Method I. Use 0.25 g.

ASSAY

Prepare a solution containing 4% v/v *glacial acetic acid* in *methanol* (solvent A).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient of solvent A to produce 100 mL and dilute with sufficient of the same solvent mixture to produce a final solution containing the equivalent of 0.01% w/v of anhydrous melphalan.
(2) 0.01% w/v *melphalan BPCRS* in solvent A.
(3) 0.01% w/v of *melphalan for system suitability EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances A may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and melphalan is at least 12.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{18}Cl_2N_2O_2$ in the sealed container using the declared content of $C_{13}H_{18}Cl_2N_2O_2$ in *melphalan BPCRS*.

Repeat the procedure with a further nine sealed containers and calculate the average content of $C_{13}H_{18}Cl_2N_2O_2$ per container from the 10 individual results thus obtained.

STORAGE

The sealed container should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous melphalan.

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IMPURITIES

The impurities limited by the requirements of this monograph include D, G, H and J listed under Melphalan.

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Melphalan Tablets

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Melphalan Tablets contain Melphalan. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of melphalan, $C_{13}H_{18}Cl_2N_2O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 25 mg of Melphalan with 50 mL of hot *methanol*, filter and dilute 5 mL of the filtrate to 500 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, exhibits a maximum at 260 nm and a less well-defined maximum at 301 nm.

B. To the remainder of the filtrate obtained in test A add 1 mL of a 5% w/v solution of *4-(4-nitrobenzyl)pyridine* in *acetone* and evaporate to dryness. Dissolve the residue in 1 mL of hot *methanol* and add 0.1 mL of 13.5M *ammonia*. A red colour is produced.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.1M *hydrochloric acid* if necessary, expected to contain about 0.0002% w/v of Melphalan.

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(2) Dilute a suitable volume of a 0.10% w/v solution of *melphalan BPCRS* in a mixture of 4 volumes of *acetonitrile* and 1 volume of 0.1M *hydrochloric acid* with sufficient 0.1M *hydrochloric acid* to produce a solution containing 0.0002% w/v.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

2.7 volumes of *glacial acetic acid*, 180 volumes of *methanol* and 200 volumes of a 0.375% w/v solution of *ammonium carbonate*.

DETERMINATION OF CONTENT

Calculate the content of melphalan, $C_{13}H_{18}Cl_2N_2O_2$ in the medium using the declared content of $C_{13}H_{18}Cl_2N_2O_2$ in *melphalan BPCRS*.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Melphalan comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.01% w/v of *melphalan BPCRS* in a mixture of 4 volumes of *acetonitrile* and 1 volume of 0.1M *hydrochloric acid*.

(2) Add 20 mL of a mixture of 4 volumes of *acetonitrile* and 1 volume of 0.1M *hydrochloric acid* to one tablet, mix with the aid of ultrasound for 10 minutes or until the tablet has disintegrated, filter, discarding the first 5 mL of filtrate, and use the filtrate.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

2.7 volumes of *glacial acetic acid*, 180 volumes of *methanol* and 200 volumes of a 0.375% w/v solution of *ammonium carbonate*.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{18}Cl_2N_2O_2$ in each tablet using the declared content of $C_{13}H_{18}Cl_2N_2O_2$ in *melphalan BPCRS*.

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ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Melphalan

Use the average of the 10 individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Melphalan

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.01% w/v of *melphalan BPCRS* in a mixture of 4 volumes of *acetonitrile* and 1 volume of 0.1M *hydrochloric acid*.

(2) Add about 300 mL of a mixture of 4 volumes of *acetonitrile* and 1 volume of 0.1M *hydrochloric acid* to 10 tablets, shake until the tablets have disintegrated (about 30 minutes), mix with the aid of ultrasound for 5 minutes, dilute to 500 mL with the same solvent mixture, filter, discarding the first 20 mL of filtrate, and use the filtrate.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{18}Cl_2N_2O_2$ in the tablets using the declared content of $C_{13}H_{18}Cl_2N_2O_2$ in *melphalan BPCRS*.

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Menadiol Phosphate Tablets

General Notices

Action and use

Vitamin K analogue.

DEFINITION

Menadiol Phosphate Tablets contain Menadiol Sodium Phosphate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of menadiol phosphate, $C_{11}H_{12}O_8P_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 0.15 g of menadiol phosphate with 15 mL of *water*, centrifuge and filter the supernatant liquid. To 10 mL of the filtrate add 10 mL of 1M *sulfuric acid*, 10 mL of 0.1M *cerium(IV) sulfate* and 1 mL of *hydrogen peroxide solution (20 vol)* and extract with two 10 mL quantities of *chloroform*. Evaporate the combined chloroform extracts to dryness in a water bath and dry the residue at 40° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of menadione *(RS 214)*.

B. To 50 mg of the residue obtained in test A add 5 mL of *water* followed by 75 mg of *sodium metabisulfite*, heat in a water bath, shaking vigorously, until an almost colourless solution is obtained and dilute to 50 mL with *water*. To 2 mL of the resulting solution add 2 mL of a mixture of equal volumes of 13.5M *ammonia* and *ethanol (96%)*, shake and add 0.15 mL of *ethyl cyanoacetate*. A deep purplish-blue colour is produced which changes to green on the addition of 1 mL of 10M *sodium hydroxide*.

TESTS

Related substances

Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 50 volumes of *propan-1-ol*, 50 volumes of a 2% w/v solution of *ammonium chloride*, 5 volumes of *butan-1-ol* and 1.5 volumes of *diethylamine* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing the equivalent of 0.25 g of menadiol phosphate with 10 mL of *methanol (50%)* and filter. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *methanol (50%)*. Solution (3) contains 0.0080% w/v of *2-methyl-1,4-naphthoquinone* in *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3). Examine the

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plate under *ultraviolet light (365 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 10 mg of menadiol phosphate with 100 mL of 0.1 M *hydrochloric acid* for 30 minutes. Dilute to 250 mL with 0.1M *hydrochloric acid*, filter and measure the *absorbance* of the filtrate at the maximum at 290 nm, Appendix II B. Calculate the content of $C_{11}H_{12}O_8P_2$ taking the value of A(1%, 1 cm), for a solution of $C_{11}H_8Na_4O_8P_2$ in 0.1M *hydrochloric acid*, to be 138 at the maximum at 290 nm. Each mg of $C_{11}H_8Na_4O_8P_2$ (menadiol sodium phosphate) is equivalent to 0.792 mg of $C_{11}H_{12}O_8P_2$ (menadiol phosphate).

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of menadiol phosphate.

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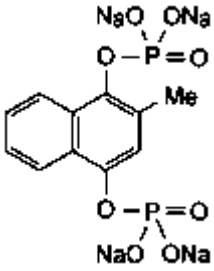
Menadiol Sodium Phosphate

General Notices



$C_{11}H_8Na_4O_8P_2,6H_2O$ 530.2 *6700-42-1*

Action and use

Vitamin K analogue.

Preparation

Menadiol Phosphate Tablets

DEFINITION

Menadiol Sodium Phosphate is tetrasodium 2-methylnaphthalene-1,4-diyl di(orthophosphate) hexahydrate. It contains not less than 98.0% and not more than 100.5% of $C_{11}H_8Na_4O_8P_2$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white to pink, crystalline powder; hygroscopic.

Very soluble in *water*; practically insoluble in *ethanol (96%)*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of menadiol sodium phosphate *(RS 213)*.

B. To 10 mL of a 2% w/v solution add 10 mL of 1M *sulfuric acid*, 10 mL of 0.1M *cerium(IV) sulfate* and 1 mL of *hydrogen peroxide solution (20 vol)* and extract with two 10 mL quantities of *chloroform*. Evaporate the combined chloroform extracts to dryness on a water bath and dry the residue at 40° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of menadione.

C. Dissolve 40 mg in 2 mL of *water*, heat gently with 2 mL of *sulfuric acid* until white fumes are evolved, add *nitric acid* dropwise until digestion is complete and cool. Add 2 mL of *water*, heat until white fumes are evolved again, cool, add a further 10 mL of *water* and

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neutralise to *litmus paper* with 5M *ammonia*. The solution yields reaction A characteristic of *sodium salts* and reaction B characteristic of *phosphates*, Appendix VI.

TESTS

Inorganic phosphate

Dissolve 25 mg in 10 mL of *water*, add 4 mL of 1M *sulfuric acid*, 1 mL of a 10% w/v solution of *ammonium molybdate* and 2 mL of *methylaminophenyl-sulfite reagent* and allow to stand for 15 minutes. The *absorbance* of the solution at 730 nm, Appendix II B, is not more than the *absorbance* of a solution prepared in the same manner but using 10 mL of a 0.0025% w/v solution of *potassium dihydrogen orthophosphate* in place of the solution of the substance being examined (0.7%).

Total phosphate

Dissolve 85 mg in 50 mL of *glacial acetic acid*, add 5 mL of *mercury(II) acetate solution* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Not less than 7.7 mL and not more than 8.3 mL of *0.1M perchloric acid VS* is required.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, in subdued light using the following solutions in *methanol (50%)*.

(1) 4.0% w/v of the substance being examined.
(2) 0.020% w/v of the substance being examined.
(3) 0.0080% w/v of *2-methyl-1,4-naphtha-quinone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air, examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.5 volumes of *diethylamine*, 5 volumes of *butan-1-ol*, 50 volumes of *propan-1-ol* *and* 50 volumes of a 2% w/v solution of *ammonium chloride*.

LIMITS

Any spot corresponding to 2-methyl-1,4-naphthaquinone (menadione) in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2).

Water

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19.0 to 21.5% w/w, Appendix IX A. Use 0.25 g.

ASSAY

Dissolve 0.1 g in 25 mL of *water*, add 25 mL of *glacial acetic acid* and 25 mL of *3M hydrochloric acid* and titrate with 0.02M *cerium(IV) sulfate VS* using platinum and calomel electrodes and determining the end point potentiometrically. Each mL of 0.02M *cerium(IV) sulfate VS* is equivalent to 4.221 mg of $C_{11}H_8Na_4O_8P_2$.

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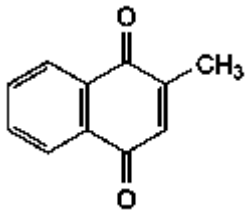
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Menadione

General Notices

(Ph. Eur. monograph 0507)



$C_{11}H_8O_2$ 172.2 *58-27-5*

Action and use

Vitamin K analogue.

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DEFINITION

Menadione contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 2-methylnaphthalene-1,4-dione, calculated with reference to the dried substance.

CHARACTERS

A pale-yellow, crystalline powder, practically insoluble in water, freely soluble in toluene, sparingly soluble in ethanol (96 per cent) and in methanol. It is unstable in light.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 105 °C to 108 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *menadione CRS*.

C. Dissolve about 1 mg in 5 mL of *alcohol R*, add 2 mL of *ammonia R* and 0.2 mL of *ethyl cyanoacetate R*. An intense bluish-violet colour develops. Add 2 mL of *hydrochloric acid R*. The colour disappears.

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D. Dissolve about 10 mg in 1 mL of *alcohol R*, add 1 mL of *hydrochloric acid R* and heat in a water-bath. A red colour develops.

TESTS

Related substances

Carry out the test protected from bright light Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 0.2 g of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution Dilute 0.5 mL of the test solution to 100 mL with *acetone R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *nitromethane R*, 2 volumes of *acetone R*, 5 volumes of *ethylene chloride R* and 90 volumes of *cyclohexane R*. Dry the plate in a current of hot air. Repeat the development and drying a further two times. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* for 4 h.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 15 mL of *glacial acetic acid R* in a flask with a stopper fitted with a valve. Add 15 mL of *dilute hydrochloric acid R* and 1 g of *zinc powder R*. Close the flask. Allow the mixture to stand for 60 min, protected from light, with occasional shaking. Filter the solution over a cotton wad, wash with three quantities, each of 10 mL, of *carbon dioxide-free water R*. Add 0.1 mL of *ferroin R* and immediately titrate the combined filtrate and washings with *0.1 M ammonium and cerium nitrate*.

1 mL of *0.1 M ammonium and cerium nitrate* is equivalent to 8.61 mg of $C_{11}H_8O_2$.

STORAGE

Store protected from light.

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Menotrophin

General Notices

9002-68-0

Action and use

Gonadotrophin; treatment of infertility.

Preparation

Menotrophin Injection

DEFINITION

Menotrophin is a dry preparation containing glycoprotein gonadotrophins possessing follicle-stimulating and luteinising activities. The follicle-stimultating activity is of pituitary origin. The luteinising activity is predominantly of pituitary origin, but may also contain luteinising activity of placental origin. Menotrophin is obtained from the urine of post-menopausal women but, where necessary, chorionic gonadotrophin obtained from the urine of pregnant women may be added to achieve the ratio stated below.

Potency

It contains not less than 40 IU of follicle-stimulating hormone activity per mg. The ratio of IU of luteinising hormone (LH) activity to IU of follicle-stimulating hormone (FSH) activity is approximately 1. For each component the estimated potency is not less than 80% and not more than 125% of the stated potency.

PRODUCTION

Menotrophin is prepared by suitable collection and extraction procedures followed by purification steps. The method of preparation includes steps that have been shown to remove and/or inactivate extraneous agents, including viral agents as determined by a suitable risk-based approach. In addition, the process is designed to minimise microbial contamination.

CHARACTERISTICS

An almost white or slightly yellow powder.

Soluble in water.

IDENTIFICATION

Causes enlargement of the ovaries of immature female rats and increases the weight of the seminal vesicles and prostate gland of immature male rats when administered as directed in the Assay.

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TESTS

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit is not more than 0.78 IU per IU of follicle stimulating hormone.

Water

Not more than 5.0% w/w, Appendix IX C, Method III. Use 4 mg.

ASSAY

Carry out the *biological assay of menotrophin* described below. The fiducial limits of error are not less than 64% and not more than 156% of the stated potency.

STORAGE

Menotrophin should be kept in an airtight, tamper-evident container and protected from light.

LABELLING

The label states (1) the number of IU (Units) of follicle-stimulating hormone activity and the number of IU (Units) of luteinising hormone activity in the container; (2) the number of IU (Units) of follicle-stimulating hormone activity per mg and the number of IU (Units) of luteinising hormone activity per mg; (3) where applicable, the number of IU (Units) of chorionic gonadotrophin activity per mg; (4) the date after which the material is not intended to be used; (5) the conditions under which it should be stored; (6) where applicable, that it is sterile.

Menotrophin intended for use in the manufacture of a parenteral dosage form without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility

Complies with the *test for sterility*, Appendix XVI A.

BIOLOGICAL ASSAY OF MENOTROPHIN

The potency of menotrophin with respect to its follicle-stimulating hormone activity is estimated by comparing its effect in enlarging the ovaries of immature female rats with that of the Standard Preparation of human urinary FSH and human urinary LH under the conditions of a suitable method of assay. The potency of menotrophin with respect to its luteinising hormone activity is estimated by comparing its effect in increasing the weight of the seminal vesicles or the prostate gland of immature male rats with that of the Standard Preparation of human urinary FSH and human urinary LH under the conditions of a suitable method of assay.

Standard Preparation

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The Standard Preparation is the International Standard preparation of human urinary follicle-stimulating hormone and luteinising hormone, consisting of a freeze-dried extract of urine from post-menopausal women together with lactose, or another suitable preparation the potency of which has been determined in relation to the International Standard.

SUGGESTED METHOD

Follicle-stimulating hormone activity

Select female rats of the same strain, 19 to 28 days old and differing in age by not more than 3 days, and having weights such that the difference between the heaviest rat and the lightest rat is not more than 10 g. Assign the rats at random to six equal groups of at least five animals. If sets of six litter mates are available, allot one litter mate from each set to each group and mark according to litter.

Choose three doses of the Standard Preparation and three doses of the preparation being examined such that the smallest dose produces a positive response in some of the rats and the largest dose does not produce a maximum response in all of the rats. Use doses in geometric progression. As an initial approximation, total doses of 1.5, 3.0 and 6.0 IU may be tried although the dose will depend on the sensitivity of the animals used, which may vary widely.

Dissolve separately the total quantities of the preparation being examined, and of the Standard Preparation, corresponding to the daily doses to be used in sufficient *albumin-phosphate buffer pH 7.2* containing not less than 70 IU of *chorionic gonadotrophin* per mL so that the daily dose is about 0.2 mL. Add a suitable antimicrobial preservative such as 0.4% w/v of *phenol* or 0.002% w/v of *thiomersal*. Store the solutions at a temperature of 2° to 8°. Inject subcutaneously into each rat the daily dose allocated to its group. Repeat the procedure after 24 and 48 hours. About 24 hours after the last injection, kill the rats and remove the ovaries. Remove any extraneous fluid and tissue and immediately weigh the ovaries from each animal. Record the combined weight of both ovaries from each rat. Calculate the result of the assay by standard statistical methods using the weight of the ovaries as the response. (A suitable correction of the organ weight with reference to the weight of the animal from which it was taken may be applied; an analysis of covariance may be used).

Luteinising hormone activity

Select male rats of the same strain, approximately 19 to 28 days old and differing in age by not more than 3 days, and having weights such that the difference between the heaviest rat and the lightest rat is not more than 10 g. Assign the rats at random to six equal groups of at least five animals. If sets of six litter mates are available, allot one litter mate from each set to each group and mark according to litter.

Choose three doses of the Standard Preparation and three doses of the preparation being examined such that the smallest dose is sufficient to produce a positive response in some of the rats and the largest dose does not produce a maximum response in all of the rats. Use doses in geometric progression. As an initial approximation, total doses of 7, 14 and 28 IU may be tried although the dose will depend on the sensitivity of the animals used, which may vary widely.

Dissolve separately the total quantities of the preparation being examined, and of the Standard Preparation, corresponding to the daily doses to be used in sufficient *albumin-phosphate buffer pH 7.2* so that the daily dose is about 0.2 mL. Add a suitable antimicrobial preservative such as 0.4% w/v of *phenol* or 0.002% w/v of *thiomersal*. Store the solutions at a temperature of 2° to 8°. Inject subcutaneously into each rat the daily dose allocated to its group on 4 consecutive days at the same time each day. On the fifth day, about 24 hours after the last injection, kill the rats and remove the seminal vesicles or the prostate gland. Remove any extraneous fluid and tissue and weigh immediately the seminal vesicles or the prostate gland. Calculate the result of the assay by standard statistical methods, using

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the weight of the vesicles or the prostate gland as the response. (A suitable correction of the organ weight with reference to the weight of the animal from which it was taken may be applied; an analysis of covariance may be used.)

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Menotrophin Injection

General Notices

Action and use

Gonadotrophins for the treatment of infertility.

DEFINITION

Menotrophin Injection is a sterile solution of Menotrophin in Water for Injections. It is prepared by dissolving Menotrophin for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Menotrophin Injection should be used immediately after preparation.

MENOTROPHIN FOR INJECTION

DEFINITION

Menotrophin for Injection is a sterile material consisting of Menotrophin with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Potency

The estimated potency for each component is not less than 80% and not more than 125% of the stated potency.

IDENTIFICATION

Cause enlargement of the ovaries of immature female rats and increase the weight of the seminal vesicles and prostate gland of immature male rats when administered as directed in the Assay.

TESTS

Acidity or alkalinity

Dissolve the contents of the sealed container in 3 mL of *water* (solution A). The pH is 6.0 to 8.0, Appendix V L.

Clarity and colour of solution

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Solution A is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method I.

Water

Not more than 5% w/w, Appendix IX C, Method III. Use 75 IU of follicle stimulating hormone.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit is not more than 0.78 IU per IU of follicle stimulating hormone.

ASSAY

Carry out the *biological assay of menotrophin* described under Menotrophin. The fiducial limits of error are not less than 64% and not more than 156% of the stated potency.

STORAGE

The sealed container should be protected from light.

LABELLING

The label of the sealed container states the number of IU (Units) of follicle-stimulating hormone activity, the number of IU (Units) of luteinising hormone activity and, where applicable, the number of IU (Units) of chorionic gonadotrophin activity contained in it.

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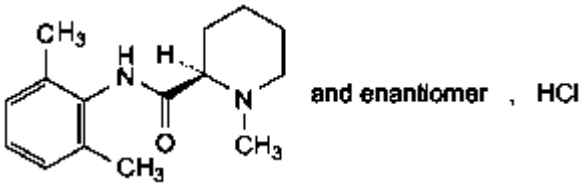
Mepivacaine Hydrochloride

General Notices

(Ph. Eur. monograph 1242)



$C_{15}H_{23}ClN_2O$ 282.8 *1722-62-9*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

(2*RS*)-*N*-(2,6-Dimethylphenyl)-1-methylpiperidine-2-carboxamide hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), very slightly soluble in methylene chloride.

mp

About 260 °C, with decomposition.

It shows polymorphism (*5.9*).

IDENTIFICATION

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First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mepivacaine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and dry in an oven at 80 °C for 45 min. Record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *mepivacaine hydrochloride CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *mepivacaine hydrochloride CRS* and 20 mg of *lidocaine hydrochloride CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *1,1-dimethylethyl methyl ether R* (1:5:100 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.500 g in *carbon dioxide-free water R* and dilute to 30.0 mL with the same solvent.

Appearance of solution

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Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

pH (*2.2.3*)

4.0 to 5.0.

Dilute 2 mL of solution S to 5 mL with *carbon dioxide-free water R*.

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of the substance to be examined and 30.0 mg of *mepivacaine impurity B CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a 2.25 g/L solution of *phosphoric acid R*, previously adjusted to pH 7.6 with *strong sodium hydroxide solution R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 3 times the retention time of mepivacaine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to mepivacaine (retention time = about 7 min): impurity B = about 0.5.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity B and mepivacaine.

Limits:

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— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity A

Head-space gas chromatography (2.2.28).

Test solution Introduce 60.0 mg of the substance to be examined into a 20 mL vial. Add 2.0 mL of a 103.0 g/L solution of *hydrochloric acid R* and 1.0 mL of a 126.0 g/L solution of *sodium hydroxide R*, and close the vial immediately.

Reference solution Dissolve 6.0 mg of *bupivacaine impurity F CRS* (impurity A) in a 103.0 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid solution. Dilute 1.0 mL of this solution to 100.0 mL with a 103.0 g/L solution of *hydrochloric acid R*. Introduce 2.0 mL of this solution into a 20 mL vial, add 1.0 mL of a 126.0 g/L solution of *sodium hydroxide R*, and close the vial immediately.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 4.0 mL/min.

Split ratio 1:1.

Static head-space conditions that may be used:

— *equilibration temperature*: 90 °C;

— *equilibration time*: 25 min;

— *pressurisation time*: 2 min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	130 → 230
	10 - 15	230
Injection port		225

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	Time (min)	Temperature (°C)
Detector		250

Detection Flame ionisation.

Retention time Impurity A = about 6 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 15.0 per cent determined on 6 injections.

Calculation of content:

— for impurity A, use the concentration of impurity A in the reference solution.

Limit:

— *impurity A*: maximum 20 ppm.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.28 mg of $C_{15}H_{23}ClN_2O$.

IMPURITIES

Specified impurities *A*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*

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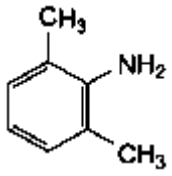
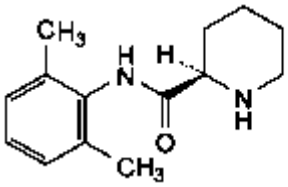
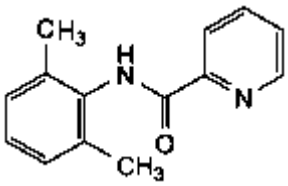


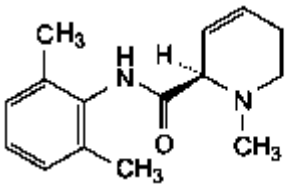
A. 2,6-dimethylaniline,


and enantiomer

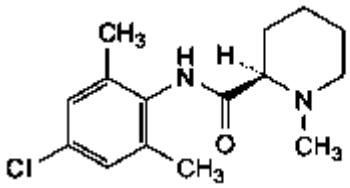
B. (2*RS*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide,



C. *N*-(2,6-dimethylphenyl)pyridine-2-carboxamide,


and enantiomer

D. (2*RS*)-*N*-(2,6-dimethylphenyl)-1-methyl-1,2,5,6-tetrahydropyridine-2-carboxamide,


and enantiomer

E. (2*RS*)-*N*-(4-chloro-2,6-dimethylphenyl)-1-methylpiperidine-2-carboxamide.

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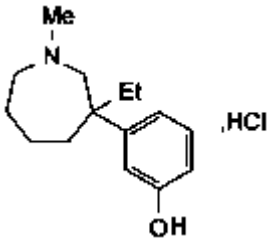
Meptazinol Hydrochloride

General Notices



$C_{15}H_{23}NO,HCl$ 269.8 *59263-76-2*

Action and use

Opioid receptor partial agonist; analgesic.

Preparations

Meptazinol Injection

Meptazinol Tablets

DEFINITION

Meptazinol Hydrochloride is 3-(3-ethyl-1-methylperhydroazepin-3-yl)phenol hydrochloride. It contains not less than 99.0% and not more than 101.0% of $C_{15}H_{23}NO,HCl$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder.

Very soluble in *water* and in *methanol*; freely soluble in *ethanol (96%)*; very slightly soluble in *acetone*. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.01% w/v solution in *ethanol (96%)* exhibits a maximum only at 275 nm. The *absorbance* at 275 nm is about 0.80.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of meptazinol hydrochloride *(RS 215)*.

TESTS

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Acidity or alkalinity

To 10 mL of a 2% w/v solution in *carbon dioxide-free water* add 0.2 mL of *0.01M sodium hydroxide VS* and 0.1 mL of *methyl red solution*; the solution is yellow. Add 0.4 mL of *0.01M hydrochloric acid VS*; the solution is red.

Colour of solution

A 10.0% w/v solution is not more intensely coloured than *reference solution Y_6*, Appendix IV B, Method II.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) 1.0% w/v of the substance being examined.
(2) 0.01% w/v of the substance being examined.
(3) 0.005% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air, examine under *ultraviolet light (254 nm)*, expose to iodine vapour for 2 hours and examine again.

MOBILE PHASE

1 volume of 18M *ammonia*, 30 volumes of *chloroform* and 70 volumes of *ethyl acetate*.

LIMITS

By each method of visualisation, any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

Loss on drying

When dried at 105° for 3 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.15 g in 50 mL of *anhydrous acetic acid* and add 5 mL of *mercury(II) acetate solution*. Carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 26.98 mg of $C_{15}H_{23}NO,HCl$.

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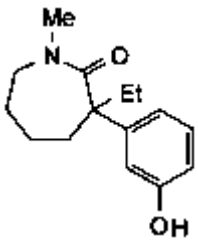
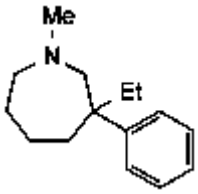
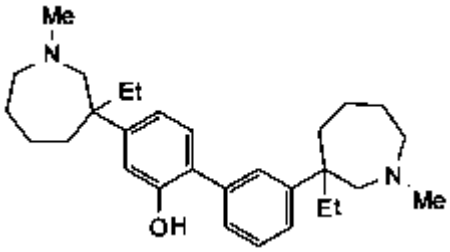
IMPURITIES



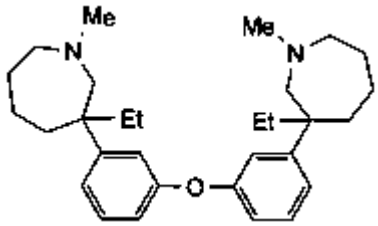
A. 3-ethyl-3-(3-hydroxyphenyl)-1-methylperhydroazepin-2-one



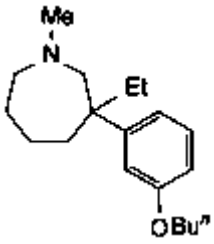
B. 3-ethyl-1-methyl-3-phenylperhydroazepine



C. 4-(3-ethyl-1-methylperhydroazepin-3-yl)-2-[3-(3-ethyl-1-methylperhydroazepin3-yl)phenyl]phenol



D. 3,3′-oxybis(3-ethyl-1-methylperhydroazepin-3-ylbenzene)



E. 3-ethyl-3-(3-butoxyphenyl)-1-methylperhydroazepine

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Meptazinol Injection

General Notices

Action and use

Opioid receptor partial agonist; analgesic.

DEFINITION

Meptazinol Injection is a sterile solution of Meptazinol Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of meptazinol, $C_{15}H_{23}NO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 220 to 330 nm of the solution obtained in the Assay exhibits a maximum at 273 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) Dilute the injection, if necessary, to contain the equivalent of 0.05% w/v of meptazinol.

(2) 0.05% w/v of *meptazinol hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia*, 20 volumes of *absolute ethanol* and 79 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in intensity, position and size to that in the chromatogram obtained with solution (2).

TESTS

Acidity

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pH, 3.5 to 6.0, Appendix V L.

Colour of solution

The injection is not more intensely coloured than *reference solution Y_5*, Appendix IV B, Method II.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute a volume of the injection, if necessary, to produce a solution containing the equivalent of 1.0% w/v of meptazinol.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 2 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, examine under *ultraviolet light (254 nm)*, expose to iodine vapour for 2 hours and examine again.

MOBILE PHASE

1 volume of 18M *ammonia*, 30 volumes of *chloroform* and 70 volumes of *ethyl acetate*.

LIMITS

By each method of visualisation, any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Dilute a suitable volume of the injection with sufficient *water* to produce a solution containing the equivalent of 0.01% w/v of meptazinol and measure the *absorbance* at the maximum at 273 nm, Appendix II B. Calculate the content of $C_{15}H_{23}NO$ from the *absorbance* obtained using a 0.01% w/v solution of *meptazinol hydrochloride BPCRS* and from the declared content of $C_{15}H_{23}NO$ in *meptazinol hydrochloride BPCRS*.

LABELLING

The label of the sealed container states the quantity of Meptazinol Hydrochloride contained in it in terms of the equivalent amount of meptazinol.

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Meptazinol Tablets

General Notices

Action and use

Opioid receptor partial agonist; analgesic.

DEFINITION

Meptazinol Tablets contain Meptazinol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of meptazinol, $C_{15}H_{23}NO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 220 to 330 nm of the solution obtained in the Assay exhibits a maximum at 273 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 50 mg of meptazinol with 5 mL of *ethanol (96%)*, centrifuge and dilute 1 volume of the supernatant liquid to 50 volumes with *ethanol (96%)*.

(2) 0.02% w/v of *meptazinol hydrochloride BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia*, 20 volumes of *absolute ethanol* and 79 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in intensity, position and size to that in the chromatogram obtained with solution (2).

TESTS

Related substances

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Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.2 g of meptazinol with 20 mL of *ethanol (96%)*, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 2 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, examine under *ultraviolet light (254 nm)*, expose to iodine vapour for 2 hours and examine again.

MOBILE PHASE

1 volume of 18M *ammonia*, 30 volumes of *chloroform* and 70 volumes of *ethyl acetate*.

LIMITS

By each method of visualisation, any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

ASSAY

To a quantity of the powdered tablets containing the equivalent of 0.2 g of meptazinol add 40 mL of 0.06M *hydrochloric acid*, shake, dilute to 50 mL with the same solvent, filter through a glass-fibre paper (Whatman GF/C paper is suitable); dilute 5 mL of the filtrate to 250 mL with 0.06M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at 273 nm, Appendix II B. Calculate the content of $C_{15}H_{23}NO$ from the *absorbance* obtained using a 0.0080% w/v solution of *meptazinol hydrochloride BPCRS* in 0.06M *hydrochloric acid* and from the declared content of $C_{15}H_{23}NO$ in *meptazinol hydrochloride BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of meptazinol.

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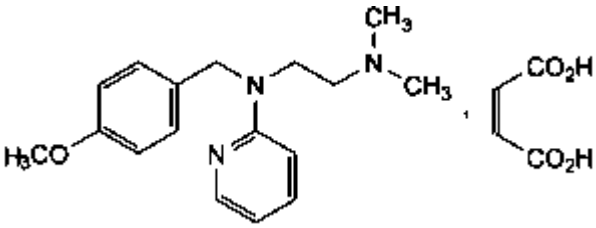
Mepyramine Maleate

General Notices

(Ph. Eur. monograph 0278)



$C_{21}H_{27}N_3O_5$ 401.5 *59-33-6*

Action and use

Anti-emetic.

Ph Eur

DEFINITION

N-(4-Methoxybenzyl)-*N*′,*N*′-dimethyl-*N*-(pyridin-2-yl)ethane-1,2-diamine (2*Z*)-but-2-enedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C, D, E.

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A. Melting point (2.2.14): 99 °C to 103 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation 50 g/L solutions in *methylene chloride R* using a 0.1 mm cell.

Comparison *mepyramine maleate CRS*.

C. Dissolve 0.100 g in *0.01 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 1.0 mL of this solution to 100.0 mL with *0.01 M hydrochloric acid*. Examined between 220 nm and 350 nm (2.2.25), the solution shows 2 absorption maxima, at 239 nm and 316 nm. The specific absorbances at the absorption maxima are 431 to 477 and 196 to 220, respectively.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 40 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 40 mg of *mepyramine maleate CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *diethylamine R*, *ethyl acetate R* (2:100 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

E. Triturate 0.1 g with 3 mL of *water R* and 1 mL of *strong sodium hydroxide solution R*. Shake with 3 quantities, each of 5 mL, of *ether R*. To 0.1 mL of the aqueous layer add a solution of 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min; no colour develops. To the rest of the aqueous layer add 1 mL of *bromine water R*. Heat on a water-bath for 15 min and then heat to boiling and cool. To 0.2 mL of this solution add a solution of 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min; a violet-pink colour develops.

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

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Dilute 5 mL of solution S to 25 mL with *carbon dioxide-free water R*.

pH (*2.2.3*)

4.9 to 5.2.

Dilute 1.0 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *anisaldehyde R* (impurity B), 5.0 mg of *mepyramine impurity A CRS* and 5.0 mg of *mepyramine impurity C CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped phenylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 0.1 volumes of *triethylamine R*, 40 volumes of a 0.771 g/L solution of *ammonium acetate R* and 60 volumes of *methanol R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 3 times the retention time of mepyramine.

Relative retention With reference to mepyramine (retention time = about 13 min): maleic acid = about 0.2; impurity C = about 0.3; impurity B = about 0.4; impurity A = about 0.5.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurities C and B.

Limits:

— *impurities A, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

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— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to maleic acid.

Chlorides (2.4.4)

Maximum 100 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Loss on drying (2.2.32)

Maximum 0.25 per cent, determined on 1.000 g by drying in an oven at 80 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Dissolve 0.150 g in 40 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

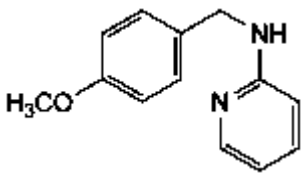
1 mL of *0.1 M perchloric acid* is equivalent to 20.07 mg of $C_{21}H_{27}N_3O_5$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. *N*-(4-methoxybenzyl)pyridin-2-amine,

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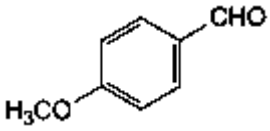
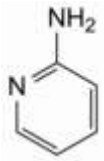


B. 4-methoxybenzaldehyde (anisaldehyde),



C. pyridin-2-amine.

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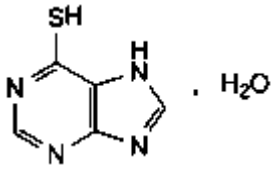
Mercaptopurine Monohydrate

General Notices

Mercaptopurine

(Ph. Eur. monograph 0096)



$C_5H_4N_4S,H_2O$ 170.2 *6112-76-1*

Action and use

Thiopurine cytotoxic.

Preparations

Mercaptopurine Oral Suspension

Mercaptopurine Tablets

Ph Eur

DEFINITION

7*H*-Purine-6-thiol monohydrate.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in heptane. It dissolves in solutions of alkali hydroxides.

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IDENTIFICATION

A. Dissolve 20 mg in 5 mL of *dimethyl sulfoxide R* and dilute to 100 mL with a 10.3 g/L solution of *hydrochloric acid R*. Dilute 5 mL of this solution to 200 mL with a 10.3 g/L solution of *hydrochloric acid R*. Examined between 230 nm and 350 nm (2.2.25), the solution shows only 1 absorption maximum, at 325 nm.

B. Dissolve about 20 mg in 20 mL of *ethanol (96 per cent) R* heated to 60 °C and add 1 mL of a saturated solution of *mercuric acetate R* in *ethanol (96 per cent) R*. A white precipitate is formed.

C. Dissolve about 20 mg in 20 mL of *ethanol (96 per cent) R* heated to 60 °C and add 1 mL of a 10 g/L solution of *lead acetate R* in *ethanol (96 per cent) R*. A yellow precipitate is formed.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 12.0 mg of the substance to be examined in 2.5 mL of *methanol R* and dilute to 100.0 mL with a 0.1 per cent *V/V* solution of *anhydrous formic acid R*.

Reference solution (a) Dissolve 3.0 mg of *mercaptopurine impurity B CRS* and 4.5 mg of *mercaptopurine impurity A CRS* in mobile phase A and dilute to 250.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a 0.1 per cent *V/V* solution of *anhydrous formic acid R*.

Reference solution (c) Dissolve 3 mg of *mercaptopurine impurity D CRS* in 10 mL of *dimethyl sulfoxide R* and dilute to 250 mL with mobile phase A. Dilute 1 mL of the solution to 100 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, 0.1 per cent *V/V* solution of *anhydrous formic acid R* (2:98 *V/V*);

— *mobile phase B*: *methanol R*, 0.1 per cent *V/V* solution of *anhydrous formic acid R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	100	0
8 - 20	100 → 0	0 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
20 - 25	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 50 µL.

Autosampler Set at 4 °C.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to mercaptopurine (retention time = about 6 min): impurity B = about 0.3; impurity A = about 0.5; impurity D = about 3.5.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurities B and A.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 0.25;

— for impurities A and B, use the concentration of the corresponding impurity in reference solution (a);

— for impurities other than A and B, use the concentration of mercaptopurine monohydrate in reference solution (b).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *impurities B, D*: for each impurity, maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

10.0 per cent to 12.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.100 g in 50 mL of *dimethylformamide R*. Titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M tetrabutylammonium hydroxide* is equivalent to 15.22 mg of $C_5H_4N_4S$.

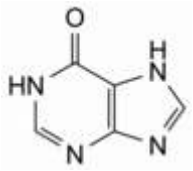
STORAGE

Protected from light.

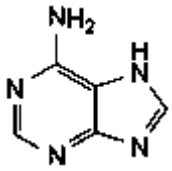
IMPURITIES

Specified impurities *A, B, D.*

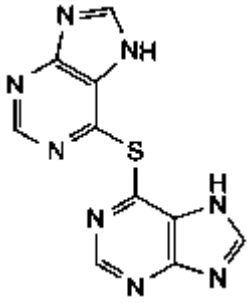
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



A. 1,7-dihydro-6*H*-purin-6-one (hypoxanthine),



B. 7*H*-purin-6-amine (adenine),



C. 6,6′-sulfanediyldi-7*H*-purine,

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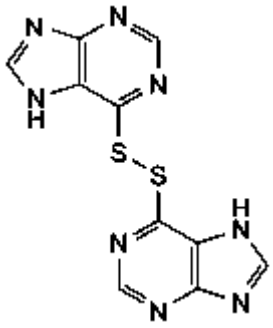

D. 6,6′-disulfanediyldi-7*H*-purine.

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Mercaptopurine Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Thiopurine cytotoxic.

DEFINITION

Mercaptopurine Oral Suspension is a suspension of Mercaptopurine Monohydrate in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of mercaptopurine monohydrate, $C_5H_4N_4S,H_2O$

90.0 to 110.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. Shake a quantity of the oral suspension containing 50 mg of Mercaptopurine Monohydrate with a mixture of 20 mL of *water* and 0.5 mL of 5M *sodium hydroxide* for not more than 5 minutes, add sufficient *water* to produce 100 mL, mix and filter. Dilute a portion of the filtrate with sufficient *0.1M hydrochloric acid* to give a final concentration of 0.0005% w/v of Mercaptopurine Monohydrate. The *light absorption* of the resulting solution, Appendix II B, exhibits a maximum at 325 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.0, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions, using 900 mL of 0.1M *hydrochloric acid* as the dissolution medium and rotating the paddle at 50 revolutions per minute. Use a volume of the oral suspension containing one dose.

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 10 mL of a mixture of equal volumes of *methanol* and *water* to a weighed quantity of the oral suspension containing 15 mg of Mercaptopurine Monohydrate, mix with the aid of ultrasound for 15 minutes, shake for 1 hour and add sufficient of the mixture of equal volumes of *methanol* and *water* to produce 100 mL.

(2) 0.015% w/v of *mercaptopurine BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS 5 µm is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 328 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of *water* containing 0.1% w/v of *sodium heptanesulfonate monohydrate* and 0.3% w/v of *sulfuric acid*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_5H_4N_4S,H_2O$, weight in volume, using the declared content of $C_5H_4N_4S,H_2O$ in *mercaptopurine BPCRS*.

STORAGE

Mercaptopurine Oral Suspension should be protected from light.

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Mercaptopurine Tablets

General Notices

Action and use

Thiopurine cytotoxic.

DEFINITION

Mercaptopurine Tablets contain Mercaptopurine Monohydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mercaptopurine monohydrate, $C_5H_4N_4S,H_2O$

90.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Mercaptopurine Monohydrate with 20 mL of *absolute ethanol*, filter and evaporate to dryness under reduced pressure. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of mercaptopurine *(RS 426)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using the following conditions.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 0.1M *hydrochloric acid* as the dissolution medium at a temperature of 37°.

Withdraw a sample of 10 mL of the medium and filter. Measure the *absorbance* of the filtrate, Appendix II B, diluted with the dissolution medium, if necessary, at the maximum at 325 nm using dissolution medium in the reference cell. Measure the *absorbance* of a suitable solution of *mercaptopurine BPCRS* in the dissolution medium using the declared content of $C_5H_4N_4S,H_2O$ in *mercaptopurine BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Add a quantity of the powdered tablets containing 0.25 g of Mercaptopurine Monohydrate to 80 mL of 0.02M *methanolic sodium hydroxide* in a 100 mL volumetric flask, mix with the aid of ultrasound for 10 minutes, dilute to 100 mL and filter through a GF/F filter (Whatman Autotop is suitable). Dilute 1 volume of the resulting solution to 20 volumes with 0.1% v/v of *anhydrous formic acid*.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.1% w/v of *anhydrous formic acid* and further dilute 1 volume of the resulting solution to 10 volumes with 0.1% w/v of *anhydrous formic acid*.

(3) 0.025% w/v of *hypoxanthine* in 0.02M *methanolic sodium hydroxide* diluted to 0.00025% w/v with 0.1% v/v of *anhydrous formic acid*.

(4) 0.03% w/v of *bis-(1,7-dihydro-6H-purine)-6,6-disulfide BPCRS* in 0.02M *methanolic sodium hydroxide* and dilute to 0.0003% w/v with 0.1% v/v of *anhydrous formic acid*.

(5) Dissolve 25 mg of *mercaptopurine impurity standard BPCRS* in 10 mL of 0.02M *methanolic sodium hydroxide*. Dilute 1 volume to 50 volumes with 0.1% v/v of *anhydrous formic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped phenylethyl silica gel for chromatography* (4 µm) (Phenomenex Synergi Polar RP is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution and prepare the samples immediately before injection.

MOBILE PHASE

Mobile phase A 2 volumes of *methanol* and 98 volumes of 0.1% v/v of *anhydrous formic acid*.

Mobile phase B 50 volumes of *methanol* and 50 volumes of 0.1% v/v of *anhydrous formic acid*.

Time (minutes)	Mobile phase A % v/v	Mobile phase B % v/v	Comments
0 -8	100	0	isocratic
8 - 20	100→0	0→100	linear gradient
20 - 25	0	100	isocratic
25 - 27	0→100	100→0	linear gradient
27 - 30	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless there is baseline resolution between the principal peaks corresponding to thioguanine, hypoxanthine and adenine in the chromatogram obtained with solution (5).

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to hypoxanthine is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (2.0%);

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the area of any peak corresponding to bis-(1,7-dihydro-6*H*-purine)-6,6-disulfide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add a quantity of the powdered tablets, containing 50 mg of Mercaptopurine Monohydrate in 100 mL of 0.02M *methanolic sodium hydroxide*, mix with the aid of ultrasound for 10 minutes and filter through a GF/F filter (Whatman Autotop is suitable). Dilute 1 volume to 20 volumes with 0.1% v/v *anhydrous formic acid*.
(2) 0.50% w/v of *mercaptopurine BPCRS* in 0.02M *methanolic sodium hydroxide* diluted to 0.0025% w/v with 0.1% v/v of *anhydrous formic acid*.
(3) Dissolve 25 mg of *mercaptopurine impurity standard BPCRS* in 10 mL of 0.02M *methanolic sodium hydroxide*. Dilute 1 volume to 50 volumes with 0.1% v/v of *anhydrous formic acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but with isocratic elution and the mobile phase described below.

MOBILE PHASE

2 volumes of *methanol* and 98 volumes of 0.1% v/v of *anhydrous formic acid*.

SYSTEM SUITABILITY

The test is not valid unless there is baseline resolution between the principal peaks corresponding to thioguanine, hypoxanthine and adenine in the chromatogram obtained with solution (3).

DETERMINATION OF CONTENT

Calculate the total content of mercaptopurine monohydrate, $C_5H_4N_4S,H_2O$, in the tablets using the chromatogram obtained and the declared content of $C_5H_4N_4S,H_2O$ in *mercaptopurine BPCRS*.

STORAGE

Mercaptopurine Tablets should be protected from light.

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Mercuric Chloride

General Notices

(Ph. Eur. monograph 0120)

$HgCl_2$ 271.5 *7487-94-7*

Ph Eur

DEFINITION

Content

99.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless or white or almost white crystals or heavy crystalline masses.

Solubility

Soluble in water and in glycerol, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives reaction (a) of chlorides (*2.3.1*).

B. Solution S (see Tests) gives the reactions of mercury (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R*. The solution is red. Add 0.5 g of *sodium chloride R*. The solution becomes yellow. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour to red.

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Mercurous chloride

Dissolve 1.0 g in 30 mL of *ether R*. The solution shows no opalescence.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 2.00 g by drying *in vacuo* for 24 h.

ASSAY

Dissolve 0.500 g in 100 mL of *water R*. Add 20.0 mL of *0.1 M sodium edetate* and 5 mL of *buffer solution pH 10.9 R*. Allow to stand for 15 min. Add 0.1 g of *mordant black 11 triturate R* and titrate with *0.1 M zinc sulfate* until the colour changes to purple. Add 3 g of *potassium iodide R*, allow to stand for 2 min, add a further 0.1 g of *mordant black 11 triturate R* and titrate with *0.1 M zinc sulfate*.

1 mL of *0.1 M zinc sulfate* used in the second titration is equivalent to 27.15 mg of $HgCl_2$.

STORAGE

Protected from light.

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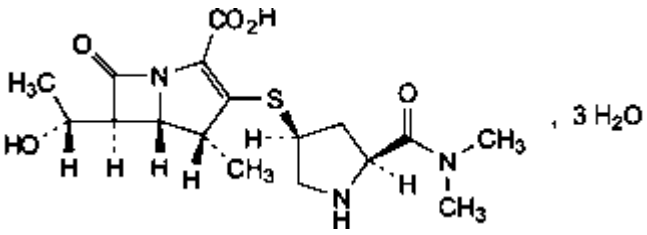
Meropenem Trihydrate

General Notices

(Ph. Eur. monograph 2234)



$C_{17}H_{25}N_3O_5S,3H_2O$ 437.5 *119478-56-7*

Action and use

Carbapenem antibacterial.

Ph Eur

DEFINITION

(4*R*,5*S*,6*S*)-3-[[(3*S*,5*S*)-5-[(Dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Semi-synthetic product derived from a fermentation product, or synthetic product.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or light yellow, crystalline powder.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

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Comparison *meropenem trihydrate CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 1.0 g in 20 mL of a 50 g/L solution of *sodium hydrogen carbonate R*.

pH (*2.2.3*)

4.0 to 6.0.

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-21 to -17 (anhydrous substance).

Dissolve 0.125 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare test solutions (a) and (b) and reference solution (c) immediately before use. Prepare and store reference solution (a) at 4 °C and use within 6 h.*

Solvent mixture To 1.0 mL of *triethylamine R* add 900 mL of *water for chromatography R*. Adjust to pH 5.0 with *dilute phosphoric acid R* and dilute to 1000.0 mL with *water for chromatography R*.

Test solution (a) Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) In order to prepare impurities A and B *in-situ*, heat 10 mL of test solution (a) to 60 °C for about 20 min or, alternatively, allow 10 mL of test solution (a) to stand at room temperature for about 8 h.

Reference solution (c) Dissolve 50.0 mg of *meropenem trihydrate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

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Mobile phase acetonitrile R1, solvent mixture (7:100 *V/V*).

Flow rate 1.6 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Run time 4 times the retention time of meropenem.

Relative retention With reference to meropenem (retention time = about 7 min): impurity A = about 0.5; impurity B = about 2.2.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and meropenem.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.6;

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than A and B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

For meropenem trihydrate produced by a fully synthetic process:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Water (*2.5.12*)

11.4 per cent to 13.4 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

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Less than 0.125 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{17}H_{25}N_3O_5S$ taking into account the assigned content of *meropenem trihydrate CRS*.

STORAGE

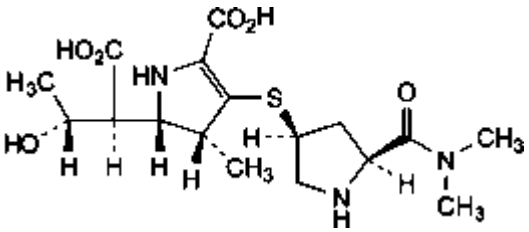
If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

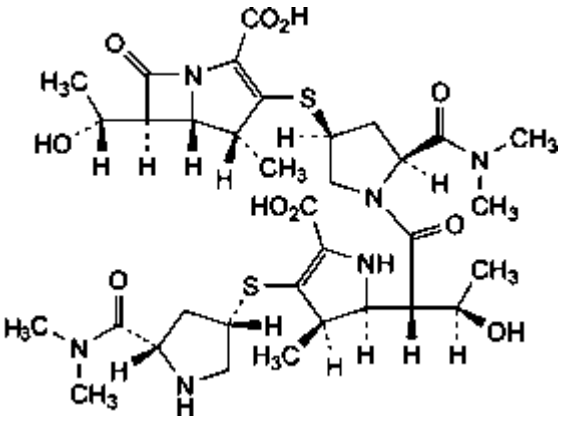
The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, B.*



A. (4*R*,5*S*)-5-[(1*S*,2*R*)-1-carboxy-2-hydroxypropyl]-3-[[(3*S*,5*S*)-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-4-methyl-4,5-dihydro-1*H*-pyrrole-2-carboxylic acid,



B. (4*R*,5*S*,6*S*)-3-[[(3*S*,5*S*)-1-[(2*S*,3*R*)-2-[(2*S*,3*R*)-5-carboxy-4-[[(3*S*,5*S*)-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-3-methyl-2,3-dihydro-1*H*-pyrrol-2-yl]-3-hydroxybutanoyl]-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-

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azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

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Mesalazine

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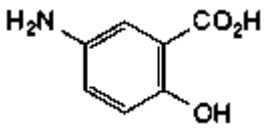

$C_7H_7NO_3$ 153.1 *89-57-6*

Action and use

Aminosalicylate; treatment of ulcerative colitis.

Preparations

Mesalazine Enema

Mesalazine Foam Enema

Mesalazine Prolonged-release Granules

Mesalazine Suppositories

Mesalazine Gastro-resistant Tablets

Mesalazine Prolonged-release Tablets

Ph Eur

DEFINITION

5-Amino-2-hydroxybenzoic acid.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Almost white or light grey or light pink powder or crystals.

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Solubility

Very slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in 10 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 5.0 mL of this solution to 200.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range 210-250 nm.

Absorption maximum At about 230 nm.

Specific absorbance at the absorption maximum 430 to 450.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *mesalazine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of a mixture of equal volumes of *glacial acetic acid R* and *water R* and dilute to 10.0 mL with *methanol R*.

Reference solution Dissolve 25 mg of *mesalazine CRS* in 5 mL of a mixture of equal volumes of *glacial acetic acid R* and *water R* and dilute to 10.0 mL with *methanol R*.

Plate A suitable silica gel as the coating substance.

Mobile phase *glacial acetic acid R*, *methanol R*, *methyl isobutyl ketone R* (10:40:50 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

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TESTS

Appearance of solution

Maintain the solutions at 40 °C during preparation and measurements Dissolve 0.5 g in a 103.0 g/L solution of *hydrochloric acid R* and dilute to 20 mL with the same solution. The solution is clear (*2.2.1*). Immediately measure the absorbance (*2.2.25*) of the solution at 440 nm and 650 nm. The absorbance is not greater than 0.15 at 440 nm and 0.10 at 650 nm.

Reducing substances

Dissolve 0.10 g in *dilute hydrochloric acid R* and dilute to 25 mL with the same solvent. Add 0.2 mL of *starch solution R* and 0.25 mL of *0.01 M iodine*. Allow to stand for 2 min. The solution is blue or violet-brown.

Impurities A and C

Liquid chromatography (*2.2.29*). *Prepare the solutions and mobile phases immediately before use.*

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 5.0 mg of *mesalazine impurity C CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 10.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 25.0 mL with mobile phase A.

Reference solution (c) Dissolve 5.0 mg of *mesalazine impurity A CRS* in mobile phase A and dilute to 250.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A.

Reference solution (d) Dilute 1 mL of the test solution to 200 mL with mobile phase A. To 5 mL of this solution add 5 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *phosphoric acid R* and 2.2 g of *perchloric acid R* in *water for chromatography R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: dissolve 1.0 g of *phosphoric acid R* and 1.7 g of *perchloric acid R* in *acetonitrile R1* and dilute to 1000 mL with the same solvent;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	100	0

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 – 25	100 → 40	0 → 60

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to mesalazine (retention time = about 9 min): impurity A = about 0.5; impurity C = about 0.9.

System suitability Reference solution (d):

— *resolution*: minimum 3.0 between the peaks due to impurity C and mesalazine.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (200 ppm);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (200 ppm).

Impurity K

Liquid chromatography (2.2.29).

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution Dissolve 27.8 mg of *aniline hydrochloride R* (equivalent to 20.0 mg of impurity K) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.20 mL of the solution to 20.0 mL with the mobile phase. Dilute 0.20 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 15 volumes of *methanol R2* and 85 volumes of a solution containing 0.47 g/L of *disodium hydrogen phosphate dihydrate R* and 1.41 g/L of *potassium dihydrogen phosphate R* previously adjusted to pH 8.0 with a 42 g/L solution of *sodium hydroxide R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 50 µL.

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Run time 1.5 times the retention time of impurity K.

Retention time Impurity K = about 14 min.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 10 for the principal peak.

Limit:

— *impurity K*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (10 ppm).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solution A 1.03 g/L solution of *hydrochloric acid R*.

Test solution Dissolve 10.0 mg of the substance to be examined in solution A using sonication and dilute to 10.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 5 mg of *mesalazine for system suitability CRS* (containing impurities F, J and P) in solution A and dilute to 5 mL with solution A.

Reference solution (c) Dissolve 5 mg of *4-aminosalicylic acid R* (impurity E), 5 mg of *2,5-dihydroxybenzoic acid R* (impurity G), 15 mg of *salicylic acid R* (impurity H), 5 mg of *2-chlorobenzoic acid R* (impurity L), 5 mg of *2-chloro-5-nitrobenzoic acid R* (impurity M), 10 mg of *sulfanilic acid R* (impurity O) and 5 mg of *3-nitrosalicylic acid R* (impurity R) in solution A and dilute to 100 mL with solution A. Dilute 1 mL of the solution to 50 mL with solution A.

Reference solution (d) Dissolve 3.0 mg of *2-chlorobenzoic acid R* (impurity L) in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 100.0 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 6.9 g of *sodium dihydrogen phosphate monohydrate R* in about 950 mL of *water for chromatography R*, adjust to pH 6.2 with *dilute sodium hydroxide solution R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*, mobile phase A (40:60 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	100	0
8 - 20	100 → 85	0 → 15
20 - 40	85 → 25	15 → 75
40 - 60	25 → 0	75 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *mesalazine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities F, J and P; use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities E, G, H, L, M, O and R.

Relative retention With reference to mesalazine (retention time = about 6 min): impurity O = about 0.5; impurity J = about 0.6; impurity E = about 0.8; impurity F = about 1.36; impurity G = about 1.44; impurity P = about 1.5; impurity L = about 2.0; impurity M = about 3.3; impurity H = about 3.5; impurity R = about 5.1.

System suitability:

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity L in the chromatogram obtained with reference solution (d).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 1.3; impurity G = 1.4; impurity H = 1.4; impurity J = 2.0; impurity L = 4.5; impurity M = 1.7; impurity O = 0.6; impurity P = 0.6; impurity R = 1.3;

— *impurity H*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities F, J, O, P*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurities E, G, L, M, R*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

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— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Chlorides

Maximum 0.1 per cent.

Dissolve 1.50 g in 50 mL of *anhydrous formic acid R*. Add 100 mL of *water R* and 5 mL of *dilute nitric acid R*. Titrate with *0.005 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.005 M silver nitrate* is equivalent to 0.1773 mg of Cl.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Shake 1.0 g with 20 mL of *distilled water R* for 1 min and filter. 15 mL of the filtrate complies with the test.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 50.0 mg in 100 mL of boiling *water R*. Cool rapidly to room temperature and titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 15.31 mg of $C_7H_7NO_3$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, C, E, F, G, H, J, K, L, M, O, P, R.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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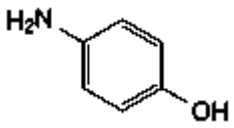
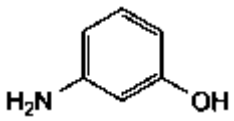
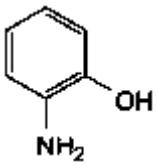
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, I, N, Q, S.*



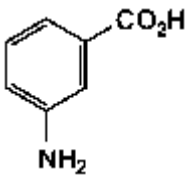
A. 4-aminophenol,



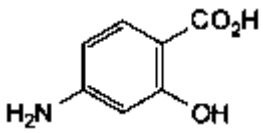
B. 3-aminophenol,



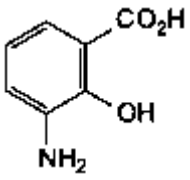
C. 2-aminophenol,



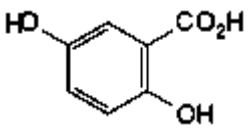
D. 3-aminobenzoic acid,



E. 4-amino-2-hydroxybenzoic acid (4-aminosalicylic acid),



F. 3-amino-2-hydroxybenzoic acid (3-aminosalicylic acid),



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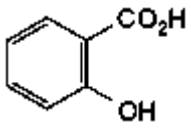
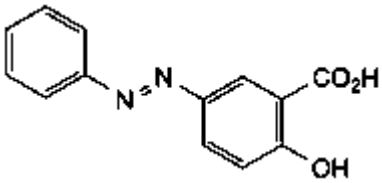
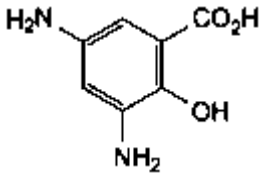
G. 2,5-dihydroxybenzoic acid,



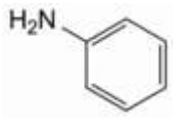
H. 2-hydroxybenzoic acid (salicylic acid),



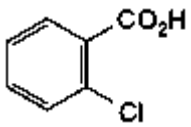
I. 2-hydroxy-5-(phenyldiazenyl)benzoic acid (phenylazosalicylic acid),



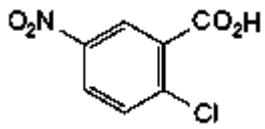
J. 3,5-diamino-2-hydroxybenzoic acid (3,5-diaminosalicylic acid),



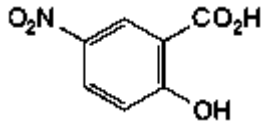
K. aniline,



L. 2-chlorobenzoic acid,



M. 2-chloro-5-nitrobenzoic acid,



N. 2-hydroxy-5-nitrobenzoic acid (5-nitrosalicylic acid),

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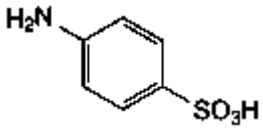
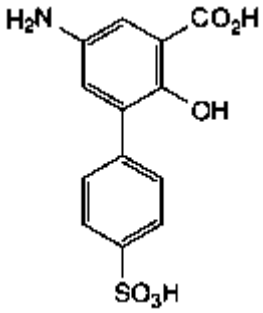
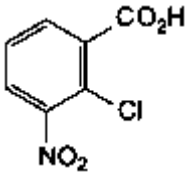


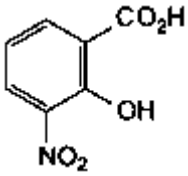
O. 4-aminobenzenesulfonic acid (sulfanilic acid),



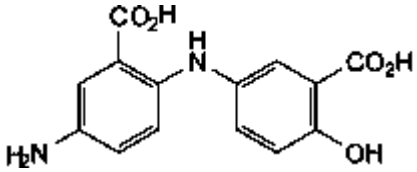
P. 5-amino-2-hydroxy-3-(4-sulfophenyl)benzoic acid (3-(4-sulfophenyl)-5-aminosalicylic acid),



Q. 2-chloro-3-nitrobenzoic acid,



R. 2-hydroxy-3-nitrobenzoic acid (3-nitrosalicylic acid),



S. 2-hydroxy-5-[(2-carboxy-4-aminophenyl)amino]benzoic acid.

Ph Eur

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Mesalazine Enema

General Notices

Mesalazine Rectal Suspension

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Mesalazine Enema is a *rectal suspension* containing Mesalazine in a suitable vehicle.

The enema complies with the requirements stated under Rectal Preparations and with the following requirements.

Content of mesalazine, $C_7H_7NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Filter a quantity of the enema containing 1.0 g of Mesalazine and discard the filtrate. Dry the residue at 110°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of mesalazine *(RS 454)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix a quantity of the enema containing 1 g of Mesalazine with 700 mL of 0.01M *hydrochloric acid* for 10 minutes with the aid of ultrasound, add sufficient 0.01M *hydrochloric acid* to produce 1 L, mix and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.01M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 10 volumes with 0.01M *hydrochloric acid*.

(3) 0.1% w/v of *mesalazine for system suitability EPCRS* in 0.01M *hydrochloric acid*.

(4) 0.0001% w/v each of *4-aminosalicylic acid* (impurity E), *2,5-dihydroxybenzoic acid* (impurity G), *2-chlorobenzoic acid* (impurity L), *2-chloro-5-nitrobenzoic acid* (impurity M), *5-nitrosalicylic acid* (impurity N), *sulfanilic acid* (impurity O), *3-nitrosalicylic acid* (impurity R) and 0.0003% w/v of *salicylic acid* (impurity H) in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 20	100 → 85	0 → 15	linear gradient
20 - 40	85 → 25	15 → 75	linear gradient
40 - 60	25 → 0	75 → 100	linear gradient
60 - 61	0 → 100	100 → 0	linear gradient
61 - 70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 6 minutes) are: impurity O, about 0.55; impurity J, about 0.6; impurity E, about 0.8; impurity F, about 1.36; impurity G, about 1.4; impurity P, about 1.5; impurity L, about 2.0; impurity M, about 3.3; impurity H, about 3.5; impurity R, about 5.1 and impurity N, about 5.5.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

LIMITS

Use the chromatogram supplied with *mesalazine for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify any peaks due to impurities F, J and P and the chromatogram obtained with solution (4) to identify any peaks due to impurities E, G, H, L, M, N, O and R, in the chromatogram obtained with solution (1). Multiply the area of these peaks by the corresponding correction factors:

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impurity E, 1.3; impurity G, 1.4; impurity H, 1.4; impurity J, 2.0; impurity L, 4.5; impurity M, 1.7; impurity O, 0.6; impurity P, 0.6; impurity R, 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E, F, G, J, L, M, P or R is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Impurity C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and freshly prepared mobile phases.

(1) To a weighed quantity of the enema containing 1 g of Mesalazine, add 400 mL of mobile phase A and mix for 10 minutes with the aid of ultrasound with occasional shaking. Add sufficient mobile phase A to produce 1 L, mix and filter through a 0.45-µm membrane filter.
(2) 0.00002% w/v of *2-aminophenol* (impurity C) in mobile phase A.
(3) To 1 volume of solution (1) add sufficient of mobile phase A to produce 200 volumes, mix 1 volume of this solution with 1 volume of 0.0005% w/v of *2-aminophenol* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil C18e is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.22% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* *in* *water*.

Mobile phase B 0.17% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* in *acetonitrile R1*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 25	100 → 40	0 → 60	linear gradient
25 - 30	40 → 100	60 → 0	linear gradient
30 - 40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (200 ppm).

Impurity K

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 drops of 1M *sodium hydroxide* to a quantity of the enema containing 50 mg of Mesalazine, add 15 mL of the mobile phase, mix for 20 minutes with the aid of ultrasound, add sufficient of the mobile phase to produce 25 mL and filter through a 0.45-µm membrane filter.
(2) 0.00000278% w/v of *aniline hydrochloride* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP18e is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 205 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

15 volumes of *methanol R2* and 85 volumes of a solution containing 0.141% w/v of *potassium dihydrogen orthophosphate* and 0.047% w/v of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 8.0 with 4.2% w/v of *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of aniline is about 15 minutes.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to aniline (impurity K) is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (10 ppm).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the enema containing 25 mg of Mesalazine, add 15 mL of 0.1M *hydrochloric acid* and mix for 50 minutes with the aid of ultrasound, with additional vortex mixing at 10 minute intervals. Add sufficient 0.1M *hydrochloric acid* to produce 25 mL, mix and filter. To 1 volume of the filtrate add sufficient 0.1M *hydrochloric acid* to produce 50 volumes.

(2) 0.002% w/v of *mesalazine BPCRS* prepared by dissolving in 0.1M *hydrochloric acid* with the aid of ultrasound.

(3) Prepare a 0.01% w/v solution of *3-aminosalicylic acid* in 0.1M *hydrochloric acid* and dilute 1 volume of this solution to 100 volumes with a 0.1% w/v solution of *mesalazine BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide solution*.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to 3-aminosalicylic acid and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the enema, Appendix V G, and calculate the content of $C_7H_7NO_3$ in the enema using the declared content of $C_7H_7NO_3$ in *mesalazine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C, D, E, F, G, H, J, K, L, M, N, O, P, Q, R and S listed under Mesalazine.

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Mesalazine Foam Enema

General Notices

Mesalazine Rectal Foam

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Mesalazine Foam Enema is a *rectal foam* containing Mesalazine in a suitable vehicle.

The foam enema complies with the requirements stated under Rectal Preparations and with the following requirements.

Content of mesalazine, $C_7H_7NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Filter a quantity of the foam enema containing 1.0 g of Mesalazine and discard the filtrate. Dry the residue at 110°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of mesalazine *(RS 454)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix for 10 minutes with the aid of ultrasound, a quantity of the foam enema containing 1 g of Mesalazine in 600 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 1 L, mix using a vortex mixer and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.01M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 10 volumes with 0.01M *hydrochloric acid*.

(3) 0.1% w/v of *mesalazine for system suitability EPCRS* in 0.01M *hydrochloric acid*.

(4) 0.0001% w/v each of *4-aminosalicylic acid* (impurity E), *2,5-dihydroxybenzoic acid* (impurity G), *2-chlorobenzoic acid* (impurity L), *2-chloro-5-nitrobenzoic acid* (impurity M), *5-nitrosalicylic acid* (impurity N), *sulfanilic acid* (impurity O), *3-nitrosalicylic acid* (impurity R) and 0.0003% w/v of *salicylic acid* (impurity H) in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 20	100 → 85	0 → 15	linear gradient
20 - 40	85 → 25	15 → 75	linear gradient
40 - 60	25 → 0	75 → 100	linear gradient
60 - 61	0 → 100	100 → 0	linear gradient
61 - 70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 6 minutes) are: impurity O, about 0.55; impurity J, about 0.6; impurity E, about 0.8; impurity F, about 1.36; impurity G, about 1.4; impurity P, about 1.5; impurity L, about 2.0; impurity M, about 3.3; impurity H, about 3.5; impurity R, about 5.1 and impurity N, about 5.5.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

LIMITS

Use the chromatogram supplied with *mesalazine for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify any peaks due to impurities F, J and P and the chromatogram obtained with solution (4) to identify any peaks due to impurities E, G, H,

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L, M, N, O and R in the chromatogram obtained in solution (1). Multiply the area of these peaks by the corresponding correction factors: impurity E, 1.3; impurity G, 1.4; impurity H, 1.4; impurity J, 2.0; impurity L, 4.5; impurity M, 1.7; impurity O, 0.6; impurity P, 0.6; impurity R, 1.3.

the area of any peak corresponding to impurity H is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E, F, G, J, L, M, P or R is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Impurity C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and freshly prepared mobile phase.

(1) To a weighed quantity of the enema containing 1 g of Mesalazine, add 400 mL of mobile phase A and mix for 10 minutes with the aid of ultrasound with occasional shaking. Add sufficient mobile phase A to produce 1 L, mix and filter through a 0.45-µm membrane filter.
(2) 0.00002% w/v of *2-aminophenol* (impurity C) in mobile phase A.
(3) To 1 volume of solution (1) add sufficient of mobile phase A to produce 200 volumes, mix 1 volume of this solution with 1 volume of 0.0005% w/v of *2-aminophenol* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.22% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* *in* *water*.

Mobile phase B 0.17% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* in *acetonitrile R1*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 25	100 → 40	0 → 60	linear gradient
25 - 30	40 → 100	60 → 0	linear gradient
30 - 40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (200 ppm).

Impurity K

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 2 mL of 1M *sodium hydroxide* to a quantity of the foam enema containing 1 g of Mesalazine, add 300 mL of the mobile phase, mix for 20 minutes with the aid of ultrasound, add sufficient of the mobile phase to produce 500 mL and filter through a 0.45-µm membrane filter.

(2) 0.00000278% w/v of *aniline hydrochloride* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 50 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of aniline (impurity K).

MOBILE PHASE

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15 volumes of *methanol* and 85 volumes of a solution containing 0.141% w/v of *potassium dihydrogen orthophosphate* and 0.047% w/v of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 8.0 with 4.2% w/v of *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of aniline is about 15 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to aniline (impurity K) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (10 ppm).

ASSAY

Prepare a mixture of 2 volumes of *methanol* and 5 volumes of *water* (solvent A).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake and invert the container. Dissolve a weighed quantity of the foam containing 1 g of Mesalazine in 250 mL of 1M *methanolic hydrochloric acid* and mix with the aid of ultrasound. Add sufficient 1M *methanolic hydrochloric acid* to produce 500 mL and filter (Whatman GF/A is suitable). Dilute 1 volume of this solution to 10 volumes with solvent A.

(2) Dissolve 20 mg of *mesalazine BPCRS* in 10 mL of 1M *methanolic hydrochloric acid* and mix with the aid of ultrasound. Dilute with a sufficient quantity of solvent A to produce a solution containing 0.02% w/v of Mesalazine.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of a 0.007% w/v solution of *ammonium carbamate* previously adjusted to pH 3.68 with 2M *hydrochloric acid*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the foam enema, Appendix V G, and calculate the content of $C_7H_7NO_3$ using the declared content of $C_7H_7NO_3$ in *mesalazine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C, D, E, F, G, H, J, K, L, M, N, O, P, Q, R and S listed under Mesalazine.

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Mesalazine Gastro-resistant Tablets

General Notices

Gastro-resistant Mesalazine Tablets

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Mesalazine Gastro-resistant Tablets contain Mesalazine. They are made gastro-resistant by gastro-resistant coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mesalazine, $C_7H_7NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity of the powdered tablets containing 25 mg of Mesalazine in 15 mL of 0.01M *hydrochloric acid* for 50 minutes with the aid of ultrasound, with additional vortex mixing at 10 minute intervals; add sufficient 0.01M *hydrochloric acid* to produce 25 mL, mix and filter. To 1 volume of the filtrate add sufficient 0.01M *hydrochloric acid* to produce 50 volumes. The *light absorption*, Appendix II B, in the range 190 to 400 nm exhibits maxima at 302 nm and 232 nm and minima at 258 nm and 219 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix for 10 minutes with the aid of ultrasound, a quantity of the powdered tablets containing 50 mg of Mesalazine in 30 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.01M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 10 volumes with 0.01M *hydrochloric acid*.

(3) 0.1% w/v of *mesalazine for system suitability EPCRS* in 0.01M *hydrochloric acid*.

(4) 0.0001% w/v each of *4-aminosalicylic acid* (impurity E), *2,5-dihydroxybenzoic acid* (impurity G), *2-chlorobenzoic acid* (impurity L), *2-chloro-5-nitrobenzoic acid* (impurity M), *5-nitrosalicylic acid* (impurity N), *sulfanilic acid* (impurity O), *3-nitrosalicylic acid* (impurity R) and

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0.0003% w/v of *salicylic acid* (impurity H) in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 20	100 → 85	0 → 15	linear gradient
20 - 40	85 → 25	15 → 75	linear gradient
40 - 60	25 → 0	75 → 100	linear gradient
60 - 61	0 → 100	100 → 0	linear gradient
61 - 70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 6 minutes) are: impurity O, about 0.55; impurity J, about 0.6; impurity E, about 0.8; impurity F, about 1.36; impurity G, about 1.4; impurity P, about 1.5; impurity L, about 2.0; impurity M, about 3.3; impurity H, about 3.5; impurity R, about 5.1 and impurity N, about 5.5.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

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LIMITS

Use the chromatogram supplied with *mesalazine for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify any peaks due to impurities F, J and P and the chromatogram obtained with solution (4) to identify any peaks due to impurities E, G, H, L, M, N, O and R, in the chromatogram obtained in solution (1). Multiply the area of these peaks by the corresponding correction factors: impurity E, 1.3; impurity G, 1.4; impurity H, 1.4; impurity J, 2.0; impurity L, 4.5; impurity M, 1.7; impurity O, 0.6; impurity P, 0.6; impurity R, 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salicylic acid is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity H is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E, F, G, J, L, M, P or R is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Impurities A and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and freshly prepared mobile phases.

(1) Mix a quantity of the powdered tablets containing 50 mg of Mesalazine in 30 mL of mobile phase A for 10 minutes with the aid of ultrasound, add sufficient mobile phase A to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane filter.
(2) Mix 1 volume of a 0.002% w/v solution of *4-aminophenol* (impurity A) in mobile phase A with 1 volume of 0.002% w/v of *2-aminophenol* (impurity C) in mobile phase A, add sufficient mobile phase A to produce 100 volumes and mix.
(3) To 1 volume of solution (1) add sufficient mobile phase A to produce 200 volumes, mix 1 volume of this solution with 1 volume of 0.0005% w/v *2-aminophenol* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

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MOBILE PHASE

Mobile phase A 0.22% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* *in* *water*.

Mobile phase B 0.17% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* in *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 25	100 → 40	0 → 60	linear gradient
25 - 30	40 → 100	60 → 0	linear gradient
30 - 40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A or impurity C is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (200 ppm of each).

Impurity K

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 2 mL of 0.01M *sodium hydroxide* and 5 drops of 1M *sodium hydroxide* to a quantity of the powdered tablets containing 50 mg of Mesalazine, add 15 mL of the mobile phase and mix for 20 minutes with the aid of ultrasound, add sufficient of the mobile phase to produce 25 mL and filter through a 0.45-µm membrane filter.

(2) 0.00000278% w/v of *aniline hydrochloride* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP18e is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 50 µL of each solution.

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MOBILE PHASE

15 volumes of *methanol* and 85 volumes of a solution containing 0.141% w/v of *potassium dihydrogen orthophosphate* and 0.047% w/v of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 8.0 with 4.2% w/v *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of aniline is about 15 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to aniline (impurity K) is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (10 ppm).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 25 mg of Mesalazine in 15 mL of 0.1M *hydrochloric acid* for 50 minutes with the aid of ultrasound, with additional vortex mixing at 10 minute intervals; add sufficient 0.1M *hydrochloric acid* to produce 25 mL, mix and filter. To 1 volume of the filtrate add sufficient 0.1M *hydrochloric acid* to produce 50 volumes.
(2) 0.002% w/v of *mesalazine BPCRS* prepared by dissolving in 0.1M *hydrochloric acid* with the aid of ultrasound.
(3) Prepare a 0.01% w/v solution of *3-aminosalicylic acid* in 0.1M *hydrochloric acid* and dilute 1 volume of this solution to 100 volumes with a 0.1% w/v solution of *mesalazine BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide solution*.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to 3-aminosalicylic acid and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_7NO_3$ in the tablets using the declared content of $C_7H_7NO_3$ in *mesalazine BPCRS*.

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IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mesalazine.

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Mesalazine Prolonged-release Granules

General Notices

Mesalazine Prolonged-release Granules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Mesalazine Prolonged-release Granules contain Mesalazine. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Mesalazine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The granules comply with the requirements stated under Granules and with the following requirements.

Content of mesalazine, $C_7H_7NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Boil a quantity of the powdered granules containing 1.0 g of Mesalazine with 50 mL of *water* for 1 minute and filter the hot supernatant fluid. Cool the solution to room temperature, allow to stand, filter and dry the crystals at 110°. The *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of mesalazine *(RS 454)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix for 10 minutes with the aid of ultrasound a quantity of the powdered granules containing 50 mg of Mesalazine in 30 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane filter.

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(2) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 10 volumes with 0.1M *hydrochloric acid*.

(3) 0.1% w/v of *mesalazine for system suitability EPCRS* in 0.01M *hydrochloric acid*.

(4) 0.0001% w/v each of *4-aminosalicylic acid* (impurity E), *2,5-dihydroxybenzoic acid* (impurity G), *2-chlorobenzoic acid* (impurity L), *2-chloro-5-nitrobenzoic acid* (impurity M), *5-nitrosalicylic acid* (impurity N), *sulfanilic acid* (impurity O), *3-nitrosalicylic acid* (impurity R) and 0.0003% w/v of *salicylic acid* (impurity H) in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 20	100 → 85	0 → 15	linear gradient
20 - 40	85 → 25	15 → 75	linear gradient
40 - 60	25 → 0	75 → 100	linear gradient
60 - 61	0 → 100	100 → 0	linear gradient
61 - 70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 6 minutes) are: impurity O, about 0.55; impurity J, about 0.6; impurity E, about 0.8; impurity F, about 1.36; impurity G, about 1.4; impurity P, about 1.5; impurity L, about 2.0; impurity M, about 3.3; impurity H, about 3.5; impurity R, about 5.1 and impurity N, about 5.5.

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SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

LIMITS

Use the chromatogram supplied with *mesalazine for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify any peaks due to impurities F, J and P and the chromatogram obtained with solution (4) to identify any peaks due to impurities E, G, H, L, M, N, O and R, in the chromatogram obtained in solution (1). Multiply the area of these peaks by the corresponding correction factors: impurity E, 1.3; impurity G, 1.4; impurity H, 1.4; impurity J, 2.0; impurity L, 4.5; impurity M, 1.7; impurity O, 0.6; impurity P, 0.6; impurity R, 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E, F, G, J, L, M, P or R is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5 %).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Impurities A and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and freshly prepared mobile phases.

(1) Mix for 10 minutes with the aid of ultrasound, a quantity of the powdered granules containing 50 mg of Mesalazine in 30 mL of mobile phase A, add sufficient mobile phase A to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane filter.
(2) Mix 1 volume of a 0.002% w/v solution of *4-aminophenol* (impurity A) in mobile phase A with 1 volume of 0.002% w/v of *2-aminophenol* (impurity C) in mobile phase A, add sufficient mobile phase A to produce 100 volumes and mix.
(3) To 1 volume of solution (1) add sufficient of mobile phase A to produce 200 volumes, mix 1 volume of this solution with 1 volume of 0.0005% w/v of *2-aminophenol* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.

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(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.22% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* *in* *water*.

Mobile phase B 0.17% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* in *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 25	100 → 40	0 → 60	linear gradient
25 - 30	40 → 100	60 → 0	linear gradient
30 - 40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (200 ppm);

the area of any peak corresponding to impurity C is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (200 ppm).

Impurity K

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 2 mL of 0.01M *sodium hydroxide* and 5 drops of 1M *sodium hydroxide* to a quantity of the powdered granules containing 50 mg of Mesalazine, add 15 mL of the mobile phase and mix for 20 minutes with the aid of ultrasound, add sufficient of the mobile phase to produce 25 mL and filter through a 0.45 µm membrane filter.

(2) 0.00000278% w/v of *aniline hydrochloride* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP18e is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

15 volumes of *methanol* and 85 volumes of a solution containing 0.141% w/v of *potassium dihydrogen orthophosphate* and 0.047% w/v of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 8.0 with 4.2% w/v of *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of aniline is about 15 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to aniline (impurity K) is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (10 ppm).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered granules containing 25 mg of Mesalazine in 15 mL of 0.1M *hydrochloric acid* for 50 minutes with the aid of ultrasound, with additional vortex mixing at 10 minute intervals; add sufficient 0.1M *hydrochloric acid* to produce 25 mL, mix and filter. To 1 volume of the filtrate add sufficient 0.1M *hydrochloric acid* to produce 50 volumes.

(2) 0.002% w/v of *mesalazine BPCRS* prepared by dissolving in 0.1M *hydrochloric acid* with the aid of ultrasound.

(3) Prepare a 0.01% w/v of *3-aminosalicylic acid* (impurity F) in 0.1M *hydrochloric acid* and dilute 1 volume of this solution to 100 volumes with a 0.1% w/v solution of *mesalazine BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide solution*.

SYSTEM SUITABILITY

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In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_7NO_3$ in the granules using the declared content of $C_7H_7NO_3$ in *mesalazine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mesalazine.

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Mesalazine Prolonged-release Tablets

General Notices

Prolonged-release Mesalazine Tablets

Mesalazine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Mesalazine Prolonged-release Tablets contain Mesalazine. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Mesalazine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mesalazine, $C_7H_7NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Boil a quantity of the powdered tablets containing 1.0 g of Mesalazine with 50 mL of *water* for 1 minute and filter the hot supernatant fluid. Cool the solution to room temperature, allow to stand, filter and dry the crystals at 110°. The *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of mesalazine *(RS 454)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix for 10 minutes with the aid of ultrasound, a quantity of the powdered tablets containing 50 mg of Mesalazine in 30 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane

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filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.01M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 10 volumes with 0.01M *hydrochloric acid*.

(3) 0.1% w/v of *mesalazine for system suitability EPCRS* in 0.01M *hydrochloric acid*.

(4) 0.0001% w/v each of *4-aminosalicylic acid* (impurity E), *2,5-dihydroxybenzoic acid* (impurity G), *2-chlorobenzoic acid* (impurity L), *2-chloro-5-nitrobenzoic acid* (impurity M), *5-nitrosalicylic acid* (impurity N), *sulfanilic acid* (impurity O), *3-nitrosalicylic acid* (impurity R) and 0.0003% w/v of *salicylic acid* (impurity H) in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 20	100 → 85	0 → 15	linear gradient
20 - 40	85 → 25	15 → 75	linear gradient
40 - 60	25 → 0	75 → 100	linear gradient
60 - 61	0 → 100	100 → 0	linear gradient
61 - 70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 6 minutes) are: impurity O, about 0.55; impurity J, about 0.6; impurity E, about 0.8; impurity F, about 1.36; impurity G, about 1.4; impurity P, about 1.5; impurity L, about 2.0; impurity M, about 3.3; impurity H, about 3.5; impurity R, about 5.1 and impurity N, about 5.5.

SYSTEM SUITABILITY

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In the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

LIMITS

Use the chromatogram supplied with *mesalazine for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify any peaks due to impurities F, J and P and the chromatogram obtained with solution (4) to identify any peaks due to impurities E, G, H, L, M, N, O and R, in the chromatogram obtained in solution (1). Multiply the area of these peaks by the corresponding correction factors: impurity E, 1.3; impurity G, 1.4; impurity H, 1.4; impurity J, 2.0; impurity L, 4.5; impurity M, 1.7; impurity O, 0.6; impurity P, 0.6; impurity R, 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E, F, G, J, L, M, P or R is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5 %).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Impurities A and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and freshly prepared mobile phases.

(1) Mix for 10 minutes with the aid of ultrasound, a quantity of the powdered tablets containing 50 mg of Mesalazine in 30 mL of mobile phase A, add sufficient mobile phase A to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane filter.
(2) Mix 1 volume of a 0.002% w/v solution of *4-aminophenol* (impurity A) in mobile phase A with 1 volume of 0.002% w/v of *2-aminophenol* (impurity C) in mobile phase A, add sufficient mobile phase A to produce 100 volumes and mix.
(3) To 1 volume of solution (1) add sufficient of mobile phase A to produce 200 volumes, mix 1 volume of this solution with 1 volume of 0.0005% w/v of *2-aminophenol* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil C18 is suitable).
(b) Use gradient elution and the mobile phases described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.22% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* *in* *water*.

Mobile phase B 0.17% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* in *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 25	100 → 40	0 → 60	linear gradient
25 - 30	40 → 100	60 → 0	linear gradient
30 - 40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (200 ppm);

the area of any peak corresponding to impurity C is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (200 ppm).

Impurity K

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 2 mL of 0.01M *sodium hydroxide* and 5 drops of 1M *sodium hydroxide* to a quantity of the powdered tablets containing 50 mg of Mesalazine, add 15 mL of the mobile phase and mix for 20 minutes with the aid of ultrasound, add sufficient of the mobile phase to produce 25 mL and filter through a 0.45-µm membrane filter.

(2) 0.00000278% w/v of *aniline hydrochloride* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP18e is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

15 volumes of *methanol* and 85 volumes of a solution containing 0.141% w/v of *potassium dihydrogen orthophosphate* and 0.047% w/v of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 8.0 with 4.2% w/v of *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of aniline is about 15 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to aniline (impurity K) is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (10 ppm).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix for 50 minutes with the aid of ultrasound, a quantity of the powdered tablets containing 25 mg of Mesalazine in 15 mL of 0.1M *hydrochloric acid*, with additional vortex mixing at 10 minute intervals; add sufficient 0.1M *hydrochloric acid* to produce 25 mL, mix and filter. To 1 volume of the filtrate add sufficient 0.1M *hydrochloric acid* to produce 50 volumes.

(2) 0.002% w/v of *mesalazine BPCRS* prepared by dissolving in 0.1M *hydrochloric acid* with the aid of ultrasound.

(3) Prepare a 0.01% w/v of *3-aminosalicylic acid* (impurity F) in 0.1M *hydrochloric acid* and dilute 1 volume of this solution to 100 volumes with a 0.1% w/v solution of *mesalazine BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate* the pH of which is adjusted to 6.2 with *dilute sodium hydroxide solution*.

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SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to 3-aminosalicylic acid and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_7NO_3$ in the tablets using the declared content of $C_7H_7NO_3$ in *mesalazine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mesalazine.

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You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Mesalazine Suppositories

General Notices

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Mesalazine Suppositories contain Mesalazine in a suitable suppository basis.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of mesalazine, $C_7H_7NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Boil a quantity of the suppositories containing 1.0 g of Mesalazine with 50 mL of *water* until completely melted and filter the hot supernatant fluid. Cool the solution to room temperature, allow to stand, filter and dry at 110°. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of mesalazine *(RS 454)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound, a quantity of the suppositories containing 1 g of Mesalazine in 750 mL of 0.01M *hydrochloric acid* until the suppositories disintegrate, add sufficient 0.01M *hydrochloric acid* to produce 1 L, mix using a vortex mixer and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.01M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 10 volumes with 0.01M *hydrochloric acid*.

(3) 0.1% w/v of *mesalazine for system suitability EPCRS* in 0.01M *hydrochloric acid*.

(4) 0.0001% w/v each of *4-aminosalicylic acid* (impurity E), *2,5-dihydroxybenzoic acid* (impurity G), *2-chlorobenzoic acid* (impurity L), *2-chloro-5-nitrobenzoic acid* (impurity M), *5-nitrosalicylic acid* (impurity N), *sulfanilic acid* (impurity O), *3-nitrosalicylic acid* (impurity R) and 0.0003% w/v of *salicylic acid* (impurity H) in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 20	100 → 85	0 → 15	linear gradient
20 - 40	85 → 25	15 → 75	linear gradient
40 - 60	25 → 0	75 → 100	linear gradient
60 - 61	0 → 100	100 → 0	linear gradient
61 - 70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 6 minutes) are: impurity O, about 0.55; impurity J, about 0.6; impurity E, about 0.8; impurity F, about 1.36; impurity G, about 1.4; impurity P, about 1.5; impurity L, about 2.0; impurity M, about 3.3; impurity H, about 3.5; impurity R, about 5.1 and impurity N, about 5.5.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

LIMITS

Use the chromatogram supplied with *mesalazine for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify any peaks due to impurities F, J and P and the chromatogram obtained with solution (4) to identify any peaks due to impurities E, G, H,

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L, M, N, O and R, in the chromatogram obtained in solution (1). Multiply the area of these peaks by the corresponding correction factors: impurity E, 1.3; impurity G, 1.4; impurity H, 1.4; impurity J, 2.0; impurity L, 4.5; impurity M, 1.7; impurity O, 0.6; impurity P, 0.6; impurity R, 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E, F, G, J, L, M, P or R is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Impurities A and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and freshly prepared mobile phases.

(1) Cut a suitable number of the suppositories containing 50 mg of Mesalazine into small pieces, add 25 mL of mobile phase A, mix for 10 minutes with the aid of ultrasound and occasional shaking, add sufficient mobile phase A to produce 50 mL, shake for 30 seconds and filter through a 0.45-µm membrane filter.
(2) Mix 1 volume of a 0.002% w/v solution of *4-aminophenol* (impurity A) in mobile phase A with 1 volume of 0.002% w/v of *2-aminophenol* (impurity C) in mobile phase A, add sufficient mobile phase A to produce 100 volumes and mix.
(3) To 1 volume of solution (1) add sufficient of mobile phase A to produce 200 volumes, mix 1 volume of this solution with 1 volume of 0.0005% w/v of *2-aminophenol* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.
When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

MOBILE PHASE

Mobile phase A A solution containing 0.22% w/v *perchloric acid* and 0.1% w/v *orthophosphoric acid* *in* *water*.

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Mobile phase B A solution containing 0.17% w/v *perchloric acid* and 0.1% w/v *orthophosphoric acid* in *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 25	100 → 40	0 → 60	linear gradient
25 - 30	40 → 100	60 → 0	linear gradient
30 - 40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A or impurity C is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (200 ppm of each).

Impurity K

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Cut a suitable number of the suppositories containing 50 mg of Mesalazine into small pieces, add 5 drops of 1M *sodium hydroxide* and 15 mL of the mobile phase, mix for 20 minutes with the aid of ultrasound, add sufficient of the mobile phase to produce 25 mL and filter through a 0.45-µm membrane filter.

(2) 0.00000278% w/v of *aniline hydrochloride* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP18e is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

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15 volumes of *methanol* and 85 volumes of a solution containing 0.141% w/v of *potassium dihydrogen orthophosphate* and 0.047% w/v of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 8.0 with 4.2% w/v of *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of aniline is about 15 minutes

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to aniline (impurity K) is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (10 ppm).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Cut a suitable number of the suppositories containing 100 mg of Mesalazine into small pieces and add 75 mL of 0.1M *hydrochloric acid*, mix for 50 minutes with the aid of ultrasound with additional vortex mixing at 10 minute intervals; add sufficient 0.1M *hydrochloric acid* to produce 100 mL, mix and filter through a 0.45-µm membrane filter. To 1 volume of the filtrate add sufficient 0.1M *hydrochloric acid* to produce 50 volumes.

(2) 0.002% w/v of *mesalazine BPCRS* prepared by dissolving in 0.1M *hydrochloric acid* with the aid of ultrasound.

(3) Prepare a 0.01% w/v of *3-aminosalicylic acid* in 0.1M *hydrochloric acid* and dilute 1 volume of this solution to 100 volumes with a 0.1% w/v solution of *mesalazine BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH to 6.2 with *dilute sodium hydroxide solution*.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to 3-aminosalicylic acid and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_7NO_3$ in the suppositories using the declared content of $C_7H_7NO_3$ in *mesalazine BPCRS*.

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IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mesalazine.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Mesna

General Notices

(Ph. Eur. monograph 1674)

$C_2H_5NaO_3S_2$ 164.2 *19767-45-4*

Action and use

Preventing adverse effects of cyclophosphamide and ifosfamide.

Ph Eur

DEFINITION

Sodium 2-sulfanylethanesulfonate.

Content

96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder, hygroscopic.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of mesna*.

B. It gives reaction (a) of sodium (*2.3.1*).

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TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.0.

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 4.0 mg of *mesna impurity C CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 6.0 mg of *mesna impurity D CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 3.0 mL of the test solution to 10.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 100.0 mL with the mobile phase.

Reference solution (e) Dilute 6 mL of reference solution (c) to 20 mL with the mobile phase. To 10 mL of this solution add 10 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Dissolve 2.94 g of *potassium dihydrogen phosphate R*, 2.94 g of *dipotassium hydrogen phosphate R* and 2.6 g of *tetrabutylammonium hydrogen sulfate R* in about 600 mL of *water for chromatography R*. Adjust to pH 2.3 with *phosphoric acid R*, add 335 mL of *methanol R1* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

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Run time 4 times the retention time of mesna.

Relative retention With reference to mesna (retention time = about 4.8 min): impurities A and B = about 0.6; impurity E = about 0.8; impurity C = about 1.4; impurity D = about 2.3.

System suitability Reference solution (e):

— *resolution*: minimum 3.0 between the peaks due to mesna and impurity C.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of impurities A, B and E by 0.01;

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *impurities A, B, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than one third of the area of the principal peak in the chromatogram obtained with reference solution (d) (0.10 per cent);

— *sum of other impurities*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *disregard limit*: 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.045 per cent).

Chlorides (2.4.4)

Maximum 250 ppm.

Dilute 1 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 300 ppm.

Dilute 5 mL of solution S to 30 mL with *distilled water R*. 15 mL of the solution complies with the test.

Disodium edetate

Maximum 500 ppm.

Dissolve 4.000 g in 90 mL of *water R* and adjust to pH 4.5 using *0.1 M hydrochloric acid*. Add 10 mL of *acetate buffer solution pH 4.5 R* and 50 mL of *2-propanol R*. Add 2 mL of a 0.25 g/L solution of *dithizone R* in *2-propanol R*. Titrate with *0.01 M zinc sulfate* until the colour changes from bluish-grey to pink.

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1 mL of *0.01 M zinc sulfate* is equivalent to 3.72 mg of $C_{10}H_{14}N_2Na_2O_8,2H_2O$.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g under vacuum at 60 °C for 2 h.

ASSAY

Dissolve 0.120 g in 10 mL of *water R*. Add 10 mL of *dilute sulfuric acid R* and 10.0 mL of *0.1 M iodine*. Titrate with *0.1 M sodium thiosulfate* adding 1 mL of *starch solution R* near the endpoint. Carry out a blank titration.

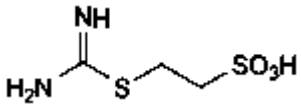
1 mL of *0.1 M sodium thiosulfate* is equivalent to 16.42 mg of $C_2H_5NaO_3S_2$.

STORAGE

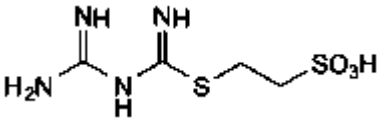
In an airtight container.

IMPURITIES

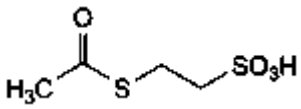
Specified impurities *A, B, C, D, E*.



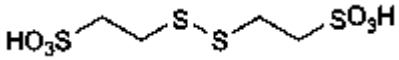
A. 2-(carbamimidoylsulfanyl)ethanesulfonic acid,



B. 2-[[(guanidino)(imino)methyl]sulfanyl]ethanesulfonic acid,



C. 2-(acetylsulfanyl)ethanesulfonic acid,



D. 2,2′-(disulfanediyl)bis(ethanesulfonic acid),

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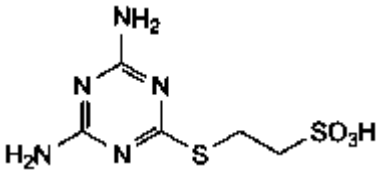

E. 2-(4,6-diamino-1,3,5-triazin-2-yl)sulfanylethanesulfonic acid.

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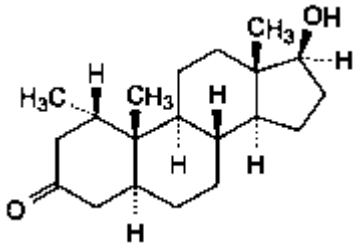
Mesterolone

General Notices

(Ph. Eur. monograph 1730)



$C_{20}H_{32}O_2$ 304.5 *1424-00-6*

Action and use

Androgen.

Ph Eur

DEFINITION

17β-Hydroxy-1α-methyl-5α-androstan-3-one.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone, in ethyl acetate and in methanol.

IDENTIFICATION

A. Melting point (*2.2.14*): 206 °C to 211 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *mesterolone CRS*.

TESTS

Specific optical rotation (*2.2.7*)

+ 20 to + 24 (dried substance).

Dissolve 0.200 g in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Impurity B

Thin-layer chromatography (*2.2.27*).

Solvent mixture *methanol R*, *methylene chloride R* (50:50 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *mesterolone impurity A CRS* in reference solution (a) and dilute to 100 mL with the same solution.

Plate *TLC silica gel plate R*.

Mobile phase *methanol R*, *acetone R*, *toluene R* (2:15:85 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 366 nm; spray with a 200 g/L solution of *toluenesulfonic acid R* in *ethanol (96 per cent) R* and heat at 120 °C for 10 min.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated spots (blue spot due to mesterolone and yellow spot due to impurity A).

Limit:

— *impurity B*: any blue spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *water R*, *acetonitrile R* (20:80 *V/V*).

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Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of *mesterolone CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *mesterolone for system suitability CRS* (containing impurity C) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *acetonitrile R1*, *water for chromatography R*, *methanol R2* (20:40:60 *V/V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Run time 3 times the retention time of mesterolone.

Identification of impurities Use the chromatogram supplied with *mesterolone for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to mesterolone (retention time = about 22 min): impurity C = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity C and mesterolone.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 0.2;

— for each impurity, use the concentration of mesterolone in reference solution (c).

Limits:

— *impurity C*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

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Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

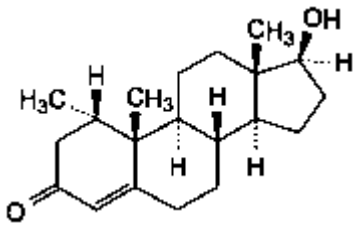
Injection 10 µL of the test solution and reference solution (a).

Calculate the percentage content of $C_{20}H_{32}O_2$ taking into account the assigned content of *mesterolone CRS*.

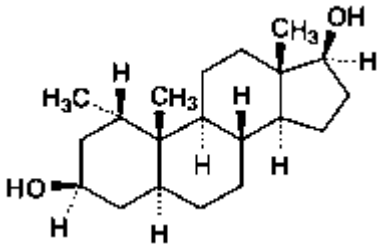
IMPURITIES

Specified impurities *B*, *C*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



A. 17β-hydroxy-1α-methylandrost-4-en-3-one,



B. 1α-methyl-5α-androstane-3β,17β-diol,

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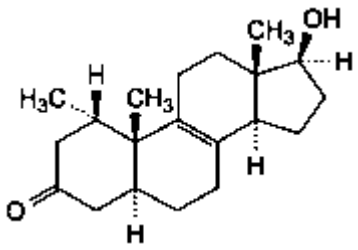

C. 17β-hydroxy-1α-methyl-5α-androst-8-en-3-one.

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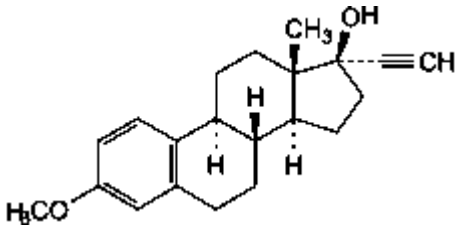
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Mestranol

General Notices

(Ph. Eur. monograph 0509)



$C_{21}H_{26}O_2$ 310.4 *72-33-3*

Action and use

Estrogen.

Ph Eur

DEFINITION

Mestranol contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 3-methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 150 °C to 154 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *mestranol CRS*.

C. Examine the chromatograms obtained in the test for related substances in daylight and in ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour, fluorescence and size to the principal spot in the chromatogram obtained with reference solution (a).

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D. Dissolve about 5 mg in 1 mL of *sulfuric acid R*. A red colour develops with a greenish-yellow fluorescence in ultraviolet light at 365 nm. Add the solution to 10 mL of *water R* and mix. The solution becomes pink and a pink to violet precipitate is formed on standing.

TESTS

Specific optical rotation (*2.2.7*)

Dissolve 0.100 g in *anhydrous pyridine R* and dilute to 10.0 mL with the same solvent. The specific optical rotation is -20 to -24, calculated with reference to the dried substance.

Absorbance (*2.2.25*)

Dissolve 25.0 mg in *alcohol R* and dilute to 25.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *alcohol R*. Examined between 260 nm and 310 nm, the solution shows two absorption maxima, at 279 nm and 288 nm, and a minimum at 286 nm. The specific absorbances at the maxima are 62 to 68 and 59 to 64, respectively.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *chloroform R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *chloroform R*.

Reference solution (a) Dissolve 10 mg of *mestranol CRS* in *chloroform R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1 mL of test solution (b) to 10 mL with *chloroform R*.

Reference solution (c) Dilute 5 mL of reference solution (b) to 10 mL with *chloroform R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *alcohol R* and 90 volumes of *toluene R*. Allow the plate to dry in air until the solvent has evaporated. Heat at 110 °C for 10 min. Spray the hot plate with *alcoholic solution of sulfuric acid R*. Heat again at 110 °C for 10 min. Examine in daylight and in ultraviolet light at 365 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (1.0 per cent) and at most one such spot is more intense than the spot in the chromatogram obtained with reference solution (c) (0.5 per cent).

Loss on drying (*2.2.32*)

Not more than 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.200 g in 40 mL of *tetrahydrofuran R* and add 5 mL of a 100 g/L solution of *silver nitrate R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.04 mg of $C_{21}H_{26}O_2$.

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STORAGE

Store protected from light.

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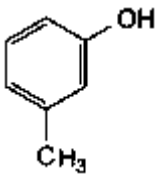
Metacresol

General Notices

(Ph. Eur. monograph 2077)



C_7H_8O 108.1 *108-39-4*

Action and use

Antiseptic; antimicrobial preservative.

Ph Eur

DEFINITION

3-Methylphenol.

CHARACTERS

Appearance

Colourless or yellowish liquid.

Solubility

Sparingly soluble in water, miscible with ethanol (96 per cent) and with methylene chloride.

Relative density

About 1.03.

mp

About 11 °C.

bp

About 202 °C.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of metacresol*.

TESTS

Solution S

Dissolve 1.5 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Freshly prepared solution S is not more opalescent than reference suspension III (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Acidity

To 25 mL of solution S add 0.15 mL of *methyl red solution R*. The solution is red. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Dissolve 1.00 g of the substance to be examined in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 0.10 g of *cresol R*, 0.10 g of *p-cresol R* and 0.10 g of the substance to be examined in *methanol R* and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 20.0 mL with *methanol R*.

Column:

— *material*: fused silica,

— *size*: *l* = 25 m, Ø = 0.25 mm,

— *stationary phase*: *cyanopropyl(25)phenyl(25)methyl(50)polysiloxane R* (0.2 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.8 mL/min.

Split ratio 1:30.

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Temperature:

	Time (min)	Temperature (°C)
Column	0 - 35	100
	35 - 40	100 → 150
	40 - 50	150
Injection port		200
Detector		200

Detection Flame ionisation.

Injection 1.0 µL.

Relative retention With reference to metacresol (retention time = about 28 min): impurity B = about 0.75; impurity C = about 0.98.

System suitability Reference solution (a):

— *resolution*: minimum 1.4 between the peaks due to impurity C and metacresol.

Limits:

— *impurities B, C*: for each impurity, not more than 0.5 per cent,

— *any other impurity*: for each impurity, not more than 0.1 per cent,

— *total*: not more than 1.0 per cent.

— *disregard limit*: the area of the peak due to metacresol in the chromatogram obtained with reference solution (b) (0.05 per cent).

Residue on evaporation

Maximum 0.1 per cent.

Evaporate 2.0 g to dryness on a water-bath in a fume cupboard and dry at 100-105 °C for 1 h. The residue weighs a maximum of 2 mg.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *B, C.*

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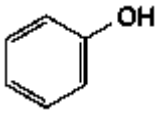
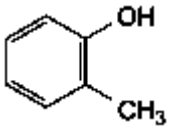
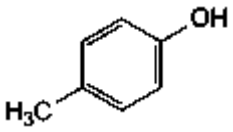
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, F, G, H, I, J, K, L, M.*



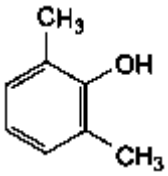
A. phenol,



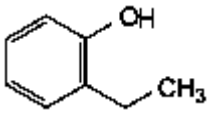
B. 2-methylphenol (*o*-cresol, cresol),



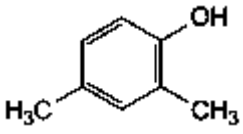
C. 4-methylphenol (*p*-cresol),



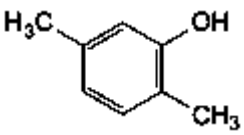
D. 2,6-dimethylphenol (2,6-xylenol),



E. 2-ethylphenol (*o*-ethylphenol),



F. 2,4-dimethylphenol (2,4-xylenol),



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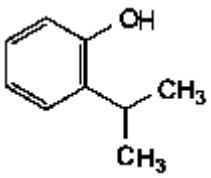
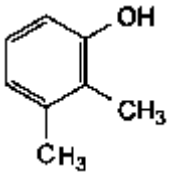
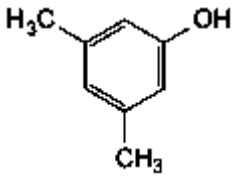
G. 2,5-dimethylphenol (2,5-xylenol),



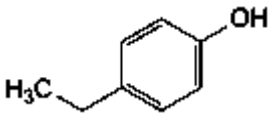
H. 2-(1-methylethyl)phenol,



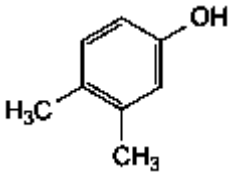
I. 2,3-dimethylphenol (2,3-xylenol),



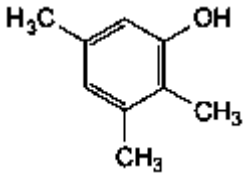
J. 3,5-dimethylphenol (3,5-xylenol),



K. 4-ethylphenol (*p*-ethylphenol),



L. 3,4-dimethylphenol (3,4-xylenol),



M. 2,3,5-trimethylphenol.

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Metaraminol Injection

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Metaraminol Injection is a sterile solution of Metaraminol Tartrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of metaraminol, $C_9H_{13}NO_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (5).

B. Dilute a volume containing the equivalent of 5 mg of metaraminol to 10 mL with *water* and extract with four 15 mL quantities of *chloroform*. To 0.5 mL of the aqueous layer add 0.5 mL of *phosphomolybdotungstic reagent* and 5 mL of *dilute sodium carbonate solution* and allow to stand for 5 minutes. An intense blue colour is produced.

C. To 4 mL of the aqueous layer obtained in test B add 5 mL of *borate buffer pH 9.6* and 1 mL of a freshly prepared 0.5% w/v solution of *sodium 1,2-naphthoquinone-4-sulfonate* and allow to stand for 1 minute. Add 0.2 mL of a 2% v/v solution of *benzalkonium chloride solution* and 5 mL of *toluene* and shake. A mauve colour is produced immediately in the toluene layer (distinction from phenylephrine).

TESTS

Acidity

pH, 3.2 to 4.5, Appendix V L.

Related substances

Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using a silica gel precoated plate (Merck silica gel 60 plates are suitable) and a mixture of 10 volumes of 13.5M *ammonia*, 80 volumes of *chloroform* and 80 volumes of *methanol* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) evaporate a volume of the injection containing the equivalent of 20 mg of metaraminol to dryness, dissolve the residue as completely as possible in 2 mL of *methanol* and filter. For solution (2) dilute 1 volume of solution (1) to 20 volumes with *methanol*. For solution (3) dilute 1 volume of solution (1) to 100 volumes with *methanol*. Solution (4) contains 0.1% w/v of *methyl 4-hydroxybenzoate* in *methanol*. Solution (5) contains 0.050% w/v of *metaraminol*

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tartrate BPCRS in *methanol*. After removal of the plate, allow it to dry in air and spray with a solution prepared in the following manner. Mix 25 mL of a 0.45% w/v solution of *sulfanilic acid* in 1M *hydrochloric acid* with 1.5 mL of a 5% w/v solution of *sodium nitrite*, allow to stand for 5 minutes and mix cautiously with 25 mL of 2M *sodium carbonate*. Any *secondary spot* in the chromatogram obtained with solution (1), other than any spot corresponding to methyl 4-hydroxybenzoate, is not more intense than the spot in the chromatogram obtained with solution (3) (1%).

ASSAY

To a quantity containing the equivalent of 10 mg of metaraminol add sufficient *water* to produce 200 mL. Wash 25 mL with four 25 mL quantities of *chloroform*, discard the washings and filter the aqueous solution. Measure the *absorbance* of the filtrate at the maximum at 272 nm, Appendix II B. Calculate the content of $C_9H_{13}NO_2$ taking 111 as the value of A(1%, 1 cm) at the maximum at 272 nm.

STORAGE

Metaraminol Injection should be protected from light.

LABELLING

The strength is stated in terms of the equivalent amount of metaraminol in a suitable dose-volume.

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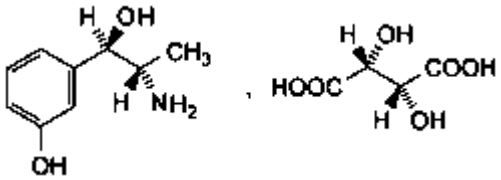
Metaraminol Tartrate

General Notices



$C_9H_{13}NO_2,C_4H_6O_6$ 317.3 *17171-57-2*

Action and use

Adrenoceptor agonist.

Preparation

Metaraminol Injection

DEFINITION

Metaraminol Tartrate is (1*R*,2*S*)-2-amino-1-(3-hydroxyphenyl)propan-1-ol hydrogen (2*R*,3*R*)-tartrate. It contains not less than 99.0% and not more than 101.0% of $C_9H_{13}NO_2,C_4H_6O_6$, calculated with reference to the dried substance.

CHARACTERISTICS

A white, crystalline powder.

Freely soluble in *water*; sparingly soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. In the test for Related substances the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).

B. To 0.5 mL of a 0.05% w/v solution add 0.5 mL of *phosphomolybdotungstic reagent* and 5 mL of *dilute sodium carbonate solution* and allow to stand for 5 minutes. An intense blue colour is produced.

C. To 4 mL of a 0.05% w/v solution add 5 mL of *borate buffer pH 9.6* and 1 mL of a freshly prepared 0.5% w/v solution of *sodium 1,2-naphthaquinone-4-sulfonate* and allow to stand for 1 minute. Add 0.2 mL of a 2% v/v solution of *benzalkonium chloride solution* and 5 mL of *toluene* and shake. A mauve colour is immediately produced in the toluene layer (distinction from phenylephrine).

TESTS

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Acidity

pH of a 5% w/v solution, 3.2 to 3.5, Appendix V L.

Phenones

Absorbance of a 0.2% w/v solution at 310 nm, not more than 0.2, calculated with reference to the dried substance, Appendix II B.

Related substances

Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) 1.0% w/v of the substance being examined.

(2) 0.050% w/v of the substance being examined.

(3) 0.0050% w/v of the substance being examined.

(4) 0.050% w/v of *metaraminol tartrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with a solution prepared in the following manner. Mix 25 mL of a 0.45% w/v solution of *sulfanilic acid* in 1M *hydrochloric acid* with 1.5 mL of a 5% w/v solution of *sodium nitrite*, allow to stand for 5 minutes and mix cautiously with 25 mL of 2M *sodium carbonate*.

MOBILE PHASE

10 volumes of 13.5M *ammonia*, 80 volumes of *chloroform* and 80 volumes of *methanol*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.6 g and *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 31.73 mg of $C_9H_{13}NO_2,C_4H_6O_6$.

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Metformin and Sitagliptin Prolonged-release Tablets

General Notices

Metformin and Sitagliptin Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Biguanide + Dipeptidylpeptidase-4 inhibitor; treatment of diabetes mellitus.

DEFINITION

Metformin and Sitagliptin Prolonged-release Tablets contain Metformin Hydrochloride and Sitagliptin Phosphate Monohydrate. They are formulated so that the Metformin Hydrochloride is released over a period of several hours.

The tablets complies with the requirements stated under Tablets and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Metformin Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

A suitable test is carried out to demonstrate that the content of 1-cyanoguanidine (metformin impurity A) is not more than 0.02%.

Content of metformin hydrochloride, $C_4H_{11}N_5$,HCl

95.0 to 105.0% of the stated amount.

Content of sitagliptin, $C_{16}H_{15}F_6N_5O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. In the Assay for metformin hydrochloride, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.
The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

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B. In the Assay for sitagliptin, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

For sitagliptin

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of a solution containing 0.37% w/v of *potassium dihydrogen orthophosphate* and 0.39% w/v of *dipotassium hydrogen orthophosphate*, adjusted to pH 6.8 with 50% w/w of *sodium hydroxide* or *orthophosphoric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.0055% w/v of sitagliptin.

(2) 0.0072% w/v of *sitagliptin phosphate monohydrate EPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *strong cation-exchange silica gel for chromatography* (5 µm) (Phenomenex Luna SCX is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of *acetonitrile R1* and 75 volumes of 0.05M *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of sitagliptin is about 2 minutes and the retention time of metformin is about 3 minutes.

DETERMINATION OF CONTENT

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Calculate the total content of sitagliptin, $C_{16}H_{15}F_6N_5O$, in the medium from the chromatograms obtained and using the declared content of $C_{16}H_{15}F_6N_5O$ in *sitagliptin phosphate monohydrate EPCRS*.

LIMITS

The amount of sitagliptin released is not less than 70% (Q) of the stated amount.

Related substances

For metformin

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solution A 20 volumes of 0.1% v/v of *orthophosphoric acid* and 80 volumes of *methanol*.

Solution B 5 volumes of *acetonitrile R1* and 95 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL of solution A to a number of whole tablets containing 2 g of Metformin Hydrochloride and shake until the tablets are dispersed. Dilute to 500 mL with solution A, mix and filter. Dilute 1 volume of the resulting solution to 20 volumes with solution B.
(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 10 volumes with solution B.
(3) To 20 mL of 0.02% w/v of *metformin hydrochloride BPCRS* in solution B, add 0.1 mL of 0.1M *sodium hydroxide*, heat at 80° for 2 hours, allow to cool to room temperature and add 3 mL of *orthophosphoric acid* (generation of impurities 6 and 7). Add 2 mL of 0.01% w/v of *sitagliptin phosphate monohydrate EPCRS* in solution B and mix.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with the mobile phase described below and an injection volume of 20 µL. Allow the chromatography to proceed for 1.5 times the retention time of metformin.

MOBILE PHASE

18 volumes of *acetonitrile R1* and 82 volumes of 0.05M *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to metformin (about 4 minutes) are: impurity 6, about 0.4; impurity 7, about 0.55 and sitagliptin, about 0.65.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity 7 and sitagliptin is at least 1.0;

the *resolution* between the peaks due to sitagliptin and metformin is at least 1.6.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any *secondary peak* is not greater than the area of the peak due to metformin in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the peak due to metformin in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak due to sitagliptin and any peak with an area less than half the area of the peak due to metformin in the chromatogram obtained with solution (2) (0.05%).

For sitagliptin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 20 volumes of 0.1% v/v of *orthophosphoric acid* and 80 volumes of *methanol*.

Solution B 5 volumes of *acetonitrile R1* and 95 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL of solution A to a number of whole tablets containing the equivalent of 0.25 g of sitagliptin and shake until the tablets are dispersed. Dilute to 500 mL with solution A, mix and filter. Dilute 4 volumes of the resulting solution to 25 volumes with solution B.
(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 5 volumes with solution B.

For tablets containing sodium stearyl fumarate

(3) Add 10 mL of *water* to 1 tablet and mix with the aid of ultrasound until the tablet is dispersed. Heat in a tightly closed vial at 80° for about 30 hours. Cool, dilute to 100 mL with solution B and stir for 1 hour. Centrifuge a portion of the solution and use the supernatant liquid (generation of impurities 1 and 5).

For tablets that do not contain sodium stearyl fumarate

(3) Add 1 mL of *water* to 1 mg of *sodium stearyl fumarate* and 10 mg of *sitagliptin phosphate monohydrate EPCRS*. Heat in a tightly closed vial at 80° for about 30 hours. Cool, dilute to 100 mL with solution B and stir for 1 hour. Centrifuge a portion of the solution and use the supernatant liquid (generation of impurities 1 and 5).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Waters YMC-PAC ODS-AM is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 205 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile R1* and 95 volumes of 0.025M *potassium dihydrogen orthophosphate*, previously adjusted to pH 2.5 with *orthophosphoric acid*.

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Mobile phase B acetonitrile R1.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	87	13	isocratic
2-25	87→46	13→54	linear gradient
25-25.1	46→25	54→75	linear gradient
25.1-29	25	75	isocratic
29-29.1	25→87	75→13	linear gradient
29.1-37	87	13	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to sitagliptin (retention time about 7 minutes) are: metformin, about 0.2; impurity 5, about 0.5; impurity 1, about 1.1; impurity 2, about 1.5, impurity 3, about 2.5 and impurity 4, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between sitagliptin and impurity 1 is at least 1.5;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (2) is at least 20.

LIMITS

Identify any peak corresponding to impurity 5 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 1.5. Identify any peak corresponding to impurity 4 in the chromatogram obtained with solution (1), using the relative retention time and multiply the area of this peak by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 5 is not greater than 1.5 times the area of the peak due to sitagliptin in the chromatogram obtained with solution (2) (0.3%);

the area of any *secondary peak* is not greater than the area of the peak due to sitagliptin in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 2.5 times the area of the peak due to sitagliptin in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak due to metformin and any peak with an area less than half the area of the peak due to sitagliptin in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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For metformin hydrochloride

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solution A 20 volumes of 0.1% v/v of *orthophosphoric acid* and 80 volumes of *methanol*.

Solution B 5 volumes of *acetonitrile R1* and 95 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL of solution A to a number of whole tablets containing 1 g of Metformin Hydrochloride and shake until the tablets are dispersed. Dilute to 500 mL with solution A, mix and filter. Further dilute 1 volume to 10 volumes with solution B.
(2) 0.02% w/v of *metformin hydrochloride BPCRS* in solution B.
(3) Prepare a solution of *sitagliptin phosphate monohydrate EPCRS* in solution (2) at a concentration of sitagliptin equivalent to that expected in solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with the mobile phase described below and an injection volume of 20 µL.

MOBILE PHASE

18 volumes of *acetonitrile R1* and 82 volumes of 0.05M *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sitagliptin and metformin is at least 1.6.

DETERMINATION OF CONTENT

Calculate the content of metformin hydrochloride, $C_4H_{11}N_5$,HCl, in the tablets from the chromatograms obtained and using the declared content of $C_4H_{11}N_5$,HCl in *metformin hydrochloride BPCRS*.

For sitagliptin

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solution A 20 volumes of 0.1% v/v of *orthophosphoric acid* and 80 volumes of *methanol*.

Solution B 5 volumes of *acetonitrile R1* and 95 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL of solution A to a number of whole tablets containing the equivalent of 250 mg of sitagliptin and shake until the tablets are dispersed. Dilute to 500 mL with solution A, mix and filter. Dilute 4 volumes of the resulting solution to 25 volumes with solution B.
(2) 0.008% w/v of *sitagliptin phosphate monohydrate EPCRS* in solution B.
(3) Prepare a solution of *metformin hydrochloride BPCRS* in solution (2) at a concentration of metformin equivalent to that expected in solution (1).

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Related substances for sitagliptin may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to metformin and sitagliptin is at least 10.0.

DETERMINATION OF CONTENT

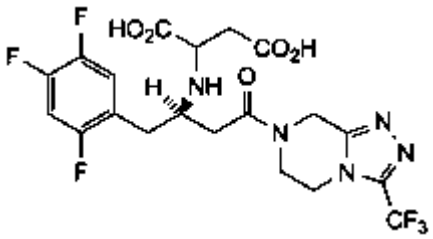
Calculate the content of sitagliptin, $C_{16}H_{15}F_6N_5O$, in the tablets from the chromatograms obtained and using the declared content of $C_{16}H_{15}F_6N_5O$ in *sitagliptin phosphate monohydrate EPCRS*.

LABELLING

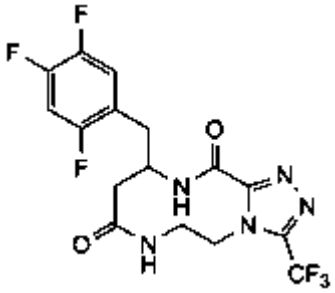
The quantity of sitagliptin phosphate monohydrate is stated in terms of the equivalent amount of sitagliptin.

IMPURITIES

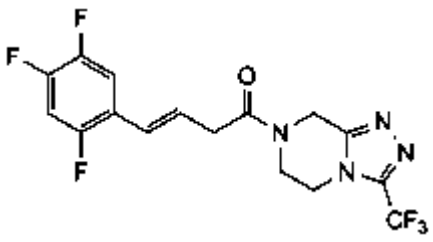
The impurities limited by the requirements of this monograph include impurity A listed under Metformin Hydrochloride and:



1. 2-[[(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-yl]amino]butanedioic acid (Sitagliptin Tablets FP-A; sitagliptin fumarate adduct)



2. 3-(trifluoromethyl)-10-[(2,4,5-trifluorophenyl)methyl]-6,7,10,11-tetrahydro[1,2,4]triazolo[3,4-*c*][1,4,7]triazecine-8,12(5*H*,9*H*)-dione (Sitagliptin Tablets FP-B)



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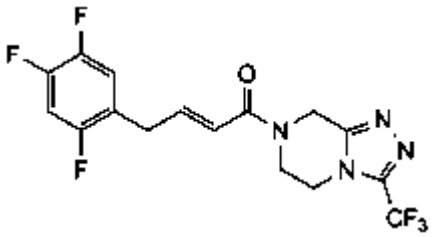
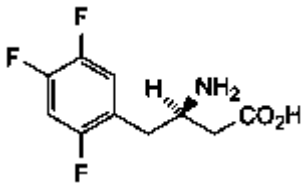
3. (3*E*)-1-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-3-en-1-one (Sitagliptin Tablets FP-C)



4. (2*E*)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-2-en-1-one (Sitagliptin Tablets FP-D)



5. (3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid (Sitagliptin Tablets FP-E; sitagliptin acid hydrolysis product)

6. unknown structure (metformin degradant)

7. unknown structure (metformin degradant)

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Metformin and Sitagliptin Tablets

General Notices

Action and use

Biguanide + Dipeptidylpeptidase-4 inhibitor; treatment of diabetes mellitus.

DEFINITION

Metformin and Sitagliptin Tablets contain Metformin Hydrochloride and Sitagliptin Phosphate Monohydrate.

The tablets complies with the requirements stated under Tablets and with the following requirements.

PRODUCTION

A suitable test is carried out to demonstrate that the content of 1-cyanoguanidine (metformin impurity A) is not more than 0.02%.

Content of metformin hydrochloride, $C_4H_{11}N_5$,HCl

95.0 to 105.0% of the stated amount.

Content of sitagliptin, $C_{16}H_{15}F_6N_5O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay for metformin hydrochloride, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.
The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

B. In the Assay for sitagliptin, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.
The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

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TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.025M *sodium chloride*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 20 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.0055% w/v of sitagliptin.

(2) 0.0072% w/v of *sitagliptin phosphate monohydrate EPCRS* and a quantity of *metformin hydrochloride BPCRS* to produce the same concentrations as that expected for solution (1), in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *strong cation-exchange silica gel for chromatography* (5 µm) (Phenomenex Luna SCX is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 255 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of 0.05M *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of sitagliptin is about 2 minutes and the retention time of metformin is about 3 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to sitagliptin and metformin is at least 1.6.

DETERMINATION OF CONTENT

Calculate the total content of metformin hydrochloride, $C_4H_{11}N_5$,HCl and sitagliptin, $C_{16}H_{15}F_6N_5O$, in the medium from the chromatograms obtained and using the declared content of $C_4H_{11}N_5$,HCl in *metformin hydrochloride BPCRS* and the declared content of $C_{16}H_{15}F_6N_5O$ in *sitagliptin phosphate monohydrate EPCRS*.

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LIMITS

The amount of metformin hydrochloride released is not less than 80% (Q) of the stated amount.

The amount of sitagliptin released is not less than 80% (Q) of the stated amount.

Related substances

For metformin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A, unless otherwise stated.

Solution A 1 volume of *acetonitrile R1* and 19 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL to a number of whole tablets containing the equivalent of 250 mg of sitagliptin and shake until the tablets are dispersed. Dilute to 500 mL, mix and filter. Further dilute to produce a solution expected to contain 0.01% w/v of Metformin Hydrochloride.
(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 10 volumes.
(3) To 20 mL of 0.02% w/v of *metformin hydrochloride BPCRS* in solution B, add 0.1 mL of 0.1M *sodium hydroxide*, heat at 80° for 2 hours, allow to cool to room temperature and add 3 mL of *orthophosphoric acid* (generation of impurities 6 and 7). Add 2 mL of 0.01% w/v of *sitagliptin phosphate monohydrate EPCRS* in solution B and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *strong cation-exchange silica gel for chromatography* (5 µm) (Phenomenex Luna SCX is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 205 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 1.5 times the retention time of metformin.

MOBILE PHASE

16 volumes of *acetonitrile R1* and 84 volumes of 0.05M *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of sitagliptin is about 2 minutes and the retention time of metformin is about 3 minutes.

CHROMATOGRAPHIC CONDITIONS

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to metformin (about 3 minutes) are: impurity 6, about 0.4; impurity 7, about 0.6 and sitagliptin, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

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the *resolution* between the peaks due to impurity 7 and sitagliptin is at least 1.0;

the *resolution* between the peaks due to sitagliptin and metformin is at least 1.6.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the peak due to metformin in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the peak due to metformin in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak due to sitagliptin and any peak with an area less than half the area of the peak due to metformin in the chromatogram obtained with solution (2) (0.05%).

For sitagliptin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A, unless otherwise stated.

Solution A 1 volume of *acetonitrile* and 19 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL to a number of whole tablets containing the equivalent of 0.25 g of sitagliptin and shake until the tablets are dispersed. Dilute to 500 mL, mix and filter. Dilute 4 volumes of the resulting solution to 25 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 5 volumes.

For tabletsb containing sodium stearyl fumarate

(3) Add 10 mL of *water* to 1 tablet and mix with the aid of ultrasound until the tablet is dispersed. Heat in a tightly closed vial at 80° for about 30 hours. Cool, dilute to 100 mL with solution B and stir for 1 hour. Centrifuge a portion of the solution and use the supernatant liquid (generation of impurities 1 and 5).

For tablets that do not contain sodium stearyl fumarate

(3) Add 1 mL of *water* to 1 mg of *sodium stearyl fumarate* and 10 mg of *sitagliptin phosphate monohydrate EPCRS*. Heat in a tightly closed vial at 80° for about 30 hours. Cool, dilute to 100 mL with solution B and stir for 1 hour. Centrifuge a portion of the solution and use the supernatant liquid (generation of impurities 1 and 5).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.75 mL per minute.
(d) Use a column temperature of 42°.
(e) Use a detection wavelength of 267 nm.

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(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile* and 95 volumes of 0.025M *potassium dihydrogen orthophosphate*, previously adjusted to pH 2.5 with *orthophosphoric acid*.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-14	87→35	13→65	linear gradient
14-14.1	35→87	65→13	linear gradient
14.1-17	87	13	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to sitagliptin (retention time about 5 minutes) are: metformin, about 0.1; impurity 5, about 0.5; impurity 1, about 1.2; impurity 2, about 1.7, impurity 3, about 2.3 and impurity 4, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between sitagliptin and impurity 1 is at least 1.5;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (2) is at least 20.

LIMITS

Identify any peaks corresponding to impurities 1 and 5 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of these peaks by a correction factor of 0.6 and 0.8, respectively.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the peak due to sitagliptin in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than the area of the peak due to sitagliptin in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak due to metformin and any peak with an area less than half the area of the peak due to sitagliptin in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For metformin hydrochloride

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A, unless otherwise stated.

Solution A 1 volume of *acetonitrile R1* and 19 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL to a number of whole tablets containing the equivalent of 250 mg of sitagliptin and shake until the tablets are dispersed. Dilute to 500 mL, mix and filter. Further dilute to produce a solution expected to contain 0.01% w/v of Metformin Hydrochloride.
(2) 0.01% w/v of *metformin hydrochloride BPCRS*.
(3) Prepare a solution of *sitagliptin phosphate monohydrate EPCRS* in solution (2) at a concentration of sitagliptin equivalent to that expected in solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances for metformin may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sitagliptin and metformin is at least 1.6.

DETERMINATION OF CONTENT

Calculate the content of metformin hydrochloride, $C_4H_{11}N_5$,HCl, in the tablets from the chromatograms obtained and using the declared content of $C_4H_{11}N_5$,HCl in *metformin hydrochloride BPCRS*.

For sitagliptin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A, unless otherwise stated.

Solution A 1 volume of *acetonitrile* and 19 volumes of 0.1% v/v of *orthophosphoric acid*.

(1) Add 150 mL to a number of whole tablets containing the equivalent of 0.25 g of sitagliptin and shake until the tablets are dispersed. Dilute to 500 mL, mix and filter. Further dilute to 4 volumes to 25 volumes.
(2) 0.008% w/v of *sitagliptin phosphate monohydrate EPCRS*.

For tablets containing sodium stearyl fumarate

(3) Add 10 mL of *water* to 1 tablet and mix with the aid of ultrasound until the tablet is dispersed. Heat in a tightly closed vial at 80° for about 30 hours. Cool, dilute to 100 mL with solution B and stir for 1 hour. Centrifuge a portion of the solution and use the supernatant liquid (generation of impurities 1 and 5).

For tablets that do not contain sodium stearyl fumarate

(3) Add 1 mL of *water* to 1 mg of *sodium stearyl fumarate* and 10 mg of *sitagliptin phosphate monohydrate EPCRS*. Heat in a tightly closed vial at 80° for about 30 hours. Cool, dilute to 100 mL with solution B and stir for 1 hour. Centrifuge a portion of the solution and use the supernatant liquid (generation of impurities 1 and 5).

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Related substances for sitagliptin may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sitagliptin and impurity 1 is at least 2.5.

DETERMINATION OF CONTENT

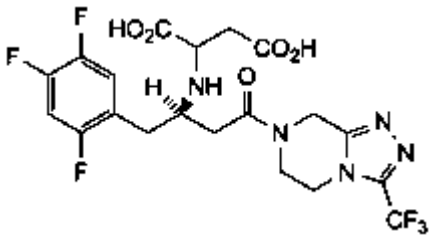
Calculate the content of sitagliptin, $C_{16}H_{15}F_6N_5O$, in the tablets from the chromatograms obtained and using the declared content of $C_{16}H_{15}F_6N_5O$ in *sitagliptin phosphate monohydrate EPCRS*.

LABELLING

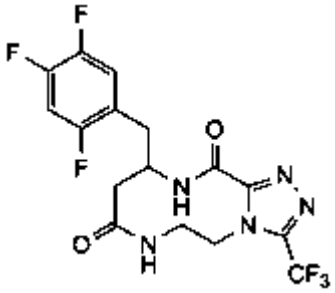
The quantity of sitagliptin phosphate monohydrate is stated in terms of the equivalent amount of sitagliptin.

IMPURITIES

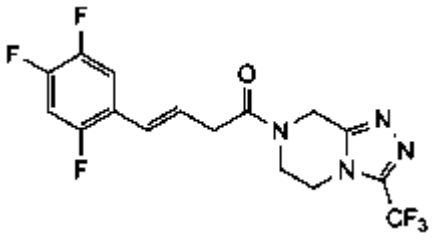
The impurities limited by the requirements of this monograph include impurity A listed under Metformin Hydrochloride and:



1. 2-[[(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-yl]amino]butanedioic acid (Sitagliptin Tablets FP-A; sitagliptin fumarate adduct)



2. 3-(trifluoromethyl)-10-[(2,4,5-trifluorophenyl)methyl]-6,7,10,11-tetrahydro[1,2,4]triazolo[3,4-*c*][1,4,7]triazecine-8,12(5*H*,9*H*)-dione (Sitagliptin Tablets FP-B)



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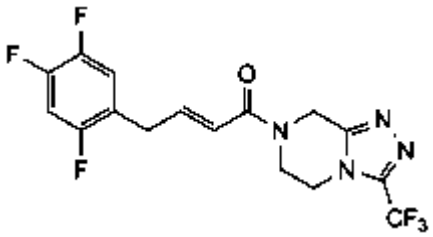
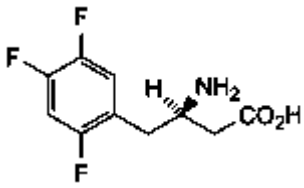
3. (3*E*)-1-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-3-en-1-one (Sitagliptin Tablets FP-C)



4. (2*E*)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-2-en-1-one (Sitagliptin Tablets FP-D)



5. (3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid (Sitagliptin Tablets FP-E; sitagliptin acid hydrolysis product)

6. unknown structure (metformin degradant)

7. unknown structure (metformin degradant)

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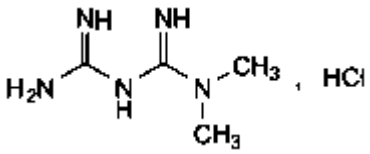
Metformin Hydrochloride

General Notices

(Ph. Eur. monograph 0931)



$C_4H_{12}ClN_5$ 165.6 *1115-70-4*

Action and use

Biguanide; treatment of diabetes mellitus.

Preparations

Metformin Oral Solution

Metformin Tablets

Metformin Prolonged-release Tablets

Metformin and Sitagliptin Prolonged-release Tablets

Metformin and Sitagliptin Tablets

Ph Eur

DEFINITION

1,1-Dimethylbiguanide hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystals.

Solubility

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Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone and in methylene chloride.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 222 °C to 226 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *metformin hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 20 mg of *metformin hydrochloride CRS* in *water R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *glacial acetic acid R*, *butanol R*, *water R* (10:40:50 *V/V/V*); use the upper layer.

Application 5 µL.

Development Over 3/4 of the plate.

Drying At 100-105 °C for 15 min.

Detection Spray with a mixture of equal volumes of a 100 g/L solution of *sodium nitroprusside R*, a 100 g/L solution of *potassium ferricyanide R* and a 100 g/L solution of *sodium hydroxide R*, prepared 20 min before use.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 5 mg in *water R* and dilute to 100 mL with the same solvent. To 2 mL of the solution add 0.25 mL of *strong sodium hydroxide solution R* and 0.10 mL of *α-naphthol solution R*. Mix and allow to stand in iced water for 15 min. Add 0.5 mL of *sodium hypobromite solution R* and mix. A pink colour develops.

E. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*). Heat the solution to 50 °C and cool to room temperature.

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Impurity F

Liquid chromatography (2.2.29).

Derivatisation solution *Prepare the solution immediately before use.* Dilute 1 mL of fluorodinitrobenzene R in 100.0 mL of acetonitrile R.

Blank solution To 5.0 mL of acetonitrile R add 100 µL of triethylamine R1 and 1.0 mL of the derivatisation solution. Shake well and heat at 60 °C for 30 min. After cooling, dilute to 10.0 mL with acetonitrile R.

Test solution *Prepare the solution immediately before use.* Suspend 10.0 mg of the substance to be examined in 5.0 mL of acetonitrile R and sonicate for 5 min. Add 100 µL of triethylamine R1 and 1.0 mL of the derivatisation solution. Shake well and heat at 60 °C for 30 min. After cooling, dilute to 10.0 mL with acetonitrile R. Filter or centrifuge at 800 *g* for 5 min before use.

Reference solution Dilute 1.0 mL of metformin impurity F CRS in 100.0 mL of acetonitrile R. Dilute 2.5 mL of the solution to 100.0 mL with acetonitrile R. To 1.0 mL of this solution add successively 5.0 mL of acetonitrile R, 100 µL of triethylamine R1 and 1.0 mL of the derivatisation solution. Shake well and heat at 60 °C for 30 min. After cooling, dilute to 10.0 mL with acetonitrile R.

Column:

— *size*: *l* = 0.125 m, Ø = 3 mm;

— *stationary phase*: spherical end-capped octadecylsilyl silica gel for chromatography R1 (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: phosphoric acid R, water for chromatography R (0.1:99.9 *V/V*);

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	60 → 45	40 → 55
10 - 11	45 → 25	55 → 75
11 - 15	25	75

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 380 nm.

Injection 5 µL.

Identification of impurities Use the chromatograms obtained with the blank solution and the reference solution to identify the peak due to the impurity F derivative.

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Retention time Impurity F derivative = about 4 min.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peak due to the impurity F derivative and the nearby eluting peaks due to the derivatisation reagent.

Limit:

— *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.05 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of *metformin impurity A CRS* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 200.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 10 mg of *melamine R* (impurity D) in about 90 mL of *water R*. Add 5 mL of the test solution and dilute to 100 mL with *water R*. Dilute 1 mL of this solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *strong cation-exchange silica gel for chromatography R* (10 µm).

Mobile phase 17 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 218 nm.

Injection 20 µL.

Run time Twice the retention time of metformin.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to metformin (retention time = about 14 min): impurity A = about 0.3; impurity D = about 0.4.

System suitability Reference solution (c):

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— *resolution*: minimum 10 between the peaks due to impurity D and metformin.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.02 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: maximum 0.2 per cent;

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent); do not disregard the peak due to impurity A.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

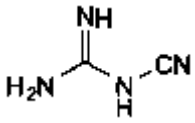
Dissolve 0.100 g in 4 mL of *anhydrous formic acid R*. Add 80 mL of *acetonitrile R*. Carry out the titration immediately. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.56 mg of $C_4H_{12}ClN_5$.

IMPURITIES

Specified impurities *A, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*



A. cyanoguanidine,

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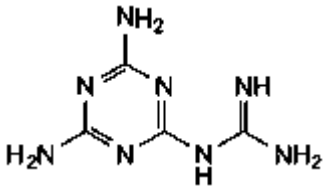
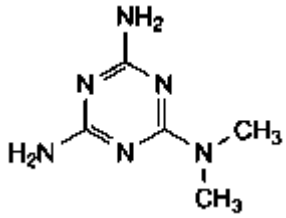
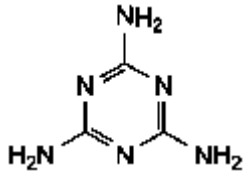


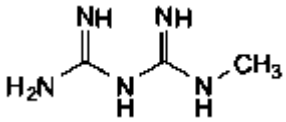
B. (4,6-diamino-1,3,5-triazin-2-yl)guanidine,



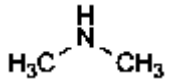
C. N^2,N^2-dimethyl-1,3,5-triazine-2,4,6-triamine (*N*,*N*-dimethylmelamine),



D. 1,3,5-triazine-2,4,6-triamine (melamine),



E. 1-methylbiguanide,



F. *N*-methylmethanamine (dimethylamine).

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Metformin Oral Solution

General Notices

Action and use

Biguanide; treatment of diabetes mellitus.

DEFINITION

Metformin Oral Solution is a solution of Metformin Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of metformin hydrochloride, $C_4H_{11}N_5,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the oral solution with *water* to produce a solution containing 0.5% w/v of Metformin Hydrochloride.

(2) 0.5% w/v of *metformin hydrochloride BPCRS*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* precoated plate.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with a mixture of equal volumes of a 10% w/v solution of *sodium nitroprusside*, a 10% w/v solution of *potassium ferricyanide* and a 10% w/v solution of *sodium hydroxide*, prepared 20 minutes before use.

MOBILE PHASE

Shake 10 volumes of *glacial acetic acid*, 40 volumes of *butanol* and 50 volumes of *water*, allow to separate and use the upper layer.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to the spot in the chromatogram obtained with solution (2). The chromatogram obtained with solution (3) shows a single, compact spot at the same Rf value as the spot in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the peak in the chromatogram obtained with solution (2).

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TESTS

Acidity or alkalinity

pH, 6.0 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the oral solution with the mobile phase to produce a solution containing 0.5% w/v of Metformin Hydrochloride and filter through a 0.45-µm filter if necessary.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(3) Dissolve 20 mg of *1-cyanoguanidine* in *water*, dilute to 100 mL with *water* and dilute 1 mL of the resulting solution to 200 mL with the mobile phase.
(4) 0.00025% w/v of *melamine* and 0.0001% w/v of *metformin hydrochloride BPCRS* in the mobile phase.
(5) Dilute 1 volume of solution (2) to 2 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with a regular, porous silica gel to which benzenesulfonic acid groups have been chemically bonded (5 µm) (Partisphere 5µ SCX is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 218 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1.7% w/v *ammonium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to melamine and metformin hydrochloride is at least 10.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 1-cyanoguanidine is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.02%);

the area of any other *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

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the sum of the areas of any such peaks is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

Disregard any peak, except that of 1-cyanoguanidine, with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution with sufficient of the mobile phase to produce a solution containing 0.05% w/v of Metformin Hydrochloride and filter through a 0.45-µm filter, if necessary.
(2) 0.05% w/v of *metformin hydrochloride BPCRS* in the mobile phase.
(3) 0.00025% w/v of *melamine* and 0.0001% w/v of *metformin hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to melamine and metformin hydrochloride is at least 10.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_4H_{11}N_5$,HCl, weight in volume, using the declared content of $C_4H_{11}N_5$,HCl in *metformin hydrochloride BPCRS*.

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Metformin Prolonged-release Tablets

General Notices

Prolonged-release Metformin Tablets

Metformin Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Biguanide; treatment of diabetes mellitus.

DEFINITION

Metformin Prolonged-release Tablets contain Metformin Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of metformin hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of metformin hydrochloride, $C_4H_{11}N_5,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 100 mg of Metformin Hydrochloride with 25 mL of *absolute ethanol* for 15 minutes, filter, evaporate the filtrate to dryness on a water bath and dry the residue at 105° for 1 hour. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of metformin hydrochloride *(RS 217)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 10% v/v of *acetonitrile R1* unless otherwise indicated.

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(1) Dissolve with the aid of ultrasound a quantity of powdered tablets containing 0.2 g of Metformin Hydrochloride with 700 mL for 10 minutes, mix using a magnetic stirrer, dilute to 1000 mL and filter through a 0.45-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 10 volumes.

(3) 0.000004% w/v of *1-cyanoguanidine* (impurity A) in *water*.

(4) 0.002% w/v each of *1-methylbiguanide hydrochloride* (impurity E) and *metformin hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µ-Bondapak C18 is suitable) fitted with a stainless steel guard column packed with the same material.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 218 nm.

(f) Inject 10 µL of each solution.

(g) Continue the chromatography for 4 times the retention time of metformin.

MOBILE PHASE

Dissolve 1 g of *sodium heptanesulfonate* and 1 g of *sodium chloride* in 1800 mL of *water*. Mix well, adjust to pH 3.85 with 0.35% v/v of *orthophosphoric acid* and dilute to 2000 mL with *water* (buffer solution pH 3.85).

1 volume of *acetonitrile R1* and 9 volumes of *buffer solution pH 3.85*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3) *1-cyanoguanidine* is resolved from the solvent front and the *signal-to-noise ratio* of the peak is at least 10;

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity E and metformin is not less than 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A (1-cyanoguanidine) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.02%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%) except for 1-cyanoguanidine.

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions in 10% v/v of *acetonitrile R1*.

(1) Dissolve with the aid of ultrasound a quantity of powdered tablets containing 0.2 g of Metformin Hydrochloride with 700 mL for 10 minutes, mix using a magnetic stirrer, dilute to 1000 mL and filter through a 0.45-µm nylon filter.

(2) 0.02% w/v of *metformin hydrochloride BPCRS*.

(3) 0.002% w/v each of *1-methylbiguanide hydrochloride* (impurity E) and *metformin hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and metformin is not less than 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_4H_{11}N_5$,HCl in the tablets from the chromatograms obtained and using the declared content of $C_4H_{11}N_5$,HCl in *metformin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, D and E listed under Metformin Hydrochloride.

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Metformin Tablets

General Notices

Action and use

Biguanide; treatment of diabetes mellitus.

DEFINITION

Metformin Tablets contain Metformin Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of metformin hydrochloride, $C_4H_{11}N_5$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 20 mg of Metformin Hydrochloride with 20 mL of *absolute ethanol*, filter, evaporate the filtrate to dryness on a water bath and dry the residue at 105° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of metformin hydrochloride (*RS 217*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of a 0.68% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 6.8 by the addition of 1M *sodium hydroxide* and rotating the basket at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium. Filter, dilute 10 mL of the filtrate to 100 mL with *water* and dilute 10 mL of the resulting solution to 100 mL with *water*. Measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted if necessary, at the maximum at 233 nm, Appendix II B. Calculate the total content of metformin hydrochloride, $C_4H_{11}N_5$,HCl, in the medium taking 806 as the value of *A* (1%, 1 cm) at the maximum at 233 nm.

1-Cyanoguanidine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.50 g of Metformin Hydrochloride with 100 mL of the mobile phase, filter and use the filtrate. For solution (2) dissolve 20 mg of *1-cyanoguanidine* in *water*, dilute to 100 mL with *water* and dilute 1 mL of the resulting solution to 200 mL with the mobile phase.

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The chromatographic procedure may be carried out using (a) a stainless steel column (12.5 cm × 4.6 mm) packed with a regular, porous silica gel to which benzene sulfonic acid groups have been chemically bonded (5 µm) (Partisphere 5 µ SCX is suitable), (b) a 1.7% w/v solution of *ammonium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 218 nm.

Inject 20 µL of solution (2). Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained is not less 50% of the full scale of the recorder.

Inject separately 20 µL of solutions (1) and (2). In the chromatogram obtained with solution (1) the area of any peak corresponding to 1-cyanoguanidine is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.02%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of Metformin Hydrochloride with 70 mL of *water* for 15 minutes, dilute to 100 mL with *water* and filter, discarding the first 20 mL. Dilute 10 mL of the filtrate to 100 mL with *water* and dilute 10 mL of the resulting solution to 100 mL with *water*. Measure the *absorbance* of the resulting solution at the maximum at 232 nm, Appendix II B. Calculate the content of the $C_4H_{11}N_5$,HCl taking 798 as the value of A(1%, 1 cm) at the maximum at 232 nm.

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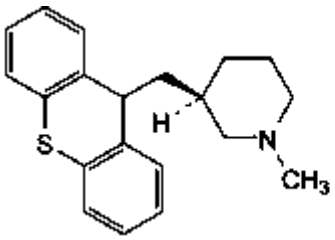
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Metixene Hydrochloride

General Notices

(Ph. Eur. monograph 1347)



and enantiomer . HCl . H_2O

$C_{20}H_{24}ClNS,H_2O$ 363.9 *7081-40-5*

Action and use

Anticholinergic.

Ph Eur

DEFINITION

Metixene hydrochloride contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of (*RS*)-1-methyl-3-[(9*H*-thioxanthen-9-yl)methyl]piperidine hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline or fine crystalline powder, soluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *metixene hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

Dissolve 0.40 g in *methanol R* and dilute to 20.0 mL with the same solvent. The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method I*).

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pH (*2.2.3*)

Dissolve 0.18 g in *carbon dioxide-free water R* heating if necessary at about 50 °C, cool and dilute to 10.0 mL with the same solvent. The pH of the solution, measured immediately, is 4.4 to 5.8.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel plate R*. *Carry out the test rapidly and protected from light.*

Test solution Dissolve 50 mg of the substance to be examined in *methylene chloride R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *metixene hydrochloride CRS* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *thioxanthene CRS* in 50 mL of *methylene chloride R*. Dilute 1.0 mL of the solution to 20.0 mL with *methylene chloride R*.

Reference solution (c) Dissolve 5 mg of *thioxanthone CRS* in 50 mL of *methylene chloride R*. Dilute 1.0 mL of the solution to 20.0 mL with *methylene chloride R*.

Reference solution (d) Dilute 4 mL of reference solution (a) to 10.0 mL with *methylene chloride R*.

Apply to the plate as narrow bands 5 µL of each solution. Develop over a path of 10 cm using a mixture of 10 volumes of *glacial acetic acid R*, 10 volumes of *methanol R* and 80 volumes of *methylene chloride R*. Dry the plate in a stream of cold air. Spray with a mixture of 1 volume of *sulfuric acid R* and 9 volumes of *alcohol R* and heat at 100 °C for 10 min. Allow the plate to cool and examine in ultraviolet light at 365 nm. Thioxanthene shows orange fluorescence and thioxanthone shows greenish-blue fluorescence. Any band corresponding to thioxanthene in the chromatogram obtained with the test solution is not more intense than the band in the chromatogram obtained with reference solution (b) (0.2 per cent); any band corresponding to thioxanthone in the chromatogram obtained with the test solution is not more intense than the band in the chromatogram obtained with reference solution (c) (0.05 per cent); any band, apart from the principal band and the bands corresponding to thioxanthene and thioxanthone, is not more intense than the band in the chromatogram obtained with reference solution (a) (0.5 per cent) and at most one such band is more intense than the band in the chromatogram obtained with reference solution (d) (0.2 per cent). The test is not valid unless the bands in the chromatograms obtained with reference solutions (b) and (c) are clearly visible and differentiated.

Loss on drying (*2.2.32*)

Not less than 4.0 per cent and not more than 6.0 per cent, determined on 0.500 g by drying in an oven at 138-142 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

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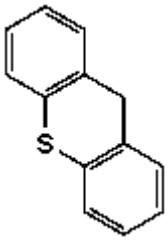
1 mL of *0.1 M sodium hydroxide* is equivalent to 34.59 mg of $C_{20}H_{24}ClNS$.

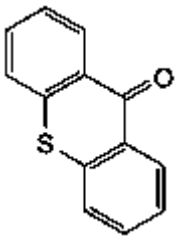
STORAGE

Store protected from light.

IMPURITIES



A. 9*H*-thioxanthene,



B. 9*H*-thioxanthen-9-one (thioxanthone).

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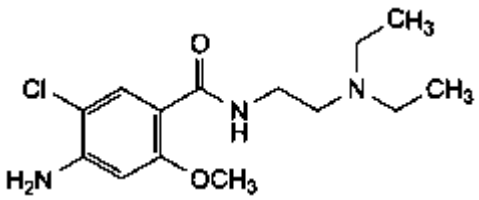
Metoclopramide

General Notices

(Ph. Eur. monograph 1348)



$C_{14}H_{22}ClN_3O_2$ 299.8 *364-62-5*

Action and use

Dopamine receptor antagonist; antiemetic.

Ph Eur

DEFINITION

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, fine powder.

Solubility

Practically insoluble in water, sparingly soluble or slightly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Melting point (2.2.14): 145 °C to 149 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison metoclopramide CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of methanol R, evaporate to dryness at room temperature then heat at 50 °C for about 1 h. Record new spectra using the residues.

C. Thin-layer chromatography (2.2.27) as described in the test for impurity E with the following modifications.

Test solution Dissolve 40 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of metoclopramide CRS in methanol R and dilute to 5 mL with the same solvent.

Detection Examine in ultraviolet light at 254 nm then spray with dimethylaminobenzaldehyde solution R1, allow to dry in air and examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution.

TESTS

Appearance of solution

The freshly prepared solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 2.5 g in 25 mL of a 103.0 g/L solution of hydrochloric acid R.

Impurity E

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.160 g of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of metoclopramide CRS and 10 mg of sulpiride CRS in methanol R and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of N,N-diethylethane-1,2-diamine R (impurity E) in methanol R and dilute to 50 mL with the same solvent. Dilute 2 mL of the solution to 25 mL with methanol R.

Plate TLC silica gel F_{254} plate R.

Mobile phase concentrated ammonia R, dioxan R, methanol R, methylene chloride R (2:10:14:90 *V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

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Detection Spray with *dimethylaminobenzaldehyde solution R1*, allow to dry in air and examine in daylight.

Retardation factors Impurity E = about 0.2; metoclopramide = about 0.6.

System suitability Reference solution (a):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity E*: any spot due to impurity E in the chromatogram obtained with the test solution is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase B, mobile phase A (5:95 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *metoclopramide impurity A CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Mix 1 mL of the solution with 0.1 mL of the test solution and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 37 °C.

Mobile phase:

— *mobile phase A*: 5 g/L solution of *ammonium acetate R* in *water for chromatography R* adjusted to pH 7.0 with *ammonia R* or *acetic acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1.5	95	5
1.5 - 16.5	95 → 42.5	5 → 57.5

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Flow rate 0.9 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to metoclopramide (retention time = about 9 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and metoclopramide.

Calculation of percentage contents:

— for each impurity, use the concentration of metoclopramide in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R* and add 5 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 29.98 mg of $C_{14}H_{22}ClN_3O_2$.

IMPURITIES

Specified impurities *E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, F, G, H.*

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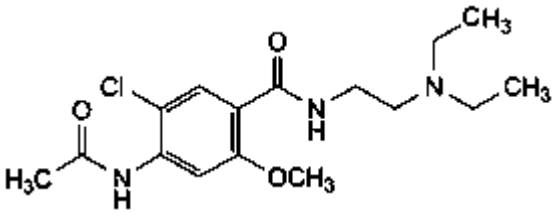
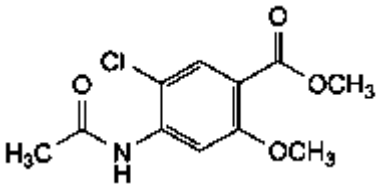
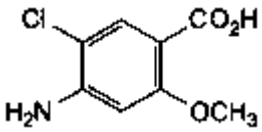


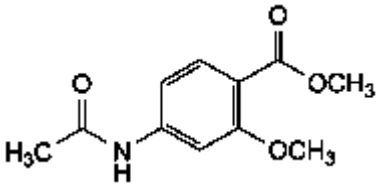
A. 4-acetamido-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide,



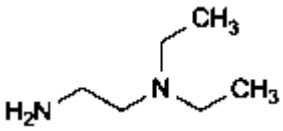
B. methyl 4-acetamido-5-chloro-2-methoxybenzoate,



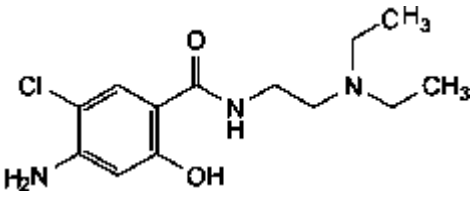
C. 4-amino-5-chloro-2-methoxybenzoic acid,



D. methyl 4-acetamido-2-methoxybenzoate,



E. *N*,*N*-diethylethane-1,2-diamine,



F. 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-hydroxybenzamide,

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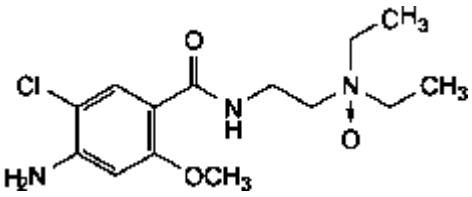
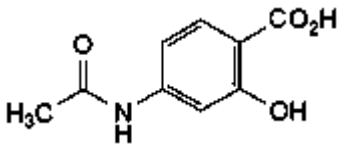


G. 2-(4-amino-5-chloro-2-methoxybenzamido)-*N*,*N*-diethylethan-1-amine N-oxide,



H. 4-acetamido-2-hydroxybenzoic acid.

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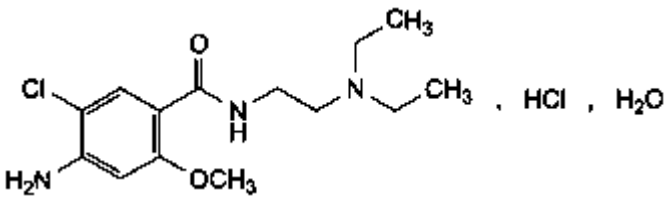
Metoclopramide Hydrochloride Monohydrate

General Notices

Metoclopramide Hydrochloride

(Ph. Eur. monograph 0674)



$C_{14}H_{23}Cl_2N_3O_2,H_2O$ 354.3 *54143-57-6*

Action and use

Dopamine receptor antagonist; antiemetic.

Preparations

Metoclopramide Injection

Metoclopramide Oral Solution

Metoclopramide Tablets

Ph Eur

DEFINITION

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide hydrochloride monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

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Very soluble in water, freely soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.

mp

About 183 °C, with decomposition.

IDENTIFICATION

First identification: A, B, D.

Second identification: A, C, D, E.

A. pH (2.2.3): 4.5 to 6.0 for solution S (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *metoclopramide hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27) as described in the test for impurity E with the following modifications.

Test solution Dissolve 40 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *metoclopramide hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Detection Examine in ultraviolet light at 254 nm then spray with *dimethylaminobenzaldehyde solution R1*, allow to dry in air and examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dilute 1 mL of solution S to 2 mL with *water R*. The solution gives reaction (a) of chlorides (2.3.1).

E. Dissolve about 2 mg in 2 mL of *water R*. The solution gives the reaction of primary aromatic amines (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Impurity E

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.40 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

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Reference solution Dissolve 10 mg of *N,N-diethylethane-1,2-diamine R* (impurity E) in *methanol R* and dilute to 50 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *dioxan R*, *methanol R*, *methylene chloride R* (2:10:14:90 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *dimethylaminobenzaldehyde solution R1*, allow to dry in air and examine in daylight.

Retardation factors Impurity E = about 0.2; metoclopramide = about 0.6.

Limit:

— *impurity E*: any spot due to impurity E in the chromatogram obtained with the test solution is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.5 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase B, mobile phase A (5:95 *V/V*).

Test solution Dissolve 24.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *metoclopramide impurity A CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Mix 1 mL of the solution with 0.1 mL of the test solution and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 37 °C.

Mobile phase:

— *mobile phase A*: 5 g/L solution of *ammonium acetate R* in *water for chromatography R* adjusted to pH 7.0 with *ammonia R* or *acetic acid R*;

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— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1.5	95	5
1.5 - 16.5	95 → 42.5	5 → 57.5

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to metoclopramide (retention time = about 9 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and metoclopramide.

Calculation of percentage contents:

— for each impurity, use the concentration of metoclopramide hydrochloride monohydrate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

4.5 per cent to 5.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 33.63 mg of $C_{14}H_{23}Cl_2N_3O_2$.

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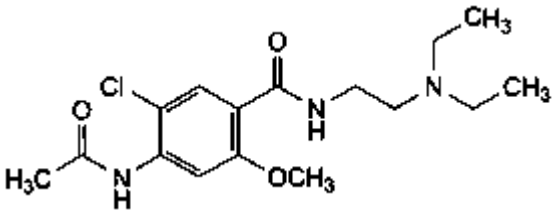
STORAGE

Protected from light.

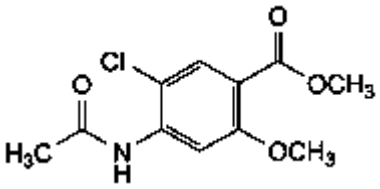
IMPURITIES

Specified impurities E.

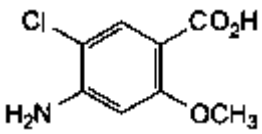
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, F, G, H.



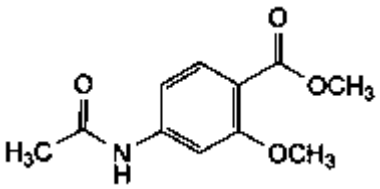
A. 4-acetamido-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide,



B. methyl 4-acetamido-5-chloro-2-methoxybenzoate,



C. 4-amino-5-chloro-2-methoxybenzoic acid,



D. methyl 4-acetamido-2-methoxybenzoate,

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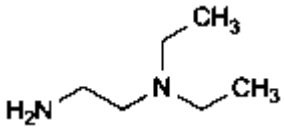
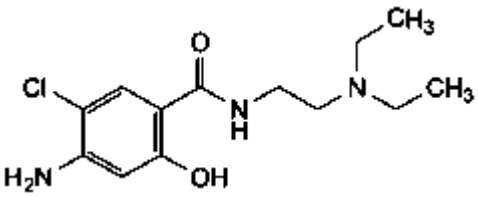
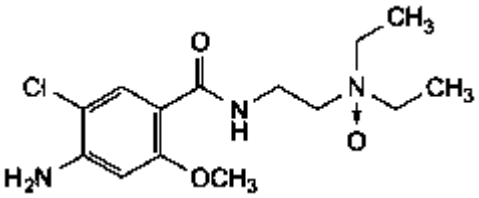


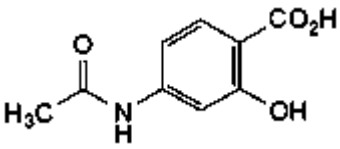
E. *N*,*N*-diethylethane-1,2-diamine,



F. 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-hydroxybenzamide,



G. 2-(4-amino-5-chloro-2-methoxybenzamido)-*N*,*N*-diethylethan-1-amine *N*-oxide,



H. 4-acetamido-2-hydroxybenzoic acid.

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Metoclopramide Injection

General Notices

Action and use

Dopamine receptor antagonist; antiemetic.

DEFINITION

Metoclopramide Injection is a sterile solution of Metoclopramide Hydrochloride Monohydrate in Water for Injections free from dissolved air.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of anhydrous metoclopramide hydrochloride, $C_{14}H_{22}ClN_3O_2,HCl$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. In the test for Related substances, the chromatogram obtained with solution (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (3).

B. To a volume containing the equivalent of 50 mg of anhydrous metoclopramide hydrochloride add 5 mL of *water* and 5 mL of a 1% w/v solution of *4-dimethylaminobenzaldehyde* in 1M *hydrochloric acid*. A yellowish-orange colour is produced.

TESTS

Acidity

pH, 3.0 to 5.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Dilute a volume of the injection with sufficient of the mobile phase to produce a solution containing the equivalent of 0.1% w/v of anhydrous metoclopramide hydrochloride.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.0005% w/v of *metoclopramide hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium hexanesulfonate* in a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile*, adjusted to pH 4.0 with *glacial acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection with sufficient *water* to produce a solution containing the equivalent of 0.01% w/v of anhydrous metoclopramide hydrochloride.

(2) 0.01% w/v of *metoclopramide hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography)* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 305 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of a solution prepared by dissolving 2.25 g of *sodium octanesulfonate* and 0.3 g of *sodium acetate* in sufficient *water* to produce 1000 mL and adjusting the pH, if necessary, to 3.8 with *glacial acetic acid* and 80 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{22}ClN_3O_2$,HCl in the injection using the declared content of $C_{14}H_{22}ClN_3O_2$,HCl in *metoclopramide hydrochloride BPCRS*.

STORAGE

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Metoclopramide Injection should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous metoclopramide hydrochloride.

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Metoclopramide Oral Solution

General Notices

Action and use

Dopamine receptor antagonist; antiemetic.

DEFINITION

Metoclopramide Oral Solution is a solution of Metoclopramide Hydrochloride Monohydrate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous metoclopramide hydrochloride, $C_{14}H_{22}ClN_3O_2,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, of the final solution obtained in the Assay exhibits a maximum at 534 nm.

B. In the test for Related substances, the retention time of the principal peak in the chromatogram obtained with solution (2) is similar to the retention time of the principal peak in the chromatogram obtained with solution (3).

Related substances

Protect the solutions from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the oral solution containing the equivalent of 2 mg of anhydrous metoclopramide hydrochloride with sufficient of the mobile phase to produce 10 mL and filter (Whatman GF/C filter paper is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.0001% w/v of *metoclopramide hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

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0.01M *sodium hexanesulfonate* in a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile*, adjusted to pH 4.0 with *glacial acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peaks with a retention time relative to the principal peak of 0.5 or less.

ASSAY

Protect the solutions from light. Dilute a quantity of the oral solution containing the equivalent of 10 mg of anhydrous metoclopramide hydrochloride to 100 mL with *water*. To 5 mL of this solution add 5 mL of 1M *hydrochloric acid*, mix, add 5 mL of a freshly prepared solution containing 1% w/v of *sodium nitrite*, mix and allow to stand for 10 minutes. Add 5 mL of a freshly prepared solution containing 5% w/v of *ammonium sulfamate*, mix and allow to stand for 25 minutes. Add 5 mL of a freshly prepared solution containing 0.5% w/v of *N-(1-naphthyl)ethylenediamine dihydrochloride* in 1M *hydrochloric acid*, mix, add sufficient *water* to produce 100 mL, mix and allow to stand for 5 minutes. Measure the *absorbance* of the resulting solution at the maximum at 534 nm, Appendix II B, using *water* in the reference cell. Calculate the content of $C_{14}H_{22}ClN_3O_2$,HCl from the *absorbance* obtained by repeating the procedure using 5 mL of a 0.01% w/v solution of *metoclopramide hydrochloride BPCRS* in place of the solution being examined, beginning at the words ‘add 5 mL of 1M *hydrochloric acid*…’, and using the declared content of $C_{14}H_{22}ClN_3O_2$,HCl in *metoclopramide hydrochloride BPCRS*.

STORAGE

Metoclopramide Oral Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous metoclopramide hydrochloride.

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Metoclopramide Tablets

General Notices

Action and use

Dopamine receptor antagonist; antiemetic.

DEFINITION

Metoclopramide Tablets contain Metoclopramide Hydrochloride Monohydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous metoclopramide hydrochloride, $C_{14}H_{22}ClN_3O_2,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances the chromatogram obtained with solution (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (3).

B. Shake a quantity of the powdered tablets containing the equivalent of 50 mg of anhydrous metoclopramide hydrochloride with 5 mL of *water*, filter and add to the filtrate 5 mL of a 1% w/v solution of *4-dimethylaminobenzaldehyde* in 1M *hydrochloric acid*. A yellowish-orange colour is produced.

Related substances

Protect the solutions from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of anhydrous metoclopramide hydrochloride with 20 mL of *methanol* for 5 minutes, filter (Whatman GF/C filter paper is suitable) and add sufficient of the mobile phase to produce 100 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.0005% w/v of *metoclopramide hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

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MOBILE PHASE

0.01M *sodium hexanesulfonate* in a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile*, adjusted to pH 4.0 with *glacial acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 20 mg of anhydrous metoclopramide hydrochloride with 80 mL of *water* with the aid of ultrasound for 10 minutes and then continue shaking mechanically for 20 minutes. Add sufficient *water* to produce 200 mL, filter and use the filtrate.

(2) 0.01% w/v of *metoclopramide hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 305 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of a solution prepared by dissolving 2.25 g of *sodium octanesulfonate* and 0.3 g of *sodium acetate* in sufficient *water* to produce 1000 mL and adjusting the pH, if necessary, to 3.8 with *glacial acetic acid* and 80 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{22}ClN_3O_2$,HCl in the tablets using the declared content of $C_{14}H_{22}ClN_3O_2$,HCl in *metoclopramide hydrochloride BPCRS*.

STORAGE

Metoclopramide Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous metoclopramide hydrochloride.

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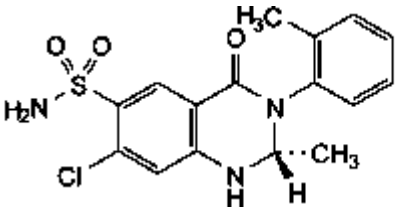
Metolazone

General Notices

(Ph. Eur. monograph 1757)



and enantiomer

$C_{16}H_{16}ClN_3O_3S$ 365.8

Action and use

Thiazide-like diuretic.

Ph Eur

DEFINITION

(2*RS*)-7-Chloro-2-methyl-3-(2-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethyl acetate, very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *metolazone CRS*.

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If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 30.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 2.0 mL of test solution (a) to 100.0 mL with *methanol R*.

Reference solution (a) Dissolve 3.0 mg of *metolazone for system suitability CRS* (containing impurities A, B, C, D and E) in 1 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 30.0 mg of *metolazone CRS* in *methanol R* and dilute to 10.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 5.44 g/L solution of *potassium dihydrogen phosphate R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	70	30
5 - 25	70 → 50	30 → 50
25 - 35	50	50
35 - 38	50 → 70	50 → 30
38 - 48	70	30

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 230 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *metolazone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D and E.

System suitability Reference solution (a):

— *resolution*: minimum 1.6 between the peaks due to impurities E and C and minimum 1.5 between the peaks due to impurities A and B.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{16}H_{16}ClN_3O_3S$ from the declared content of *metolazone CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*

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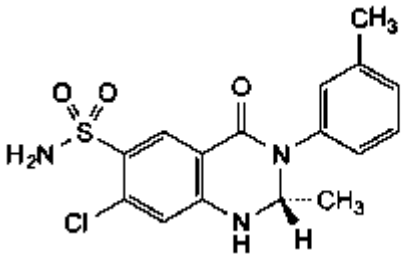
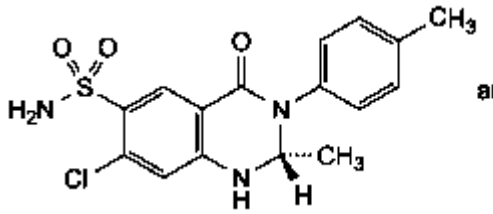


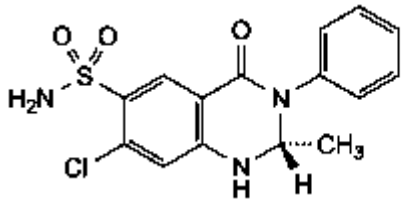
and enantiomer

A. (2*RS*)-7-chloro-2-methyl-3-(3-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide,



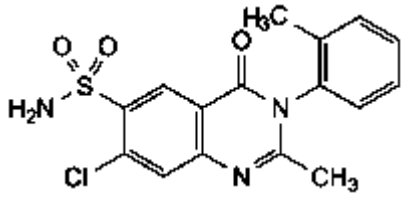
and enantiomer

B. (2*RS*)-7-chloro-2-methyl-3-(4-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide,

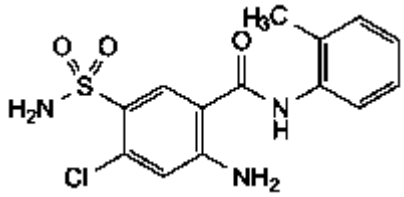


and enantiomer

C. (2*RS*)-7-chloro-2-methyl-4-oxo-3-phenyl1,2,3,4-tetrahydroquinazoline-6-sulfonamide,



D. 7-chloro-2-methyl-3-(2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-sulfonamide,



E. 2-amino-4-chloro-*N*-(2-methylphenyl)-5-sulfamoylbenzamide.

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Metoprolol Injection

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Metoprolol Injection is a sterile solution of Metoprolol Tartrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of metoprolol tartrate, $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume of the injection containing 20 mg of Metoprolol Tartrate add 2 mL of 5M *ammonia*, mix, extract with 30 mL of *dichloromethane*, filter the dichloromethane layer through *anhydrous sodium sulfate* and evaporate the filtrate to dryness using a rotary evaporator with gentle heating if necessary. Cool the residue to –18° for 30 minutes and allow to warm to room temperature. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of metoprolol *(RS 228)*.

B. In the test for Related substances, the chromatogram obtained with solution (2) shows a peak with the same retention time as that of metoprolol in the chromatogram obtained with solution (3).

C. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the injection being examined diluted, if necessary, with sufficient of the mobile phase to produce a solution containing 0.1% w/v of Metoprolol Tartrate.

(2) 0.2% w/v of *potassium sodium (+)-tartrate* in the mobile phase.

(3) Mix 1 volume of solution (2) and 2 volumes of a solution containing 0.005% w/v of *fumaric acid* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with particles of silica the surface of which has been modified by chemically bonded amine groups (10 µm) (Lichrosorb NH_2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

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1% w/v of *sodium chloride* in a mixture of 25 volumes of *methanol* and 75 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated peaks.

CONFIRMATION

The chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 5.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Evaporate a volume of the injection containing 25 mg of Metoprolol Tartrate to dryness at a temperature not exceeding 40° and dissolve the residue in 5 mL of the mobile phase.
(2) Dilute 1 volume of solution (1) to 20 volumes with mobile phase and dilute 3 volumes of this solution to 50 volumes with the mobile phase.
(3) 0.005% w/v of *metoprolol tartrate BPCRS* and 0.003% w/v of *metoprolol impurity A EPCRS* in the mobile phase.
(4) Prepare the solution in a fume cupboard in the following manner if necessary (see limits below). Place an evaporating dish 10 cm in diameter containing 10 mL of a 0.1% w/v solution of *metoprolol tartrate BPCRS* in 0.1M *hydrochloric acid* so that the surface of the solution is 5 cm from a lamp emitting *ultraviolet light at (254 nm)* for 6 hours. Dilute 1 volume of this solution to 50 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for three times the retention time of metoprolol.
When the chromatograms are recorded under the prescribed conditions, the retention time of metoprolol is about 7 minutes, the relative retention of metoprolol impurity C is 0.3 and the relative retention of metoprolol impurity A is 0.7.

MOBILE PHASE

2 volumes of *triethylamine*, 3 volumes of *orthophosphoric acid*, 10 volumes of *glacial acetic acid*, 146 volumes of *acetonitrile* and 810 volumes of a 0.39% w/v solution of *ammonium acetate*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to metoprolol and metoprolol impurity A is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any *secondary peaks* is not greater than 1.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

If any of the above limits are exceeded, and if a *secondary peak* occurs with a retention time of about 2 minutes (metoprolol impurity C), then in the chromatogram obtained with solution (1): divide the area of the peak corresponding to the principal peak in the chromatogram obtained with solution (4) (metoprolol impurity C) by 10: this divided area is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%); the sum of this divided area and the areas of any other *secondary peaks* is not greater than 1.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.17 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Dilute a volume of the injection containing 3 mg of Metoprolol Tartrate to 20 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 274 nm, Appendix II B. Calculate the content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ from the *absorbance* obtained with a 0.015% w/v solution of *metoprolol tartrate BPCRS* and from the declared content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ in *metoprolol tartrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Metoprolol Tartrate.

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Metoprolol Oral Suspension

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Metoprolol Oral Suspension is a suspension of Metoprolol Tartrate in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of metoprolol tartrate, $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Shake a quantity of the oral suspension containing 50 mg of Metoprolol Tartrate with 20 mL and shake. Dilute to 100 mL and mix.

(2) 0.05% w/v of *metoprolol tartrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Place the plate in a tank containing 2 beakers, each of which contains 30 mL of 18M *ammonia*, saturated with vapour from the mobile phase and develop to 15 cm.

(e) After removal of the plate, dry in air, expose to iodine vapour for at least 15 hours and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *methanol* and 4 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

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TESTS

Acidity

pH, 3.6 to 4.6, Appendix V L.

Dissolution

The requirement stated under Unlicensed Medicines, Oral Suspensions does not apply to Metoprolol Oral Suspension.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in mobile phase A.

(1) Disperse a quantity of the oral suspension with sufficient of the mobile phase to produce a solution containing 0.2% w/v of Metoprolol Tartrate and filter (a 0.45-µm PTFE filter is suitable).
(2) Dilute 1 volume of solution (1) to 20 volumes and dilute 3 volumes of this solution to 50 volumes.
(3) Dilute 1 volume of solution (2) to 3 volumes.
(4) 0.003% w/v of *metoprolol impurity A EPCRS* and 0.005% w/v of *metoprolol tartrate BPCRS*.
(5) Prepare the solution in a fume cupboard in the following manner (generation of impurity C). Place an evaporating dish 10 cm in diameter containing 10 mL of a 0.1% w/v solution of *metoprolol tartrate BPCRS* in 0.1M *hydrochloric acid* so that the surface of the solution is 5 cm from a lamp emitting *ultraviolet light (254 nm)* for 6 hours. Dilute 1 volume of this solution to 50 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to metoprolol (retention time, about 7 minutes) are : impurity H, about 0.3; impurity C, about 0.4; impurity G, about 0.45; impurity F, about 0.7; impurity A, about 0.8; impurity J, about 1.4; impurity D, about 1.6; impurity E, about 1.8; impurity B, about 2.

MOBILE PHASE

Mobile phase A 2 volumes of *triethylamine*, 3 volumes of *orthophosphoric acid*, 10 volumes of *glacial acetic acid*, 146 volumes of *acetonitrile* and 810 volumes of a 0.48% w/v solution of *ammonium acetate*.

Mobile phase B *acetonitrile*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100→25	0→75	linear gradient
30-31	25→100	75→0	linear gradient
31-40	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to metoprolol and metoprolol impurity A is at least 6.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity C using the chromatogram obtained with solution (5) and multiply the area of any such peak by the following correction factor: 0.1.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any *secondary peaks* is not greater than 1.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in the mobile phase.

(1) Dilute a weighed quantity of the oral suspension containing 10 mg of Metoprolol Tartrate to 100 mL.
(2) 0.01% w/v of *metoprolol tartrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 223 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

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40 volumes of *methanol* and 60 volumes of a solution containing 0.0174% w/v of *anhydrous sodium acetate*, 0.204% w/v of *sodium pentanesulfonate monohydrate* and 0.128% v/v of *glacial acetic acid*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$, weight in volume, using the declared content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ in *metoprolol tartrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, D, E, F, G, H and J listed under Metoprolol Tartrate.

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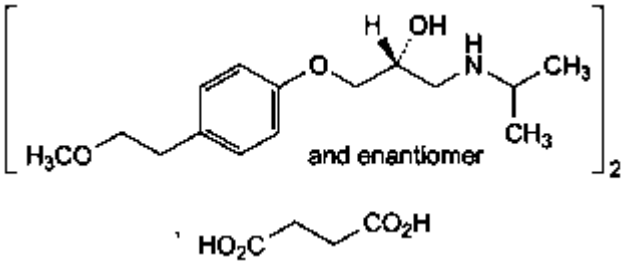
Metoprolol Succinate

General Notices

(Ph. Eur. monograph 1448)



$C_{34}H_{56}N_2O_{10}$ 653 *98418-47-4*

Action and use

Beta-adrenoceptor antagonist.

Ph Eur

DEFINITION

Bis[(2*RS*)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol] butanedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in methanol, slightly soluble in ethanol (96 per cent), very slightly soluble in ethyl acetate.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of metoprolol succinate*.

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TESTS

Solution S

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

7.0 to 7.6 for solution S.

Impurities M, N, O

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dilute 1 mL of the test solution to 50 mL with *methanol R*. Dilute 5 mL of this solution to 50 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase Place 2 beakers, each containing 30 volumes of *concentrated ammonia R*, at the bottom of a chromatographic tank containing a mixture of 20 volumes of *methanol R* and 80 volumes of *ethyl acetate R*.

Application 10 µL.

Development Over 2/3 of the plate in a tank saturated for at least 1 h.

Drying In air for at least 3 h.

Detection Expose the plate to iodine vapour for at least 15 h.

Limits:

— *any impurity*: any spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.2 per cent);

— *disregard* any spot on the line of application.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

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Reference solution (a) Dissolve 1.5 mg of *metoprolol impurity A CRS* and 2.5 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 3.9 g of *ammonium acetate R* in 810 mL of *water R*, add 2.0 mL of *triethylamine R*, 3.0 mL of *phosphoric acid R*, 10.0 mL of *glacial acetic acid R* and 146 mL of *acetonitrile R* and mix.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 3 times the retention time of metoprolol.

Relative retention With reference to metoprolol (retention time = about 7 min): impurity C = about 0.4; impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 6.0 between the peaks due to impurity A and metoprolol.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.1;

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to succinic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 40 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 32.64 mg of $C_{34}H_{56}N_2O_{10}$.

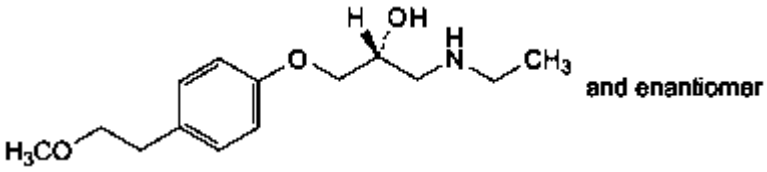
STORAGE

Protected from light.

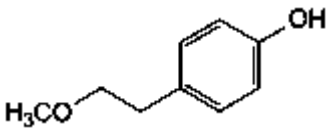
IMPURITIES

Specified impurities C, M, N, O.

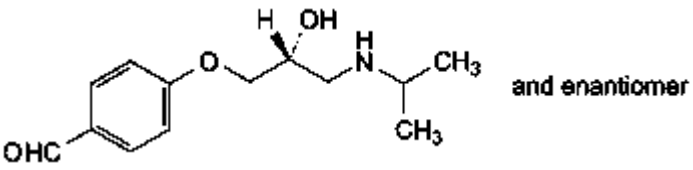
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D, E, F, G, H, J.



A. (2*RS*)-1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,



B. 4-(2-methoxyethyl)phenol,



C. 4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]benzaldehyde,

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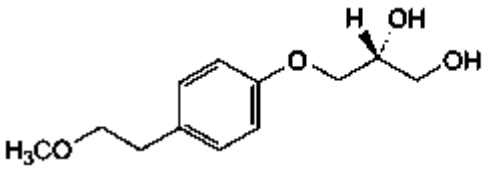
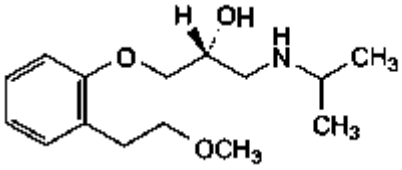


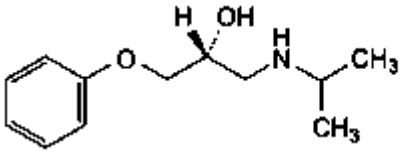
and enantiomer

D. (2*RS*)-3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol,



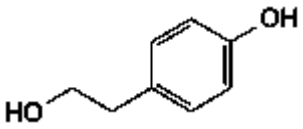
and enantiomer

E. (2*RS*)-1-[2-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,

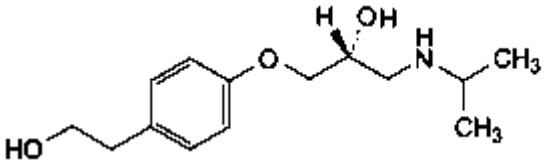


and enantiomer

F. (2*RS*)-1-[(1-methylethyl)amino]-3-phenoxypropan-2-ol,

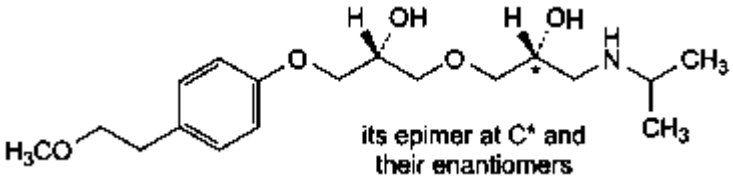


G. 2-(4-hydroxyphenyl)ethanol,

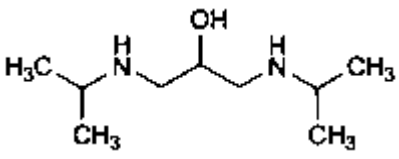


and enantiomer

H. (2*RS*)-1-[4-(2-hydroxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,



J. mixture of the 4 stereoisomers of 1-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,



M. 1,3-bis[(1-methylethyl)amino]propan-2-ol,

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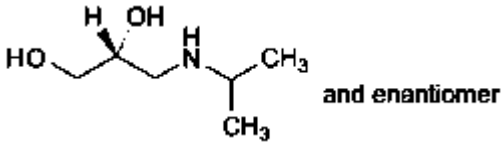
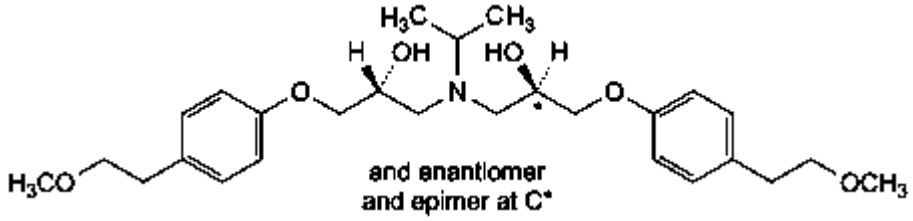


N. (2*RS*)-3-[(1-methylethyl)amino]propane-1,2-diol,



O. mixture of the 3 stereoisomers of 1,1′-[(1-methylethyl)imino]bis[3-[4-(2-methoxyethyl)phenoxy]propan-2-ol].

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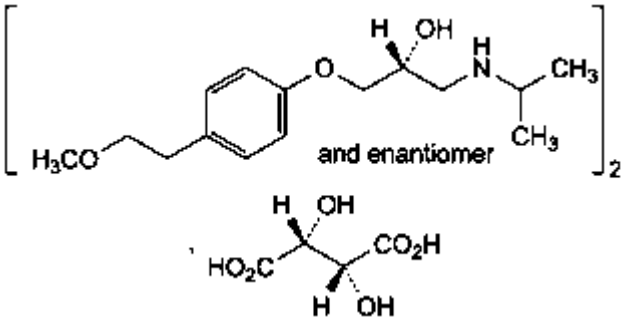
Metoprolol Tartrate

General Notices

(Ph. Eur. monograph 1028)



$C_{34}H_{56}N_2O_{12}$ 685 *56392-17-7*

Action and use

Beta-adrenoceptor antagonist.

Preparations

Metoprolol Injection

Metoprolol Oral Suspension

Metoprolol Tartrate Prolonged-release Tablets

Metoprolol Tartrate Tablets

Ph Eur

DEFINITION

Bis[(2*RS*)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol] (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

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White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *metoprolol tartrate CRS*.

If the spectra obtained in the solid state show differences, record further spectra using discs prepared by placing 25 µL of a 100 g/L solution in *methylene chloride R* on a disc of *potassium bromide R* and evaporating the solvent. Examine immediately.

TESTS

Solution S

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 7.0 for solution S.

Specific optical rotation (*2.2.7*)

+ 7.0 to + 10.0 (dried substance), determined on solution S.

Impurities M, N, O

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 20 mL with *methanol R*. Dilute 5 mL of this solution to 50 mL with *methanol R*.

Reference solution (b) Dilute 4 mL of reference solution (a) to 10 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase Place 2 beakers, each containing 30 volumes of *concentrated ammonia R*, at the bottom of a chromatographic tank containing a mixture of 20 volumes of *methanol R* and 80 volumes of *ethyl acetate R*.

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Application 5 µL.

Development Over 2/3 of the plate in a tank saturated for at least 1 h.

Drying In air for at least 3 h.

Detection Expose the plate to iodine vapour for at least 15 h.

Limits:

— *any impurity*: any spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent) and at most 1 such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard* any spot on the line of application.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 1.5 mg of *metoprolol impurity A CRS* and 2.5 mg of *metoprolol tartrate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 3.9 g of *ammonium acetate R* in 810 mL of *water R*, add 2.0 mL of *triethylamine R*, 3.0 mL of *phosphoric acid R*, 10.0 mL of *glacial acetic acid R* and 146 mL of *acetonitrile R* and mix.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 3 times the retention time of metoprolol.

Relative retention With reference to metoprolol (retention time = about 7 min): impurity H = about 0.3; impurity C = about 0.4; impurity G = about 0.45; impurity F = about 0.7; impurity A = about 0.8; impurity J = about 1.4; impurity D = about 1.6; impurity E = about 1.8; impurity B = about 2.

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System suitability Reference solution (a):

— *resolution*: minimum 6.0 between the peaks due to impurity A and metoprolol.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.1;

— *impurities A, B, C, D, E, F, G, H, J*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to tartaric acid.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* over *anhydrous calcium chloride R* for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

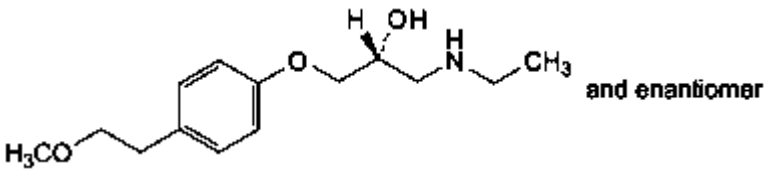
1 mL of *0.1 M perchloric acid* is equivalent to 34.24 mg of $C_{34}H_{56}N_2O_{12}$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, J, M, N, O.*



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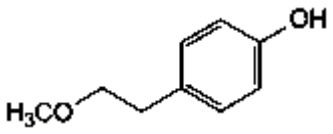
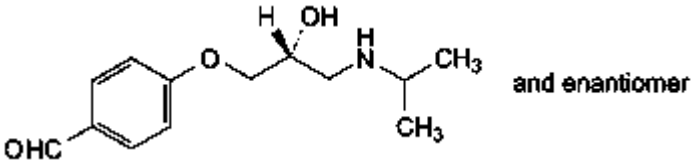
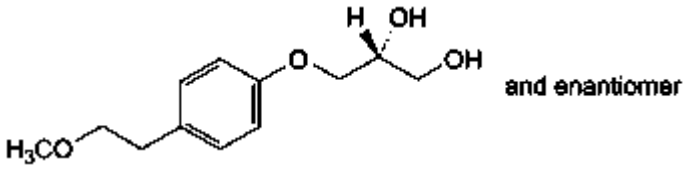
A. (2*RS*)-1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,



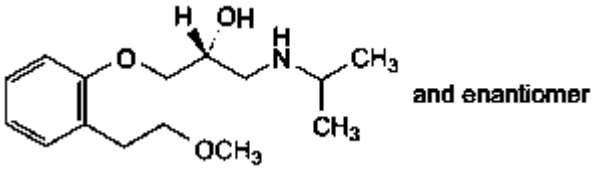
B. 4-(2-methoxyethyl)phenol,



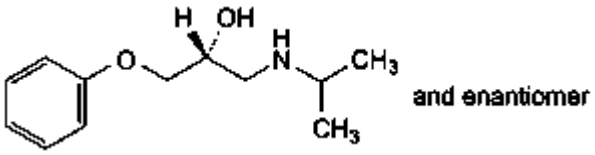
C. 4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]benzaldehyde,



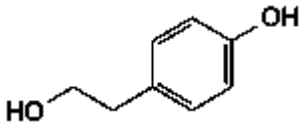
D. (2*RS*)-3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol,



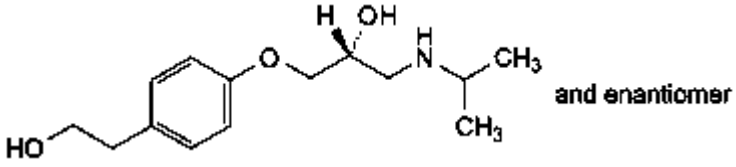
E. (2*RS*)-1-[2-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,



F. (2*RS*)-1-[(1-methylethyl)amino]-3-phenoxypropan-2-ol,



G. 2-(4-hydroxyphenyl)ethanol,



H. (2*RS*)-1-[4-(2-hydroxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,

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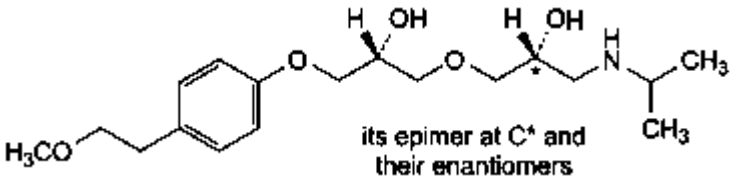
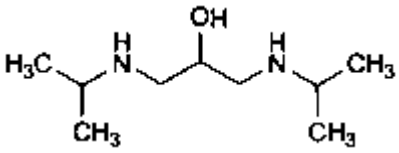
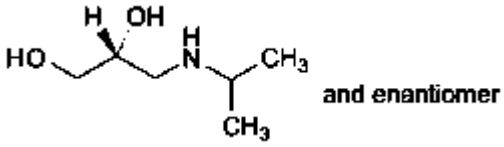


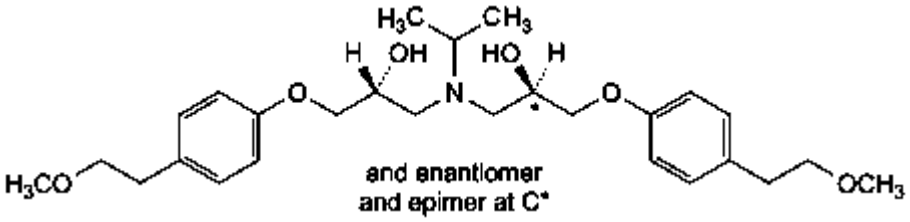
J. mixture of the 4 stereoisomers of 1-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol,



M. 1,3-bis[(1-methylethyl)amino]propan-2-ol,



N. (2*RS*)-3-[(1-methylethyl)amino]propane-1,2-diol,



O. mixture of the 3 stereoisomers of 1,1′-[(1-methylethyl)imino]bis[3-[4-(2-methoxyethyl)phenoxy]propan-2-ol].

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Metoprolol Tartrate Prolonged-release Tablets

General Notices

Prolonged-release Metoprolol Tartate Tablets

Metoprolol Tartrate Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Metoprolol Tartrate Prolonged-release Tablets contain Metoprolol Tartrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Metoprolol Tartrate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of metoprolol tartrate, $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity of the powdered tablets containing 50 mg of Metoprolol Tartrate with 25 mL of *water*, add 2 mL of 5M *ammonia*, extract with 20 mL of *dichloromethane*, filter the dichloromethane layer through *anhydrous sodium sulfate*, wash the filter with 10 mL of *dichloromethane* and evaporate the combined filtrate and washings to dryness using a rotary evaporator, using gentle heat if necessary. Cool the residue to –18° for 30 minutes and allow to warm to room temperature. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of metoprolol *(RS 228)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Metoprolol Tartrate with 15 mL of *methanol* for 1 hour, add sufficient *methanol* to produce 25 mL and mix. Filter through a glass microfibre filter (Whatman GF/F is suitable) and use the filtrate.

(2) 2.0% w/v of *metoprolol tartrate BPCRS* in *methanol*.

(3) 0.5% w/v of *(+)-tartaric acid* in *methanol*.

(4) Mix 1 volume of solution (1) with 1 volume of solution (3).

CHROMATOGRAPHIC CONDITIONS

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CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel H* precoated plate (Analtech Uniplate plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 5 cm.

(e) After removal of the plate, dry in air for about 10 minutes, dry in an oven at 100° for 20 minutes and spray the plate with a solution prepared in the following manner. Dissolve 75 mg of *bromocresol green* and 25 mg of *bromophenol blue* in 100 mL of *absolute ethanol* (solution A); dissolve 0.25 g of *potassium permanganate* and 0.5 g of *sodium carbonate* in 100 mL of *water* (solution B); mix 9 volumes of solution A and 1 volume of solution B and use immediately.

MOBILE PHASE

40 volumes of *anhydrous formic acid* and 140 volumes of *ether*.

SYSTEM SUITABILITY

The chromatogram obtained with solution (1) closely resembles the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated principal spots; the spot of lower Rf value is purple and the spot of higher Rf value, which is a single, compact spot, is yellow.

CONFIRMATION

In the chromatogram obtained with solution (1) the spot with the higher Rf value corresponds to the spot in the chromatogram obtained with solution (3).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Metoprolol Tartrate with 20 mL of *chloroform* for 10 minutes, centrifuge, remove and retain the supernatant layer. Extract the residue with a further 20 mL quantity of *chloroform*, centrifuge and remove the supernatant layer. Evaporate the combined chloroform extracts to dryness at ambient temperature, add sufficient mobile phase to produce 25 mL and mix. Dilute 5 volumes of this solution to 20 volumes with mobile phase, mix and filter.

(2) Dilute 1 volume of solution (1) to 20 volumes with mobile phase and dilute 3 volumes of this solution to 50 volumes with mobile phase.

(3) 0.005% w/v of *metoprolol tartrate BPCRS* and 0.003% w/v of *metoprolol impurity A EPCRS* in the mobile phase.

(4) Prepare the solution in a fume cupboard in the following manner if necessary (see limits below). Place an evaporating dish 10 cm in diameter containing 10 mL of a 0.1% w/v solution of *metoprolol tartrate BPCRS* in 0.1M *hydrochloric acid* so that the surface of the solution is 5 cm from a lamp emitting *ultraviolet light at (254 nm)* for 6 hours. Dilute 1 volume of this solution to 50 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

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(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of metoprolol. When the chromatograms are recorded under the prescribed conditions the retention time of metoprolol is about 7 minutes, the relative retention of metoprolol impurity C is 0.3 and the relative retention of metoprolol impurity A is 0.7.

MOBILE PHASE

2 volumes of *triethylamine*, 3 volumes of *orthophosphoric acid*, 10 volumes of *glacial acetic acid*, 146 volumes of *acetonitrile* and 810 volumes of a 0.39% w/v solution of *ammonium acetate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to metoprolol and metoprolol impurity A is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any *secondary peaks* is not greater than 1.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

If any of the above limits are exceeded, and if a *secondary peak* occurs with a retention time of about 2 minutes (metoprolol impurity C), then in the chromatogram obtained with solution (1): divide the area of the peak corresponding to the principal peak in the chromatogram obtained with solution (4) (metoprolol impurity C) by 10: this divided area is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%); the sum of this divided area and the areas of any other *secondary peaks* is not greater than 1.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.17 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Add to a quantity of the powdered tablets containing 75 mg of Metoprolol Tartrate 150 mL of *absolute ethanol*, shake with the aid of ultrasound for 15 minutes, allow to cool, add sufficient *absolute ethanol* to produce 200 mL and filter (Whatman GF/C paper is suitable). To 20 mL of the filtrate add sufficient *absolute ethanol* to produce 50 mL and measure the *absorbance* of the resulting solution at the maximum at 274 nm, Appendix II B. Calculate the content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ from the *absorbance* obtained with a 0.015% w/v solution of *metoprolol tartrate BPCRS* in *absolute ethanol* and from the declared content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ in *metoprolol tartrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Metoprolol Tartrate.

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Metoprolol Tartrate Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Metoprolol Tartrate Tablets contain Metoprolol Tartrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of metoprolol tartrate, $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity of the powdered tablets containing 50 mg of Metoprolol Tartrate with 25 mL of *water*, add 2 mL of 5M *ammonia*, extract with 20 mL of *dichloromethane*, filter the dichloromethane layer through *anhydrous sodium sulfate*, wash the filter with 10 mL of *dichloromethane* and evaporate the combined filtrate and washings to dryness using a rotary evaporator, using gentle heat if necessary. Cool the residue to –18° for 30 minutes and allow to warm to room temperature. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of metoprolol *(RS 228)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Metoprolol Tartrate with 15 mL of *methanol* for 1 hour, add sufficient *methanol* to produce 25 mL and mix. Filter through a glass microfibre filter (Whatman GF/F is suitable) and use the filtrate.

(2) 2.0% w/v of *metoprolol tartrate BPCRS* in *methanol*.

(3) 0.5% w/v of *(+)-tartaric acid* in *methanol*.

(4) Mix 1 volume of solution (1) with 1 volume of solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel H* precoated plate (Analtech Uniplate plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 5 cm.

(e) After removal of the plate, dry in air for about 10 minutes, dry in an oven at 100° for 20 minutes and spray the plate with a solution prepared in the following manner. Dissolve 75 mg of *bromocresol green* and 25 mg of *bromophenol blue* in 100 mL of *absolute ethanol* (solution A); dissolve 0.25 g of *potassium permanganate* and 0.5 g of *sodium carbonate* in 100 mL of *water* (solution B); mix 9 volumes of solution A and 1 volume of solution B and use immediately.

MOBILE PHASE

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MOBILE PHASE

40 volumes of *anhydrous formic acid* and 140 volumes of *ether*.

SYSTEM SUITABILITY

The chromatogram obtained with solution (1) closely resembles the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated principal spots; the spot of lower Rf value is purple and the spot of higher Rf value, which is a single, compact spot, is yellow.

CONFIRMATION

In the chromatogram obtained with solution (1) the spot with the higher Rf value corresponds to the spot in the chromatogram obtained with solution (3).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Metoprolol Tartrate with 20 mL of *chloroform* for 10 minutes, centrifuge, remove and retain the supernatant layer. Extract the residue with a further 20 mL quantity of *chloroform*, centrifuge and remove the supernatant layer. Evaporate the combined chloroform extracts to dryness at ambient temperature, add sufficient mobile phase to produce 25 mL and mix. Dilute 5 volumes of this solution to 20 volumes with the mobile phase, mix and filter.

(2) Dilute 1 volume of solution (1) to 20 volumes with the mobile phase and dilute 3 volumes of this solution to 50 volumes with the mobile phase.

(3) 0.005% w/v of *metoprolol tartrate BPCRS* and 0.003% w/v of *metoprolol impurity A EPCRS* in the mobile phase.

(4) Prepare the solution in a fume cupboard in the following manner if necessary (see limits below). Place an evaporating dish 10 cm in diameter containing 10 mL of a 0.1% w/v solution of *metoprolol tartrate BPCRS* in 0.1M *hydrochloric acid* so that the surface of the solution is 5 cm from a lamp emitting *ultraviolet light at (254 nm)* for 6 hours. Dilute 1 volume of this solution to 50 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of metoprolol.

When the chromatograms are recorded under the prescribed conditions, the retention time of metoprolol is about 10 minutes, the relative retention of metoprolol impurity C is 0.3 and the relative retention of metoprolol impurity A is 0.7.

MOBILE PHASE

2 volumes of *triethylamine*, 3 volumes of *orthophosphoric acid*, 10 volumes of *glacial acetic acid*, 146 volumes of *acetonitrile* and 810 volumes of a 0.39% w/v solution of *ammonium acetate*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to metoprolol and metoprolol impurity A is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any *secondary peaks* is not greater than 1.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

If any of the above limits are exceeded, and if a *secondary peak* occurs with a retention time of about 2 minutes (metoprolol impurity C), then in the chromatogram obtained with solution (1): divide the area of the peak corresponding to the principal peak in the chromatogram obtained with solution (4) (metoprolol impurity C) by 10: this divided area is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%); the sum of this divided area and the areas of any other *secondary peaks* is not greater than 1.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.17 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Add to a quantity of the powdered tablets containing 75 mg of Metoprolol Tartrate 150 mL of *absolute ethanol*, shake with the aid of ultrasound for 15 minutes, allow to cool, add sufficient *absolute ethanol* to produce 200 mL and filter (Whatman GF/C paper is suitable). To 20 mL of the filtrate add sufficient *absolute ethanol* to produce 50 mL and measure the *absorbance* of the resulting solution at the maximum at 274 nm, Appendix II B. Calculate the content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ from the *absorbance* obtained with a 0.015% w/v solution of *metoprolol tartrate BPCRS* in *absolute ethanol* and from the declared content of $(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ in *metoprolol tartrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Metoprolol Tartrate.

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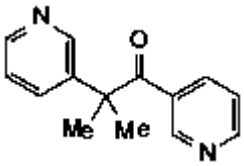
Metyrapone

General Notices



$C_{14}H_{14}N_2O$ 226.3 *54-36-4*

Action and use

11-Beta-hydroxylase inhibitor; inhibition of the formation of corticosteroids.

Preparation

Metyrapone Capsules

DEFINITION

Metyrapone is 2-methyl-1,2-di(3-pyridyl)-propan-1-one. It contains not less than 97.0% and not more than 103.0% of $C_{14}H_{14}N_2O$, calculated with reference to the dried substance.

CHARACTERISTICS

A white to light amber, crystalline powder.

Sparingly soluble in *water*; freely soluble in *ethanol (96%)*. It dissolves in dilute mineral acids.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with *reference spectrum 1* of metyrapone *(RS 230)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.002% w/v solution in *0.1M hydrochloric acid* exhibits a maximum only at 260 nm. The *absorbance* at 260 nm is about 1.0.

C. To 5 mL of a 1% w/v solution in 1M *sulfuric acid* add 0.2 mL of *potassium tetraiodomercurate solution*. A cream precipitate is produced.

TESTS

Melting point

50° to 53°, Appendix V A.

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Related substances

Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 90 volumes of *propan-2-ol*, 5 volumes of 13.5M *ammonia* and 5 volumes of *water* as the mobile phase. Apply separately to the plate 10 µL of each of two solutions of the substance being examined in *dichloromethane* containing (1) 5.0% w/v and (2) 0.010% w/v. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Loss on drying

When dried over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 6 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out the following procedure protected from light. Dissolve 0.1 g in sufficient *0.1M hydrochloric acid* to produce 100 mL. Dilute 5 mL to 50 mL with *0.1M hydrochloric acid* and dilute 5 mL of this solution to 50 mL with *0.1M hydrochloric acid*. Measure the *absorbance* of the resulting solution at the maximum at 260 nm, Appendix II B. Calculate the content of $C_{14}H_{14}N_2O$ taking 500 as the value of A(1%, 1 cm) at the maximum at 260 nm.

STORAGE

Metyrapone should be protected from light.

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Metyrapone Capsules

General Notices

Action and use

11-Beta hydroxylase inhibitor; inhibition of the formation of corticosteroids.

DEFINITION

Metyrapone Capsules contain Metyrapone.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of metyrapone, $C_{14}H_{14}N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum* of the contents of the capsules, Appendix II A, is concordant with *reference spectrum 2* of metyrapone *(RS 231)*.

B. To a quantity of the contents of the capsules containing 50 mg of Metyrapone add 5 mL of 0.5M *sulfuric acid* and 0.2 mL of *potassium tetraiodomercurate solution*. A cream precipitate is produced.

TESTS

Related substances

Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of the capsules containing 0.5 g of Metyrapone in 10 mL of *chloroform*.

(2) Dilute 1 volume of solution (1) to 500 volumes with *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of 13.5M *ammonia*, 5 volumes of *water* and 90 volumes of *propan-2-ol*.

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LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%).

ASSAY

Weigh 10 capsules. Open the capsules carefully without loss of shell material, express as much of the contents as possible and reserve the expressed material. Wash the shells with *ether*, discard the washings, allow the shells to stand at room temperature for about 5 minutes and weigh. The difference between the weights represents the weight of the total contents. Dissolve a quantity of the contents containing 0.1 g of Metyrapone in 40 mL of 0.1M *hydrochloric acid* and add sufficient 0.1M *hydrochloric acid* to produce 100 mL. Dilute 5 mL to 50 mL with 0.1M *hydrochloric acid* and dilute 5 mL of this solution to 50 mL with 0.1M *hydrochloric acid*. Measure the *absorbance* of the resulting solution at the maximum at 260 nm, Appendix II B. Calculate the content of $C_{14}H_{14}N_2O$ in the capsules taking 500 as the value of A(1%, 1 cm) at the maximum at 260 nm.

STORAGE

Metyrapone Capsules should be protected from light.

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Methacrylic Acid - Ethyl Acrylate Copolymer (1:1)

General Notices

(Ph. Eur. monograph 1128)

Action and use

Pharmaceutical aid.

Ph Eur

DEFINITION

Copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1:1. The substance is in the acid form (type A) or partially neutralised using sodium hydroxide (type B). It may contain suitable surface-active agents such as sodium dodecyl sulfate and polysorbate 80.

Content

— *type A*: 46.0 per cent to 50.6 per cent of methacrylic acid units (dried substance);

— *type B*: 43.0 per cent to 48.0 per cent of methacrylic acid units (dried substance).

CHARACTERS

Appearance

White or almost white, free-flowing powder.

Solubility

Practically insoluble in water (type A) or dispersible in water (type B), freely soluble in anhydrous ethanol, practically insoluble in ethyl acetate. It is freely soluble in a 40 g/L solution of sodium hydroxide.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dissolve 0.1 g of the substance to be examined in 1 mL of *ethanol (90 per cent V/V) R* and place 2 drops of the solution on a sodium chloride plate; dry to allow the formation of a film and cover with another sodium chloride plate.

Comparison *methacrylic acid - ethyl acrylate copolymer (1:1) - type A CRS* or *methacrylic acid - ethyl acrylate copolymer (1:1) - type B CRS*.

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B. It complies with the limits of the assay.

C. Sulfated ash (see Tests).

TESTS

Viscosity (2.2.10)

— *Type A*: 100 mPa·s to 200 mPa·s.

Dissolve a quantity of the substance to be examined corresponding to 37.5 g of the dried substance in a mixture of 7.9 g of *water R* and 254.6 g of *2-propanol R*. Determine the viscosity at 20 °C using a rotating viscometer at a shear rate of 10 s^{-1}.

— *Type B*: maximum 100 mPa·s.

Disperse a quantity of the substance to be examined corresponding to 80.0 g of the dried substance in *water R* and make up to 400 g with the same solvent. Stir for 3 h and determine the viscosity at 23 °C using a rotating viscometer and a spindle rotating at 100 r/min.

Dimensions of the spindle Diameter = 47.0 mm; height = 27.0 mm; shaft diameter = 3.18 mm.

Appearance of a film

Spread 1 mL of the solution (type A) or dispersion (type B) prepared for the test for viscosity on a glass plate and allow to dry. A clear, brittle film is formed.

Ethyl acrylate and methacrylic acid

Liquid chromatography (2.2.29).

Solution A Dissolve 3.5 g of *sodium perchlorate R* in *water R* and dilute to 100.0 mL with the same solvent.

Blank solution *methanol R*, solution A (50:50 *V/V*).

Test solution Dissolve 3.0 g of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent. To 5.0 mL of solution A add 5.0 mL of the solution dropwise whilst stirring continuously. Centrifuge until a clear supernatant is obtained. Use the clear supernatant as the test solution.

Reference solution Dissolve 50.0 mg of *ethyl acrylate R* and 50.0 mg of *methacrylic acid R* in 5 mL of *butanol R* and dilute to 100.0 mL with *methanol R*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 10.0 mL with *methanol R*. Mix 5.0 mL of this solution and 5.0 mL of solution A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 20 volumes of *methanol R2* and 80 volumes of *water for chromatography R* previously adjusted to pH 2.0 with *phosphoric acid R*.

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Flow rate 2.0 mL/min.

Detection Spectrophotometer at 202 nm.

Injection 20 µL.

Retention time Methacrylic acid = about 3 min; ethyl acrylate = about 9 min.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to methacrylic acid and ethyl acrylate in the chromatogram obtained with the reference solution;

— the chromatogram obtained with the blank solution does not show peaks with the same retention times as ethyl acrylate or methacrylic acid.

Calculation of percentage contents:

— for ethyl acrylate and methacrylic acid, use the respective concentration of these substances in the reference solution.

Limit:

— *sum of the contents of ethyl acrylate and methacrylic acid*: maximum 0.01 per cent;

— *reporting threshold*: 1 ppm.

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 6 h.

Sulfated ash (2.4.14)

Maximum 0.4 per cent (type A) or 0.5 per cent to 3.0 per cent (type B), determined on 1.0 g.

ASSAY

Dissolve 1.000 g in a mixture of 40 mL of *water R* and 60 mL of *2-propanol R*. Titrate slowly while stirring with *0.5 M sodium hydroxide*, using *phenolphthalein solution R* as indicator.

1 mL of *0.5 M sodium hydroxide* is equivalent to 43.05 mg of $C_4H_6O_2$ (methacrylic acid units).

LABELLING

The label states the type (type A or type B).

FUNCTIONALITY-RELATED CHARACTERISTICS

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This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for methacrylic acid - ethyl acrylate copolymer (1:1) used as gastro-resistant coating agent.

Viscosity

(see Tests).

Appearance of a film

(see Tests).

Solubility of a film

Take a piece of the film obtained in the test for appearance of a film (see Tests), place it in a flask containing a 10.3 g/L solution of *hydrochloric acid R* and stir; it does not dissolve within 2 h. Take another piece of the film, place it in a flask containing *phosphate buffer solution pH 6.0 R* and stir; it dissolves within 1 h.

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Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30 per cent

General Notices

(Ph. Eur. monograph 1129)

Action and use

Excipient.

Ph Eur

DEFINITION

Dispersion in water of a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1:1.

Content

46.0 per cent to 50.6 per cent of methacrylic acid units (residue on evaporation).

It may contain suitable surface-active agents such as sodium dodecyl sulfate and polysorbate 80.

CHARACTERS

Appearance

Opaque, white or almost white, slightly viscous liquid.

Solubility

Miscible with water. On addition of solvents such as acetone, anhydrous ethanol or 2-propanol, a precipitate is formed which dissolves on addition of excess solvent. It is miscible with a 40 g/L solution of sodium hydroxide.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent*.

B. It complies with the limits of the assay.

TESTS

Viscosity (*2.2.10*)

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Viscosity (2.2.10)

Maximum 15 mPa·s, determined using a rotating viscometer at 20 °C and at a shear rate of 50 s^{-1}.

Appearance of a film

Place 1 mL on a glass plate and allow to dry. A clear, brittle film is formed.

Particulate matter

Filter 100.0 g through a tared stainless steel sieve (90). Rinse with *water R* until a clear filtrate is obtained and dry at 100-105 °C. The residue weighs a maximum of 1.00 g.

Ethyl acrylate and methacrylic acid

Liquid chromatography (2.2.29).

Solution A Dissolve 3.5 g of *sodium perchlorate R* in *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Blank solution Solution A, *methanol R1* (1:2 *V/V*).

Test solution Dissolve 10.0 g of the dispersion to be examined in *methanol R1* and dilute to 50.0 mL with the same solvent. To 5.0 mL of solution A add 10.0 mL of the solution dropwise whilst stirring continuously. Centrifuge until a clear supernatant is obtained. Use the clear supernatant as the test solution.

Reference solution Dissolve 50.0 mg of *ethyl acrylate R* and 50.0 mg of *methacrylic acid R* in 5 mL of *butanol R* and dilute to 50.0 mL with *methanol R1*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R1*. Dilute 2.0 mL of this solution to 10.0 mL with *methanol R1*. Mix 10.0 mL of this solution and 5.0 mL of solution A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 20 volumes of *methanol R1* and 80 volumes of *water for chromatography R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 202 nm.

Injection 20 µL.

Retention time Methacrylic acid = about 3 min, ethyl acrylate = about 8 min.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to methacrylic acid and ethyl acrylate in the chromatogram obtained with the reference solution;

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— the chromatogram obtained with the blank solution does not show peaks with the same retention times as ethyl acrylate or methacrylic acid.

Calculation of percentage contents:

— for ethyl acrylate and methacrylic acid, use the respective concentration of these substances in the reference solution.

Limit:

— *sum of the contents of ethyl acrylate and methacrylic acid*: maximum 0.01 per cent;

— *reporting threshold*: 1 ppm.

Residue on evaporation

28.5 per cent to 31.5 per cent.

Dry 1.000 g at 110 °C for 5 h. The residue weighs not less than 0.285 g and not more than 0.315 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

ASSAY

Dissolve 1.500 g in a mixture of 40 mL of *water R* and 60 mL of *2-propanol R*. Titrate slowly while stirring with *0.5 M sodium hydroxide*, using *phenolphthalein solution R* as indicator.

1 mL of *0.5 M sodium hydroxide* is equivalent to 43.05 mg of $C_4H_6O_2$ (methacrylic acid units).

STORAGE

At a temperature of 5 °C to 25 °C, protected from freezing.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process

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and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent used as a gastro-resistant coating agent.

Viscosity

(see Tests).

Appearance of a film

(see Tests).

Solubility of a film

Take a piece of the film obtained in the test for appearance of a film (see Tests), place it in a flask containing a 10.3 g/L solution of *hydrochloric acid R* and stir; it does not dissolve within 2 h. Take another piece of the film, place it in a flask containing phosphate buffer solution pH 6.0 R and stir; it dissolves within 1 h.

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Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)

General Notices

(Ph. Eur. monograph 1127)

Action and use

Excipient.

Ph Eur

DEFINITION

Copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic groups to ester groups is about 1:1.

Content

46.0 per cent to 50.6 per cent of methacrylic acid units (dried substance).

CHARACTERS

Appearance

White or almost white, free-flowing powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol and in 2-propanol, practically insoluble in ethyl acetate. It is freely soluble in a 40 g/L solution of sodium hydroxide.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dissolve 0.1 g of the substance to be examined in 1 mL of *2-propanol R* and place 2 drops of the solution on a sodium chloride plate; dry to allow the formation of a film and cover with another sodium chloride plate.

Comparison *methacrylic acid - methyl methacrylate copolymer (1:1) CRS*.

B. It complies with the limits of the assay.

TESTS

Viscosity (*2.2.10*)

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Viscosity (2.2.10)

50 mPa·s to 200 mPa·s.

Dissolve a quantity of the substance to be examined corresponding to 37.5 g of the dried substance in a mixture of 7.9 g of *water R* and 254.6 g of *2-propanol R*. Determine the viscosity using a rotating viscometer at 20 °C and at a shear rate of 10 s^{-1}.

Appearance of a film

Place 1 mL of the solution prepared in the test for viscosity on a glass plate and allow to dry. A clear, brittle film is formed.

Methyl methacrylate and methacrylic acid

Liquid chromatography (*2.2.29*).

Blank solution Mix 3.0 mL of *methanol R1* and 10.0 mL of *0.125 M phosphate buffer solution pH 2.0 R*.

Test solution Dissolve 1.00 g of the substance to be examined in *methanol R1* and dilute to 50.0 mL with the same solvent. To 10.0 mL of *0.125 M phosphate buffer solution pH 2.0 R* add 3.0 mL of the solution dropwise whilst stirring continuously. Centrifuge until a clear supernatant is obtained. Use the clear supernatant as the test solution.

Reference solution Dissolve 50.0 mg of *methacrylic acid R* and 50.0 mg of *methyl methacrylate R* in 5 mL of *butanol R* and dilute to 100.0 mL with *methanol R1*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R1*. Mix 3.0 mL of this solution and 10.0 mL of *0.125 M phosphate buffer solution pH 2.0 R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 20 volumes of *methanol R1* and 80 volumes of *water for chromatography R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 202 nm.

Injection 20 µL.

Retention time Methacrylic acid = about 3 min; methyl methacrylate = about 9 min.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to methacrylic acid and methyl methacrylate in the chromatogram obtained with the reference solution;

— the chromatogram obtained with the blank solution does not show peaks with the same retention times as methacrylic acid or methyl methacrylate.

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Calculation of percentage contents:

— for methacrylic acid and methyl methacrylate, use the respective concentration of these substances in the reference solution.

Limits:

— *methacrylic acid*: maximum 0.03 per cent;

— *methyl methacrylate*: maximum 0.02 per cent.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 6 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 1.000 g in a mixture of 40 mL of *water R* and 60 mL of *2-propanol R*. Titrate slowly while stirring with *0.5 M sodium hydroxide*, using *phenolphthalein solution R* as indicator.

1 mL of *0.5 M sodium hydroxide* is equivalent to 43.05 mg of $C_4H_6O_2$ (methacrylic acid units).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for methacrylic acid-methyl methacrylate copolymer (1:1) used as gastro-resistant coating agent.

Viscosity

(see Tests).

Appearance of a film

(see Tests).

Solubility of a film

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Take a piece of the film obtained in the test for appearance of a film (see Tests), place it in a flask containing a 10.3 g/L solution of *hydrochloric acid R* and stir; it does not dissolve within 2 h. Take another piece of the film, place it in a flask containing phosphate buffer solution pH 6.8 R and stir; it dissolves within 1 h.

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Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)

General Notices

(Ph. Eur. monograph 1130)

Action and use

Excipient.

Ph Eur

DEFINITION

Copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic groups to ester groups is about 1:2.

Content

27.6 per cent to 30.7 per cent of methacrylic acid units (dried substance).

CHARACTERS

Appearance

White or almost white, free-flowing powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol and in 2-propanol, practically insoluble in ethyl acetate. It is freely soluble in a 40 g/L solution of sodium hydroxide.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dissolve 0.1 g of the substance to be examined in 1 mL of *2-propanol R* and place 2 drops of the solution on a sodium chloride plate; dry to allow the formation of a film and cover with another sodium chloride plate.

Comparison *methacrylic acid - methyl methacrylate copolymer (1:2) CRS*.

B. It complies with the limits of the assay.

TESTS

Viscosity (2.2.10)

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Viscosity (2.2.10)

50 mPa·s to 200 mPa·s.

Dissolve a quantity of the substance to be examined corresponding to 37.5 g of the dried substance in a mixture of 7.9 g of *water R* and 254.6 g of *2-propanol R*. Determine the viscosity using a rotating viscometer at 20 °C and at a shear rate of 10 s^{-1}.

Appearance of a film

Place 1 mL of the solution prepared in the test for viscosity on a glass plate and allow to dry. A clear, brittle film is formed.

Methyl methacrylate and methacrylic acid

Liquid chromatography (*2.2.29*).

Blank solution Mix 3.0 mL of *methanol R1* and 10.0 mL of *0.125 M phosphate buffer solution pH 2.0 R*.

Test solution Dissolve 1.00 g of the substance to be examined in *methanol R1* and dilute to 50.0 mL with the same solvent. To 10.0 mL of *0.125 M phosphate buffer solution pH 2.0 R* add 3.0 mL of the solution dropwise whilst stirring continuously. Centrifuge until a clear supernatant is obtained. Use the clear supernatant as the test solution.

Reference solution Dissolve 50.0 mg of *methacrylic acid R* and 50.0 mg of *methyl methacrylate R* in 5 mL of *butanol R* and dilute to 100.0 mL with *methanol R1*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R1*. Mix 3.0 mL of this solution and 10.0 mL of *0.125 M phosphate buffer solution pH 2.0 R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 20 volumes of *methanol R1* and 80 volumes of *water for chromatography R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 202 nm.

Injection 20 µL.

Retention time Methacrylic acid = about 3 min; methyl methacrylate = about 9 min.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to methacrylic acid and methyl methacrylate in the chromatogram obtained with the reference solution;

— the chromatogram obtained with the blank solution does not show peaks with the same retention times as methacrylic acid or methyl methacrylate.

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Calculation of percentage contents:

— for methacrylic acid and methyl methacrylate, use the respective concentration of these substances in the reference solution.

Limits:

— *methacrylic acid*: maximum 0.03 per cent;

— *methyl methacrylate*: maximum 0.02 per cent.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 6 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 1.000 g in a mixture of 40 mL of *water R* and 60 mL of *2-propanol R*. Titrate slowly while stirring with *0.5 M sodium hydroxide*, using *phenolphthalein solution R* as indicator.

1 mL of *0.5 M sodium hydroxide* is equivalent to 43.05 mg of $C_4H_6O_2$ (methacrylic acid units).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for methacrylic acid-methyl methacrylate copolymer (1:2) used as gastro-resistant coating agent.

Viscosity

(see Tests).

Appearance of a film

(see Tests).

Solubility of a film

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Take a piece of the film obtained in the test for appearance of a film (see Tests), place it in a flask containing a 10.3 g/L solution of *hydrochloric acid R* and stir; it does not dissolve within 2 h. Take another piece of the film, place it in a flask containing phosphate buffer solution pH 6.8 R and stir; it does not dissolve within 2 h. Take another piece of the film, place it in a flask containing 0.2 M phosphate buffer solution pH 7.5 R and stir; it dissolves within 1 h.

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Methadone Concentrate for Oral Solution

General Notices

Action and use

Opioid receptor agonist; analgesic; treatment of opioid dependence.

DEFINITION

Methadone Concentrate for Oral Solution contains Methadone Hydrochloride in a suitable aqueous vehicle. It is diluted in accordance with the manufacturer's instructions prior to administration.

The concentrate complies with the requirements stated under Oral Liquids and with the following requirements.

Content of methadone hydrochloride, $C_{21}H_{27}NO,HCl$

95.0 to 105.0% w/v of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the concentrate containing 50 mg of Methadone Hydrochloride, add 30 mL of *water* and sufficient 1M *sulfuric acid* to make the solution acid to *litmus paper*. Extract with two 20-mL quantities of *petroleum spirit* (*boiling range, 40° to 60°),* discarding the extracts. Make the solution alkaline to *litmus paper* with 5M *sodium hydroxide*, add 4 g of *sodium chloride*, shake to dissolve, extract with two 25-mL quantities of *ether* and wash the combined extracts with five 20-mL quantities of *water*. Shake the ether extract with *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness and dry the residue at a pressure of 2 kPa. Dissolve the residue in 10 mL of *ethanol (96%)*.

(2) 0.5% w/v of *methadone hydrochloride BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

1.5 volumes of *concentrated ammonia R1* and 100 volumes of *methanol*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

For products containing ethylcellulose

(1) Extract a quantity of the oral concentrate containing 5 mg of methadone hydrochloride with three 20-mL aliquots of *dichloromethane* and combine the organic layers. Filter through a phase separation filter, reduce the filtrate to a volume of 1 mL at a temperature not exceeding 30° under a stream of nitrogen and add sufficient *dichloromethane* to produce 5 mL.

For products not containing ethylcellulose

(1) To a weighed quantity of the oral concentrate containing 10 mg of methadone hydrochloride add 10 mL of a 10% w/v solution of *sodium carbamate*. Extract with three 20-mL aliquots of *dichloromethane* and combine the organic layers. Filter through a phase separation filter, reduce the filtrate to a volume of 1 mL at a temperature not exceeding 30° under a stream of nitrogen and add sufficient *dichloromethane* to produce 10 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with *dichloromethane*, further dilute 1 volume of this solution to 5 volumes with *dichloromethane*.

(3) 0.005% w/v each of *imipramine hydrochloride BPCRS* and *cyclobenzaprine hydrochloride BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (50 m × 0.32 mm) bonded with a 1.05-µm layer of *phenyl(5)methyl(95)polysiloxane* (Agilent HP-5 is suitable).

(b) Use helium as the carrier gas.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an inlet temperature of 200°, detector temperature of 250° and the column oven temperature described below.

(e) Use a flame ionisation detector.

(f) Inject 2 µL of each solution.

(g) Use a split ratio of 1:5

Time (Minutes)	Temperature (°C)	Comment
0-4	150→250	linear gradient
4-35	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methadone (retention time, about 23 minutes) are: imipramine, about 1.2 and cyclobenzaprine, about 1.25.

SYSTEM SUITABILITY

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The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and cyclobenzaprine is at least 3.0.

in the chromatogram obtained with solution (2), the *signal-to-noise ratio* of the principal peak is at least 20.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the concentrate with sufficient of the mobile phase to produce a 0.01% w/v solution of Methadone Hydrochloride.
(2) 0.01% w/v of *methadone hydrochloride BPCRS*.
(3) 0.01% w/v each of *methadone hydrochloride BPCRS* and *imipramine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Lichrosorb RP18 10µ is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of 0.02M *potassium dihydrogen orthophosphate*, adjust the pH of the mixture to pH 5.5 with 2M *orthophosphoric acid* or 2M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to methadone hydrochloride is about 4.5 minutes.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and methadone is at least 1.5.

DETERMINATION OF CONTENT

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Calculate the content of $C_{21}H_{27}NO,HCl$ in the oral concentrate from the chromatograms obtained and using the declared content of $C_{21}H_{27}NO,HCl$ in *methadone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Methadone Hydrochloride.

LABELLING

At the specific request of the prescriber, the concentrate may be diluted to a concentration other than 0.1% w/v in accordance with the manufacturer's instructions.

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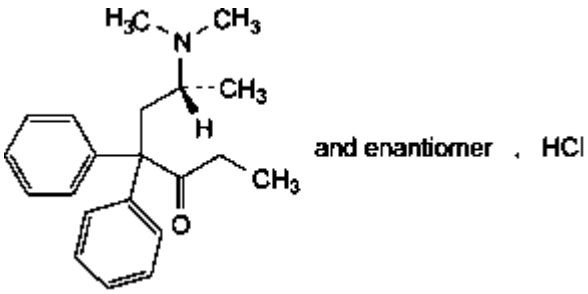
Methadone Hydrochloride

General Notices

(Ph. Eur. monograph 0408)



$C_{21}H_{28}ClNO$ 345.9 *1095-90-5*

Action and use

Opioid receptor agonist; analgesic; treatment of opioid dependence.

Preparations

Methadone Concentrate for Oral Solution

Methadone Injection

Methadone Oral Solution (1 mg per ml)

Methadone Tablets

Ph Eur

DEFINITION

(6*RS*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

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Solubility

Soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C, D.

Second identification: A, B, D.

A. Optical rotation (see Tests).

B. Melting point (2.2.14): 233 °C to 236 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of methadone hydrochloride*.

D. Dilute 1 mL of solution S (see Tests) to 5 mL with *water R* and add 1 mL of *dilute ammonia R1*. Mix, allow to stand for 5 min and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

Dilute 10 mL of solution S to 25 mL with *carbon dioxide-free water R*. To 10 mL of the solution add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Optical rotation (2.2.7)

-0.05° to + 0.05°, determined on solution S in a 2 dm tube.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *imipramine hydrochloride CRS* and 5 mg of *cyclobenzaprine hydrochloride CRS* in 100.0 mL of *methanol R*.

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Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 1.05 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.2 mL/min.

Injection liner Packed with deactivated glass wool to wipe the needle.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 4	150 → 250
	4 - 35	250
Injection port		200
Detector		250

Detection Flame ionisation.

Injection 2 µL.

Run time 1.5 times the retention time of methadone.

Relative retention With reference to methadone (retention time = about 25 min): impurity E = about 0.44; impurity C = about 0.81; impurity B = about 0.89; impurity D = about 0.98; impurity A = about 1.14; imipramine = about 1.19; cyclobenzaprine = about 1.24.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to imipramine and cyclobenzaprine.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

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— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 5 mL of *0.01 M hydrochloric acid* and 50 mL of *anhydrous ethanol R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion. Carry out a blank titration.

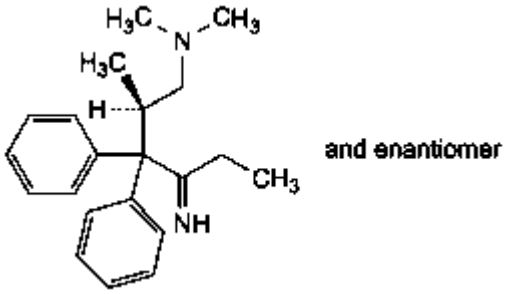
1 mL of *0.1 M sodium hydroxide* is equivalent to 34.59 mg of $C_{21}H_{28}ClNO$.

STORAGE

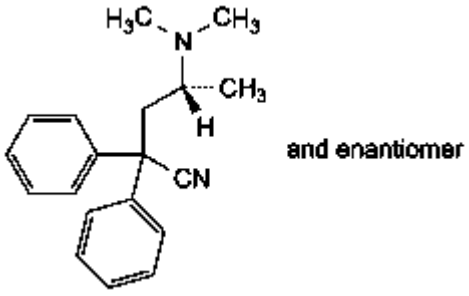
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*



A. (2*RS*)-4-imino-*N*,*N*,2-trimethyl-3,3-diphenylhexan-1-amine (isomethadone ketimine),



B. (4*RS*)-4-(dimethylamino)-2,2-diphenylpentanenitrile (didiavalo),

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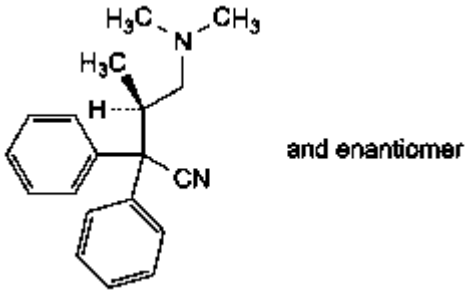
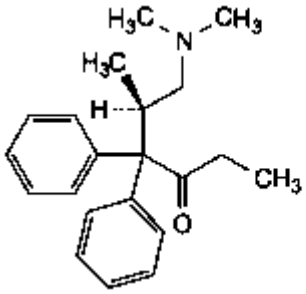


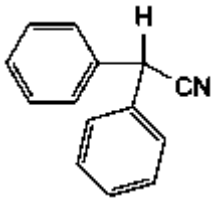
and enantiomer

C. (3*RS*)-4-(dimethylamino)-3-methyl-2,2-diphenylbutanenitrile (isodidiavalo),



and enantiomer

D. (5*RS*)-6-(dimethylamino)-5-methyl-4,4-diphenylhexan-3-one (isomethadone),



E. diphenylacetonitrile.

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Methadone Injection

General Notices

Action and use

Opioid receptor agonist; analgesic; treatment of opioid dependence.

DEFINITION

Methadone Injection is a sterile solution of Methadone Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of methadone hydrochloride, $C_{21}H_{27}NO,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Make a volume containing 0.1 g of Methadone Hydrochloride alkaline with 5M *sodium hydroxide*, stir with a glass rod until the precipitate solidifies, filter, wash with *water* and dry in a vacuum at room temperature at a pressure of 2 kPa. The *infrared absorption spectrum*, Appendix II A, of the residue is concordant with the *reference spectrum* of methadone *(RS 218)*.

TESTS

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Dilute a quantity of the injection containing 10 mg of Methadone Hydrochloride to 10 mL with *methanol*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*, further dilute 1 volume of this solution to 5 volumes with *methanol*.

(3) 0.005% w/v each of *imipramine hydrochloride BPCRS* and *cyclobenzaprine hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (50 m × 0.32 mm) bonded with a 1.05-µm layer of *phenyl(5)methyl(95)polysiloxane* (Agilent HP-5 is suitable).

(b) Use *helium* as the carrier gas.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an inlet temperature of 200°, detector temperature of 250° and the column oven temperature described below.

(e) Use a flame ionisation detector.

(f) Inject 2 µL of each solution.

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(g) Use a split ratio of 1:10

Time (Minutes)	Temperature (°C)	Comment
0-4	150→250	linear gradient
4-35	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methadone (retention time, about 23 minutes) are: imipramine, about 1.2 and cyclobenzaprine, about 1.25.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and cyclobenzaprine is at least 3.0.

in the chromatogram obtained with solution (2), the *signal-to-noise ratio* of the principal peak is at least 20.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection containing 10 mg of Methadone Hydrochloride to 100 mL with *methanol*.
(2) 0.01% w/v of *methadone hydrochloride BPCRS* in the mobile phase.
(3) 0.01% w/v each of *methadone hydrochloride BPCRS* and *imipramine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Phenomenex Bondclone C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

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50 volumes of a 0.02M solution of *potassium dihydrogen orthophosphate* and 50 volumes of *acetonitrile*, adjust the pH of the final solution to 5.5 with 2M *sodium hydroxide*

When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to methadone hydrochloride is about 4.5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and methadone hydrochloride is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of methadone hydrochloride, $C_{21}H_{27}NO,HCl$, in the injection from the chromatograms obtained and using the declared content of $C_{21}H_{27}NO,HCl$, in *methadone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Methadone Hydrochloride.

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Methadone Oral Solution (1 mg per mL)

General Notices

Action and use

Opioid receptor agonist; analgesic; treatment of opioid dependence.

DEFINITION

Methadone Oral Solution (1 mg per mL) contains 0.1% w/v of Methadone Hydrochloride in a suitable aqueous vehicle. It is supplied as a ready-to-use solution or it is prepared from Methadone Hydrochloride Oral Concentrate in accordance with the manufacturer's instructions.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of methadone hydrochloride, $C_{21}H_{27}NO,HCl$

95.0 to 105.0% w/v of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To 50 mL of the oral solution add 30 mL of *water* and sufficient 1M *sulfuric acid* to make the solution acid to *litmus paper*. Extract with two 20-mL quantities of *petroleum spirit* (*boiling range, 40° to 60°),* discarding the extracts. Make the solution alkaline to *litmus paper* with 5M *sodium hydroxide*, add 4 g of *sodium chloride*, shake to dissolve, extract with two 25-mL quantities of *ether* and wash the combined extracts with five 20-mL quantities of *water*. Shake the ether extract with *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness and dry the residue at a pressure of 2 kPa. Dissolve the residue in 10 mL of *ethanol (96%)*.

(2) 0.5% w/v of *methadone hydrochloride BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

1.5 volumes of *concentrated ammonia R1* and 100 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

For products containing ethylcellulose

(1) Extract a quantity of the oral solution containing 5 mg of methadone hydrochloride with three 20-mL aliquots of *dichloromethane* and combine the organic layers. Filter through a phase separation filter, reduce the filtrate to a volume of 1 mL at a temperature not exceeding 30° under a stream of nitrogen and add sufficient *dichloromethane* to produce 5 mL.

For products not containing ethylcellulose

(1) To a weighed quantity of the oral solution containing 10 mg of methadone hydrochloride add 10 mL of a 10% w/v solution of *sodium carbamate*. Extract with three 20-mL aliquots of *dichloromethane* and combine the organic layers. Filter through a phase separation filter, reduce the filtrate to a volume of 1 mL at a temperature not exceeding 30° under a stream of nitrogen and add sufficient *dichloromethane* to produce 10 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with *dichloromethane*, further dilute 1 volume of this solution to 5 volumes with *dichloromethane*.

(3) 0.005% w/v each of *imipramine hydrochloride BPCRS* and *cyclobenzaprine hydrochloride BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (50 m × 0.32 mm) bonded with a 1.05-µm layer of *phenyl(5)methyl(95)polysiloxane* (Agilent HP-5 is suitable).

(b) Use *helium* as the carrier gas.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an inlet temperature of 200°, detector temperature of 250° and the column oven temperature described below.

(e) Use a flame ionisation detector.

(f) Inject 2 µL of each solution.

(g) Use a split ratio of 1:5

Time (Minutes)	Temperature (°C)	Comment
0-4	150→250	linear gradient
4-35	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methadone hydrochloride (retention time, about 23 minutes) are: imipramine, about 1.2 and cyclobenzaprine, about 1.25.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and cyclobenzaprine is at least 3.0;

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in the chromatogram obtained with solution (2), the *signal-to-noise ratio* of the principal peak is at least 20.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute 1 volume of the oral solution to 10 volumes.
(2) 0.01% w/v of *methadone hydrochloride BPCRS*.
(3) 0.01% w/v each of *methadone hydrochloride BPCRS* and *imipramine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Lichrosorb RP18 10µ is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of 0.02M *potassium dihydrogen orthophosphate*, adjust the pH of the mixture to 5.5 with 2M *orthophosphoric acid* or 2M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to methadone hydrochloride is about 4.5 minutes.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and methadone is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{27}NO$,HCl in the oral solution from the chromatograms obtained and using the declared content of $C_{21}H_{27}NO$,HCl in *methadone hydrochloride BPCRS*.

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Methadone Tablets

General Notices

Action and use

Opioid receptor agonist; analgesic; treatment of opioid dependence.

DEFINITION

Methadone Tablets contain Methadone Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of methadone hydrochloride, $C_{21}H_{27}NO,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.1 g of Methadone Hydrochloride with 20 mL of *water* and centrifuge. Make the supernatant liquid alkaline with 5M *sodium hydroxide*, stir with a glass rod until the precipitate solidifies, filter, wash with *water* and dry in a *vacuum* at room temperature at a pressure of 2 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of methadone *(RS 218)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute the filtrate, if necessary, to produce a solution expected to contain 0.001% w/v of Methadone Hydrochloride. Measure the *absorbance* of the filtered sample, at the maximum at 220 nm, Appendix II B, using *water* in the reference cell.

(2) Measure the *absorbance* of a 0.001% w/v solution of *methadone hydrochloride BPCRS* in *water* using *water* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of methadone hydrochloride, $C_{21}H_{27}NO,HCl$, in the medium from the absorbances obtained and using the declared content of $C_{21}H_{27}NO,HCl$ in *methadone hydrochloride BPCRS*.

LIMITS

The amount of methadone hydrochloride released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) To a quantity of powdered tablets containing 10 mg of Methadone Hydrochloride add 7 mL of *methanol* and mix with the aid of ultrasound. Dilute to 10 mL with *methanol* and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*, further dilute 1 volume of this solution to 5 volumes with *methanol*.
(3) 0.005% w/v each of *imipramine hydrochloride BPCRS* and *cyclobenzaprine hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (50 m × 0.32 mm) bonded with a 1.05-µm layer of *phenyl(5)methyl(95)polysiloxane* (Agilent HP-5 is suitable).
(b) Use *helium* as the carrier gas.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an inlet temperature of 200°, detector temperature of 250° and the column oven temperature described below.
(e) Use a flame ionisation detector.
(f) Inject 2 µL of each solution.
(g) Use a split ratio of 1:10

Time (Minutes)	Temperature (°C)	Comment
0-4	150→250	linear gradient
4-35	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methadone (retention time, about 23 minutes) are: imipramine, about 1.2 and cyclobenzaprine, about 1.25.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and cyclobenzaprine is at least 3.0;

in the chromatogram obtained with solution (2), the *signal-to-noise ratio* of the principal peak is at least 20.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of powdered tablets containing 10 mg of Methadone Hydrochloride add 75 mL of the mobile phase, mix with the aid of ultrasound, dilute to 100 mL with the same solvent and filter.
(2) 0.01% w/v of *methadone hydrochloride BPCRS* in the mobile phase.
(3) 0.01% w/v each of *methadone hydrochloride BPCRS* and *imipramine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Phenomenex Bondclone C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of a 0.02M solution of *potassium dihydrogen orthophosphate* and 50 volumes of *acetonitrile*, adjust the pH of the final solution to 5.5 with 2M *sodium hydroxide*

When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to methadone is about 4.5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to imipramine and methadone is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of methadone hydrochloride, $C_{21}H_{27}NO,HCl$, in the tablets from the chromatograms obtained and using the declared content of $C_{21}H_{27}NO,HCl$ in *methadone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Methadone Hydrochloride.

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Methane

General Notices

(Ph. Eur. monograph 2413)

CH_4 16.04 *74-82-8*

Ph Eur

DEFINITION

Content

Minimum 99.5 per cent *V/V* of CH_4.

This monograph applies to methane obtained from natural gas and intended for medicinal use.

CHARACTERS

Appearance

Colourless gas, flammable in air.

Solubility

At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 27 volumes of water.

IDENTIFICATION

Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the gas to be examined is similar in retention time to the principal peak in the chromatogram obtained with reference gas (b).

TESTS

Nitrogen

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas Mixture containing 500 ppm *V/V* of *nitrogen R1* in *methane R1*.

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Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *molecular sieve for chromatography R* (0.5 nm).

Carrier gas *helium for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 80 °C;

— *detector*: 150 °C.

Detection Thermal conductivity.

Injection 1 mL.

Relative retention With reference to methane (retention time = about 3 min): nitrogen = about 0.7.

System suitability Reference gas:

— *resolution*: minimum 1.5 between the peaks due to nitrogen and methane.

Calculation of percentage content:

— use the concentration of nitrogen in the reference gas.

Limit:

— maximum 500 ppm *V/V*.

C_2-C_4 Hydrocarbons

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas Use the following mixture of gases in *methane R*: *ethane R* (impurity C) (100 ppm *V/V*), *propane R* (impurity D) (100 ppm *V/V*), *i-butane R* (impurity E) (100 ppm *V/V*) and *n-butane R* (impurity F) (100 ppm *V/V*).

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

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— *stationary phase*: *deactivated aluminium oxide for chromatography R*.

Carrier gas *helium for chromatography R*.

Flow rate 113 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	30
	1 - 3.4	30 → 150
	3.4 - 4.5	150
Detector		300

Detection Flame ionisation. Use appropriate fuel gases: *hydrocarbon-free air R* and *hydrogen for chromatography R*.

Injection 0.1 mL.

Relative retention With reference to methane (retention time = about 1.2 min): impurity C = about 1.2; impurity D = about 1.8; impurity E = about 2.5; impurity F = about 2.6.

System suitability Reference gas:

— *resolution*: minimum 1.5 between the peaks due to methane and impurity C; minimum 1.5 between the peaks due to impurity E and impurity F.

Calculation of percentage contents:

— for each of the impurities C, D, E and F, use the corresponding concentration in the reference gas.

Limit:

— *total* (sum of impurities C, D, E and F): maximum 100 ppm *V/V*.

Water (*2.5.28*)

Maximum 10.0 ppm *V/V*.

ASSAY

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

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Reference gas (a) Methane R1.

Reference gas (b) Mixture containing 1 per cent *V/V* of nitrogen R1 in methane R1.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: molecular sieve for chromatography R (0.5 nm).

Carrier gas helium for chromatography R.

Flow rate 30 mL/min.

Temperature:

— *column*: 80 °C;

— *detector*: 150 °C.

Detection Thermal conductivity.

Injection 10 µL.

Relative retention With reference to methane (retention time = about 3 min): nitrogen = about 0.7.

System suitability Reference gas (b):

— *resolution*: minimum 1.5 between the peaks due to nitrogen and methane.

Calculate the percentage content of CH_4, using the chromatogram obtained with reference gas (a).

STORAGE

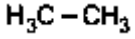
As a compressed gas, in appropriate containers complying with the legal regulations.

IMPURITIES

Specified impurities *A, B, C, D, E, F*.

A. N_2: nitrogen,

B. H_2O: water,



C. ethane,

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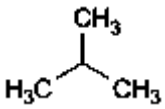
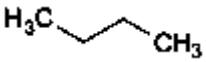
D. propane,



E. 2-methylpropane (*i*-butane),



F. butane (*n*-butane).

Ph Eur

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Methane Intermix (2 per cent) in Nitrogen

General Notices

(Ph. Eur. monograph 2905)

Ph Eur

DEFINITION

A mixture containing 2 per cent *V/V* of *Methane (2413)* in *Low-oxygen nitrogen (1685)*.

Content

1.9 per cent *V/V* to 2.1 per cent *V/V* of methane (CH_4) in nitrogen (N_2).

This monograph applies to methane intermix (2 per cent) in nitrogen used in the preparation of lung function test gas mixtures for medicinal use.

CHARACTERS

Appearance

Colourless gas.

IDENTIFICATION

A. It complies with the limits of the assay.

B. Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas *Nitrogen R1*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *molecular sieve for chromatography R* (0.5 nm).

Carrier gas *helium for chromatography R*.

Flow rate 20 mL/min.

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Temperature:

— *column*: 80 °C;

— *detector*: 130 °C.

Detection Thermal conductivity.

Injection 10 µL.

Retention time Nitrogen = about 2 min.

Results The principal peak in the chromatogram obtained with the gas to be examined is similar in retention time to the principal peak in the chromatogram obtained with the reference gas.

TESTS

Water (2.5.28)

Maximum 10 ppm *V/V*.

ASSAY

Gas chromatography (2.2.28).

Gas to be examined The substance to be examined.

Reference gas Mixture containing 2.0 per cent *V/V* of *methane R1* in *nitrogen R1*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: 3 per cent *squalane R* on alumina.

Carrier gas *helium for chromatography R*.

Flow rate 20 mL/min.

Temperature:

— *column*: 100 °C;

— *detector*: 250 °C.

Detection Flame ionisation.

Injection 100 µL.

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Retention time Methane = about 0.5 min.

Calculate the percentage content of CH_4.

STORAGE

As a compressed gas, in appropriate high-pressure cylinders complying with the legal regulations.

LABELLING

The label states the nominal content, in per cent *V/V*, of methane in nitrogen.

IMPURITIES

Specified impurities *A*.

A. water.

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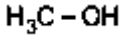
Methanol

General Notices

Methyl Alcohol

(Ph. Eur. monograph 1989)



CH_4O 32.04 *67-56-1*

Ph Eur

DEFINITION

Methyl alcohol.

CHARACTERS

Appearance

Clear, colourless, volatile, hygroscopic liquid.

Solubility

Miscible with water and with methylene chloride.

bp

About 64 °C.

It is flammable.

IDENTIFICATION

A. Refractive index (*2.2.6*): 1.328 to 1.330.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of methanol*.

TESTS

Appearance

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It is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 25 mL add 25 mL of *water R* and 0.25 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.9 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Relative density (*2.2.5*)

0.791 to 0.793.

Absorbance (*2.2.25*)

Maximum 0.15 at 230 nm, maximum 0.05 at 250 nm, maximum 0.02 at 270 nm and maximum 0.01 at 290 nm.

Examine between 230 nm and 290 nm using *water R* as the compensation liquid. The absorption curve is smooth.

Impurity A

Gas chromatography (*2.2.28*).

Test solution (a) The substance to be examined.

Test solution (b) Dilute 1.0 mL of *4-methylpentan-2-ol R* to 50.0 mL with test solution (a). Dilute 5.0 mL of this solution to 100.0 mL with test solution (a).

Reference solution (a) To 50 µL of *anhydrous ethanol R* add 50 µL of *acetone R* and dilute to 50.0 mL with test solution (a). Dilute 100 µL of this solution to 10.0 mL with test solution (a).

Reference solution (b) Dilute 100 µL of *benzene R* to 100.0 mL with test solution (a). Dilute 0.20 mL to 100.0 mL with test solution (a).

Column:

— *material*: fused silica,

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 1.8 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 35 cm/s.

Split ratio 1:20.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 12	40
	12 - 32	40 → 240
	32 - 42	240
Injection port		200
Detector		280

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity B (1st peak) and impurity C (2nd peak).

Limit:

— *impurity A*: maximum 2 ppm *V/V*.

Calculate the content of impurity A in parts per million *V/V* using the following expression:

$$\frac{2 \times A_1}{A_2 - A_1}$$

A_1 = area of the peak due to impurity A in the chromatogram obtained with test solution (a),

A_2 = area of the peak due to impurity A in the chromatogram obtained with reference solution (b).

If necessary, the identity of impurity A can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

Related substances

Gas chromatography (*2.2.28*) as described in the test for impurity A.

Limits:

— *any impurity*: for each impurity, not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with test solution (b) (0.1 per cent),

— *total*: not more than 3 times the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with test solution (b) (0.3 per cent),

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— *disregard limit*: 0.05 times the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with test solution (b) (50 ppm).

Reducing substances

To 20 mL add 0.1 mL of *0.02 M potassium permanganate*. The pink colour is not completely discharged within 5 min.

Residue on evaporation

Maximum 10 ppm.

Evaporate 100 g to dryness on a water bath and dry in an oven at 100-105 °C. The residue weighs a maximum of 1 mg.

Water (*2.5.12*)

Maximum 0.10 per cent, determined on 10.0 g.

STORAGE

In an airtight container.

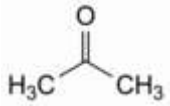
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.

A. benzene,

B. ethanol,



C. propanone (acetone).

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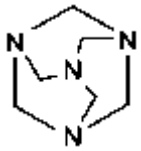
Methenamine

General Notices

(Ph. Eur. monograph 1545)



$C_6H_{12}N_4$ 140.2 *100-97-0*

Action and use

Anti-infective.

Ph Eur

DEFINITION

1,3,5,7-Tetraazotricyclo[3.3.1.1^{3,7}]decane.

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *methenamine CRS*.

B. To 1 mL of solution S (see Tests) add 1 mL of *sulfuric acid R* and immediately heat to boiling. Allow to cool. To 1 mL of the solution add 4 mL of *water R* and 5 mL of *acetylacetone reagent R1*. Heat on a water-bath for 5 min. An intense yellow colour develops.

C. To 1 mL of solution S add 1 mL of *dilute sulfuric acid R* and immediately heat to boiling. The solution gives the reaction of ammonium salts and salts of volatile bases (*2.3.1*).

D. Dissolve 10 mg in 5 mL of *water R* and acidify with *dilute hydrochloric acid R*. Add 1 mL of *potassium iodobismuthate solution R*. An orange precipitate is formed immediately.

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 5 mL of solution S add 0.1 mL of *phenolphthalein solution R*. Not more than 0.2 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Free formaldehyde

Maximum 50 ppm.

Dissolve 0.8 g in *water R* and dilute to 8 mL with the same solvent. Add 2 mL of *ammoniacal silver nitrate solution R*. After 5 min, any grey colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner with a mixture of 8 mL of freshly prepared *formaldehyde standard solution (5 ppm CH_2O) R* and 2 mL of *ammoniacal silver nitrate solution R*.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Ammonium (*2.4.1*)

Maximum 50 ppm.

Dilute 2 mL of freshly prepared solution S to 13 mL with *water R*. Add 2 mL of *dilute sodium hydroxide solution R*.

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Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in a desiccator.

ASSAY

Dissolve 0.100 g in 30 mL of *methanol R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 14.02 mg of $C_6H_{12}N_4$.

STORAGE

Protected from light.

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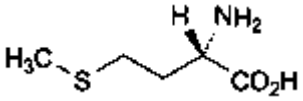
Methionine

General Notices

(Ph. Eur. monograph 1027)



$C_5H_{11}NO_2S$ 149.2 *63-68-3*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Amino-4-(methylsulfanyl)butanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison: *methionine CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *dilute hydrochloric acid R* and dilute to 50 mL with the same acid.

Reference solution Dissolve 10 mg of *methionine CRS* in *dilute hydrochloric acid R* and dilute to 50 mL with the same acid.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 0.1 g of the substance to be examined and 0.1 g of *glycine R* in 4.5 mL of *dilute sodium hydroxide solution R*. Add 1 mL of a 25 g/L solution of *sodium nitroprusside R*. Heat to 40 °C for 10 min. Allow to cool and add 2 mL of a mixture of 1 volume of *phosphoric acid R* and 9 volumes of *hydrochloric acid R*. A dark red colour develops.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.5 to 6.5 for solution S.

Specific optical rotation (*2.2.7*)

+ 22.5 to + 24.0 (dried substance).

Dissolve 1.00 g in *hydrochloric acid R1* and dilute to 50.0 mL with the same acid.

Related substances

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Liquid chromatography (2.2.29).

Test solution Dissolve 0.30 g of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 10 mg of *L-methionine sulfoxide R* (impurity A) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, 23 g/L solution of *phosphoric acid R*, *water for chromatography R* (0.5:12.5:87 *V/V/V*);

— *mobile phase B*: 23 g/L solution of *phosphoric acid R*, *water for chromatography R*, *acetonitrile R1* (12.5:40:47.5 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	100	0
6 - 50	100 → 0	0 → 100
50 - 60	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 50 µL.

Relative retention With reference to methionine (retention time = about 6 min): impurity A = about 0.5.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and methionine.

Calculation of percentage contents:

— for each impurity, use the concentration of methionine in reference solution (a).

Limits:

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— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides

Maximum 200 ppm.

Dissolve 0.5 g of the substance to be examined in 5 mL of *dilute nitric acid R* and dilute to 10 mL with the same acid. Add 10 mL of *strong hydrogen peroxide solution R* and heat on a water bath for 30 min. Cool and dilute to 50 mL with *water R*. Add 1 mL of *silver nitrate solution R2* and mix. Allow to stand protected from light for 5 min. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 2 mL of *chloride standard solution (50 ppm Cl) R*. Examine the tubes laterally against a black background.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dissolve 0.5 g in 3 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Ammonium (*2.4.1, Method B*)

Maximum 200 ppm, determined on 0.10 g.

Prepare the standard using 0.2 mL of *ammonium standard solution (100 ppm NH_4) R*.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined upper layers, add 10 mL of *water R* and shake for 3 min. Use the lower layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.125 g in 5 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 14.92 mg of $C_5H_{11}NO_2S$.

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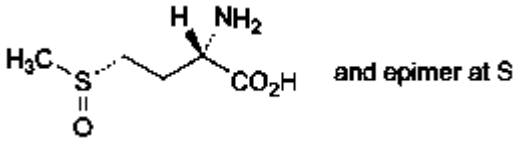
STORAGE

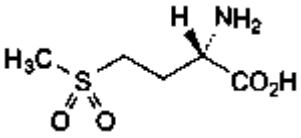
Protected from light.

IMPURITIES

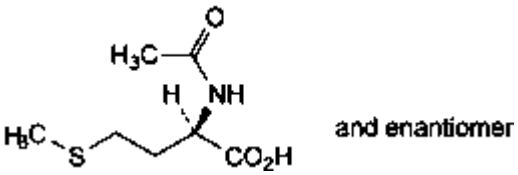
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E.*



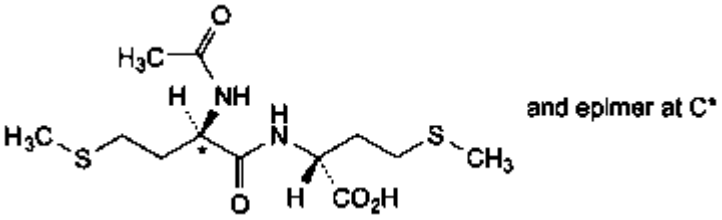
A. (2*S*)-2-amino-4-[(*RS*)-methylsulfinyl]butanoic acid (L-methiomine sulfoxide),



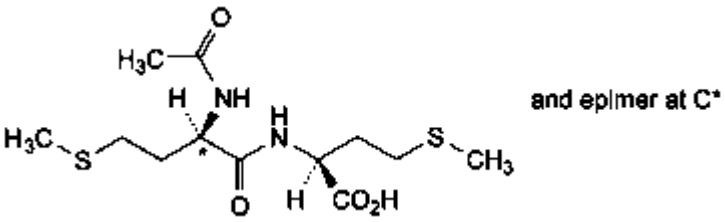
B. (2*S*)-2-amino-4-(methylsulfonyl)butanoic acid,



C. (2*RS*)-2-(acetylamino)-4-(methylsulfanyl)butanoic acid,



D. (2*R*)-2-[[(2*RS*)-2-(acetylamino)-4-(methylsulfanyl)butanoyl]amino]-4-(methylsulfanyl)butanoic acid,



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E. (2*S*)-2-[[(2*RS*)-2-(acetylamino)-4-(methylsulfanyl)butanoyl]amino]-4-(methylsulfanyl)butanoic acid.

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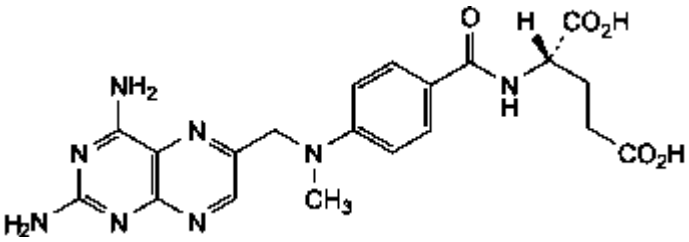
Methotrexate

General Notices

(Ph. Eur. monograph 0560)



$C_{20}H_{22}N_8O_5$ 454.4 *59-05-2*

Action and use

Dihydrofolate reductase inhibitor; cytostatic.

Preparations

Methotrexate Injection

Methotrexate Oral Solution

Methotrexate Tablets

Ph Eur

DEFINITION

(2*S*)-2-[[4-[[(2,4-Diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]pentanedioic acid.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow or orange, crystalline, hygroscopic powder.

Solubility

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Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *methotrexate CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 40.0 mg of the substance to be examined in a mixture of 0.5 mL of *dilute ammonia R1* and 5 mL of mobile phase A and dilute to 100.0 mL with mobile phase A.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in a mixture of 0.5 mL of *dilute ammonia R1* and 5 mL of mobile phase A and dilute to 50.0 mL with mobile phase A. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 25.0 mg of *methotrexate CRS* in a mixture of 0.5 mL of *dilute ammonia R1* and 5 mL of mobile phase A and dilute to 50.0 mL with mobile phase A. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase A.

Reference solution (b) Dilute 5.0 mL of test solution (a) to 100.0 mL with mobile phase A. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase A.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 25.0 mL with mobile phase A.

Reference solution (d) Dissolve 5 mg of the substance to be examined, 5 mg of 4-aminofolic acid R (impurity B), 5 mg of *methotrexate impurity C CRS*, 5 mg of *methotrexate impurity D CRS* and 5 mg of *methotrexate impurity E CRS* in a mixture of 0.5 mL of *dilute ammonia R1* and 5 mL of mobile phase A and dilute to 100 mL with mobile phase A.

Reference solution (e) Dissolve 8 mg of *methotrexate for peak identification CRS* (containing impurities H and I) in a mixture of 0.1 mL of *dilute ammonia R1* and 1 mL of mobile phase A and dilute to 20 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 5 volumes of *acetonitrile for chromatography R* and 95 volumes of a 3.4 g/L solution of *anhydrous sodium dihydrogen phosphate R* previously adjusted to pH 6.0 with a 42 g/L solution of *sodium hydroxide R*;

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— *mobile phase B*: mix 50 volumes of *acetonitrile for chromatography R* and 50 volumes of a 3.4 g/L solution of *anhydrous sodium dihydrogen phosphate R* previously adjusted to pH 6.0 with a 42 g/L solution of *sodium hydroxide R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 20	100 → 95	0 → 5
20 - 28	95 → 50	5 → 50
28 - 37	50	50

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c), (d) and (e).

Identification of impurities Use the chromatogram supplied with *methotrexate for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities H and I; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B, C and E.

Relative retention With reference to methotrexate (retention time = about 18 min): impurity B = about 0.3; impurity C = about 0.4; impurity D = about 0.9; impurity E = about 1.4; impurity I = about 1.5; impurity H = about 1.6.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurities B and C and minimum 1.5 between the peaks due to impurity D and methotrexate, in the chromatogram obtained with reference solution (d); minimum 1.5 between the peaks due to impurities I and H in the chromatogram obtained with reference solution (e); if the resolution between impurity D and methotrexate does not comply, increase the flow rate to meet the requirement.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.8; impurity I = 1.4;

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities B, E*: for each impurity, not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities H, I*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

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— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent);

— *sum of impurities other than B, C and E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.03 per cent).

Enantiomeric purity

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 4.0 mg of *methotrexate for system suitability CRS* (containing impurity F) in the mobile phase and dilute to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *bovine albumin R* bound to *silica gel for chromatography R* (7 µm) with a pore size of 30 nm.

Mobile phase Add 500 mL of a 7.1 g/L solution of *anhydrous disodium hydrogen phosphate R* to 600 mL of a 6.9 g/L solution of *sodium dihydrogen phosphate monohydrate R*, mix, and adjust to pH 6.9 with *dilute sodium hydroxide solution R*; to 920 mL of this mixture add 80 mL of *propanol R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 302 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity F.

Relative retention With reference to methotrexate (retention time = about 4 min): impurity F = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to methotrexate and impurity F.

Limit:

— *impurity F*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.0 per cent).

Water (*2.5.12*)

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Maximum 13.0 per cent, determined on 0.10 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{20}H_{22}N_8O_5$ taking into account the assigned content of *methotrexate CRS*.

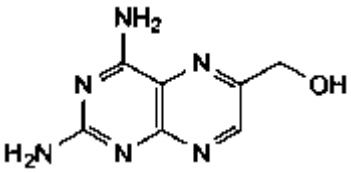
STORAGE

In an airtight container, protected from light.

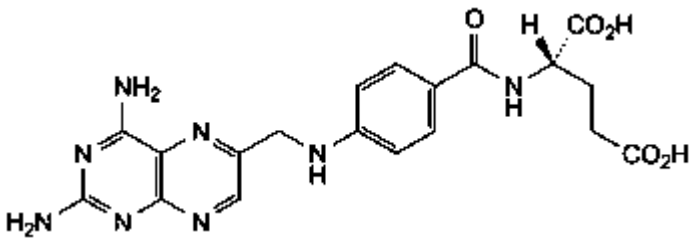
IMPURITIES

Specified impurities *B, C, E, F, H, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, G, J, K, L.*



A. (2,4-diaminopteridin-6-yl)methanol,



B. (2*S*)-2-[[4-[[(2,4-diaminopteridin-6-yl)methyl]amino]benzoyl]amino]pentanedioic acid (4-aminofolic acid, aminopterin),

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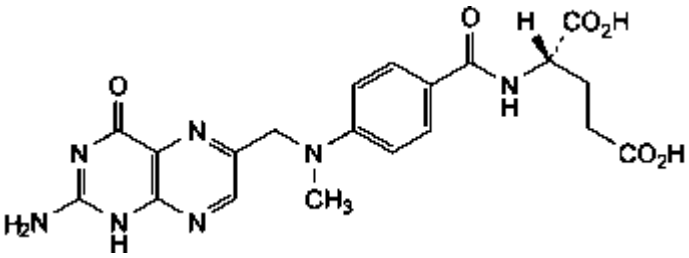
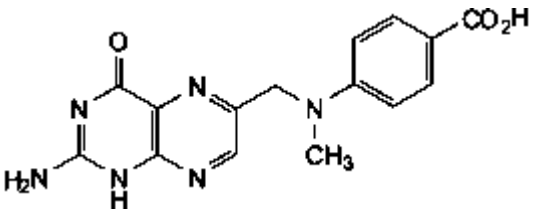
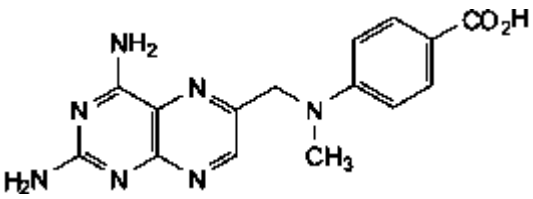


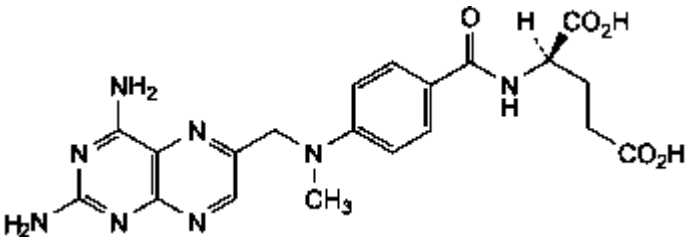
C. (2*S*)-2-[[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]methylamino]benzoyl]amino]pentanedioic acid (*N*-methylfolic acid, methopterin),



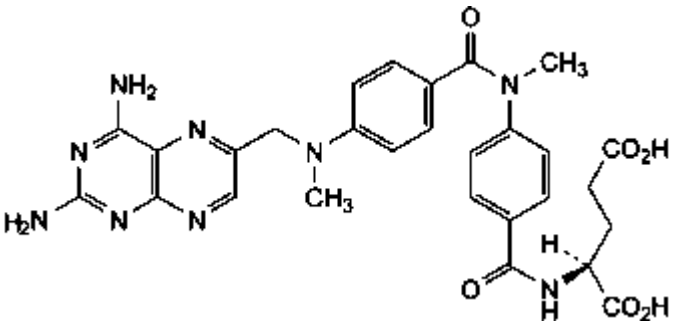
D. 4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]methylamino]benzoic acid (N^{10}-methylpteroic acid),



E. 4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoic acid (4-amino-N^{10}-methylpteroic acid, APA),



F. (2*R*)-2-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]pentanedioic acid ((*R*)-methotrexate),



G. (2*S*)-2-[[4-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]methylamino]benzoyl]amino]pentanedioic acid,

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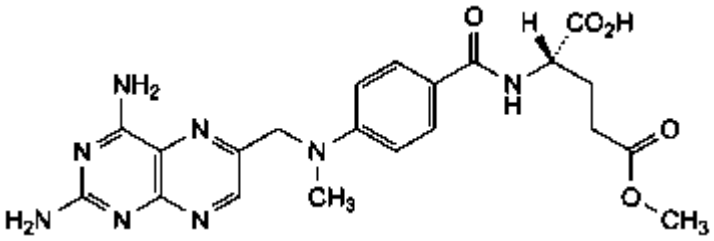
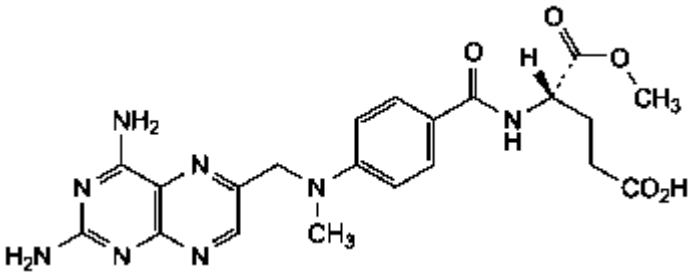
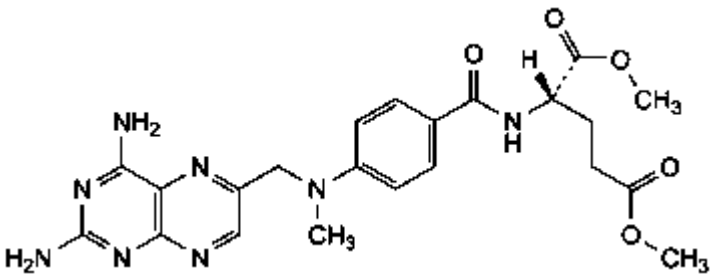


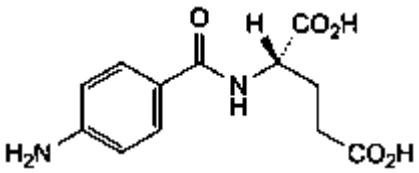
H. (2*S*)-2-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]-5-methoxy-5-oxopentanoic acid (methotrexate 5-methyl ester),



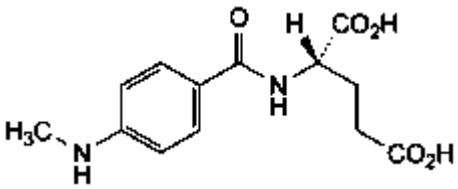
I. (4*S*)-4-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]-5-methoxy-5-oxopentanoic acid (methotrexate 1-methyl ester),



J. dimethyl (2*S*)-2-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]pentanedioate (methotrexate dimethyl ester),



K. (2*S*)-2-[(4-aminobenzoyl)amino]pentanedioic acid,



L. (2*S*)-2-[[4-(methylamino)benzoyl]amino]pentanedioic acid.

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Methotrexate Injection

General Notices

Action and use

Dihydrofolate reductase inhibitor; cytostatic.

DEFINITION

Methotrexate Injection is a sterile solution of Methotrexate in Water for Injections containing Sodium Hydroxide.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of methotrexate, $C_{20}H_{22}N_8O_5$

95.0 to 110.0% of the stated amount.

CHARACTERISTICS

A yellowish solution.

IDENTIFICATION

A. Dilute a suitable volume of the injection with 0.1M *sodium hydroxide* to produce a solution containing 0.001% w/v of Methotrexate. The *light absorption* of the resulting solution, Appendix II B, exhibits three maxima, at 258 nm, 303 nm and 371 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH, 7.0 to 9.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection, if necessary, with the mobile phase to produce a solution containing 0.01% w/v of Methotrexate.

(2) Dissolve 10 mg of *methotrexate EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 50 mL with the mobile phase. Dilute 1 volume of the resulting solution to 1000 volumes with the mobile phase.

(3) Dissolve 6 mg of *methotrexate impurity C EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

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(4) 0.0003% w/v each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS*. Dissolve 6 mg each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

(5) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS 5 µm is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of methotrexate.

MOBILE PHASE

7 volumes of *acetonitrile* and 93 volumes of a citro-phosphate buffer solution prepared by dissolving 7.8 g of *citric acid* and 17.9 g of *anhydrous disodium hydrogen orthophosphate* in sufficient *water* to produce 1000 mL.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methotrexate (retention time about 17 minutes) are: impurity A, 0.2; impurity B, 0.3; impurity C, 0.4; impurity D, 0.8; impurity E, 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to methotrexate and methotrexate impurity D is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater that the area of the principal peak in the chromatogram obtained with solution (3) (3%);

the area of any peak corresponding to impurity B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peak*s is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

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Disregard any peak with an area less than the principal peak in the chromatogram obtained with solution (5) (0.02%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection, if necessary, to produce a solution containing 0.01% w/v of Methotrexate.

(2) Dissolve 10 mg of *methotrexate EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 100 mL with the mobile phase.

(3) 0.0003% w/v each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS*. Dissolve 6 mg each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using 302 nm as the detection wavelength.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methotrexate and methotrexate impurity D is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{22}N_8O_5$ in the injection using the declared content of $C_{20}H_{22}N_8O_5$ in *methotrexate EPCRS*.

STORAGE

Methotrexate Injection should be protected from light.

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Methotrexate Oral Solution

General Notices

Action and use

Dihydrofolate reductase inhibitor; cytostatic.

DEFINITION

Methotrexate Oral Solution is a solution containing Methotrexate and Sodium Hydroxide in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of methotrexate, $C_{20}H_{22}N_8O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity of the oral solution containing 5 mg of Methotrexate with sufficient 0.1M *sodium hydroxide* to produce 50 mL, filter and dilute 1 mL of the filtrate to 10 mL with 0.1M *sodium hydroxide*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 400 nm exhibits a maximum at 371 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to the retention time of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution containing 10 mg of Methotrexate with a mixture of 0.5 mL of 6M *ammonia* and 5 mL of mobile phase A; dilute the resulting solution with sufficient mobile phase A to produce a solution containing 0.04% w/v of Methotrexate.

(2) Dilute 1 volume of solution (1) to 20 volumes with mobile phase A and further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dilute 1 volume of solution (2) to 5 volumes with mobile phase A.

(4) Dissolve 5 mg of each *of methotrexate EPCRS*, *4-aminofolic acid* (impurity B), *methotrexate impurity C EPCRS*, *methotrexate impurity D EPCRS* and *methotrexate impurity E EPCRS* in a mixture of 0.5 mL of 6M *ammonia* and 5 mL of mobile phase A and dilute to 10 mL with mobile phase A. Dilute 1 mL to 10 mL with mobile phase A.

(5) Dissolve 4 mg of *methotrexate for peak identification EPCRS* in a mixture of 0.1 mL of 6M *ammonia* and 1 mL of mobile phase A and dilute to 10 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silical gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile* and 95 volumes of a 0.34% w/v solution of *anhydrous sodium dihydrogen orthophosphate*, previously adjusted to pH 6.0 with 4.2% w/v *sodium hydroxide*.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of a 0.34% w/v solution of *anhydrous sodium dihydrogen orthophosphate*, previously adjusted to pH 6.0 with 4.2% w/v *sodium hydroxide*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100	0	isocratic
10-20	100→95	0→5	linear gradient
20-28	95→50	5→50	linear gradient
28-55	50	50	isocratic
55-55.1	50→100	50→0	linear gradient
55.1-65	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention time of methotrexate is about 22 minutes. The retention times relative to methotrexate are: impurity B, about 0.51; impurity C, about 0.46; impurity D, about 0.92; impurity E, about 1.16; impurity H, about 1.26; impurity I, about 1.24.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to methotrexate and impurity D is at least 2.0 and the *resolution* between the peaks due to impurities B and C is at least 1.5;

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurities H and I is at least 1.5.

LIMITS

Identify any peaks corresponding to impurities B, C, D and E using the chromatogram obtained with solution (4). Identify any peaks corresponding to impurities H and I using the chromatogram obtained with solution (5). Multiply the area of any peaks corresponding to impurities E and I by the corresponding correction factor: impurity E, 0.8; impurity I, 1.4.

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity B is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any peak corresponding to impurity E is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (3) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution containing 25 mg of Methotrexate with a mixture of 0.5 mL of 6M *ammonia* and 5 mL of mobile phase A. Dilute the resulting solution with sufficient mobile phase A to produce a solution containing 0.05% w/v of Methotrexate and further dilute 1 mL to 10 mL with mobile phase A.
(2) Dissolve 25 mg of *methotrexate EPCRS* in a mixture of 0.5 mL of 6M *ammonia* and 5 mL of mobile phase A, dilute the resulting solution to 50 mL with mobile phase A and further dilute 1 mL to 10 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{20}H_{22}N_8O_5$, weight in volume, using the declared content of $C_{20}H_{22}N_8O_5$ in *methotrexate EPCRS*.

STORAGE

Methotrexate Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and E listed under Methotrexate.

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Methotrexate Tablets

General Notices

Action and use

Dihydrofolate reductase inhibitor; cytostatic.

DEFINITION

Methotrexate Tablets contain Methotrexate or methotrexate sodium prepared by the interaction of Methotrexate with Sodium Hydroxide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of methotrexate, $C_{20}H_{22}N_8O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 10 mg of Methotrexate with sufficient 0.1M *sodium hydroxide* to produce 100 mL, filter and dilute 10 mL of the filtrate to 100 mL with 0.1M *sodium hydroxide*. The *light absorption* of the resulting solution, Appendix II B in the range 230 to 400 nm, exhibits three maxima, at 258, 303 and 371 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Disintegration

Maximum time, 30 minutes, Appendix XII A1.

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 303 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *methotrexate EPCRS* in the dissolution medium using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of methotrexate, $C_{20}H_{22}N_8O_5$, in the medium from the *absorbances* obtained and from the declared content of $C_{20}H_{22}N_8O_5$ in *methotrexate EPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 10 mg of Methotrexate in 70 mL of the mobile phase with the aid of ultrasound for 5 minutes and dilute to 100 mL with the mobile phase. Mix and filter through a glass fibre filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume to 5 volumes with the mobile phase.

(3) Dissolve 6 mg of *methotrexate impurity C EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

(4) 0.0003% w/v each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS*.Dissolve 6 mg each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

(5) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS 5 µm is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of methotrexate.

MOBILE PHASE

7 volumes of *acetonitrile* and 93 volumes of a citro-phosphate buffer solution prepared by dissolving 7.8 g of *citric acid* and 17.9 g of *anhydrous disodium hydrogen orthophosphate* in sufficient *water* to produce 1000 mL.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methotrexate (retention time about 17 minutes) are: impurity A, 0.2; impurity B, 0.3; impurity C, 0.4; impurity D, 0.8; impurity E, 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to methotrexate and methotrexate impurity D is at least 2.0.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater that the area of the principal peak in the chromatogram obtained with solution (3) (3%);

the area of any peak corresponding to impurity B is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the principal peak in the chromatogram obtained with solution (5) (0.02%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 10 mg of Methotrexate in 70 mL of the mobile phase with the aid of ultrasound for 5 minutes and dilute to 100 mL with the mobile phase. Mix and filter through a glass fibre filter (Whatman GF/C is suitable).
(2) 0.01% w/v of *methotrexate EPCRS* in the mobile phase.
(3) 0.0003% w/v each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS*.Dissolve 6 mg each of *methotrexate EPCRS* and *methotrexate impurity D EPCRS* in 0.1 mL of *dilute ammonia R1* and 0.5 mL of the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using 302 nm as the detection wavelength.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methotrexate and methotrexate impurity D is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{22}N_8O_5$ in the tablets using the declared content of $C_{20}H_{22}N_8O_5$ in *methotrexate EPCRS*.

STORAGE

Methotrexate Tablets should be protected from light.

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LABELLING

When the active ingredient is methotrexate sodium, the quantity is expressed in terms of the equivalent amount of Methotrexate.

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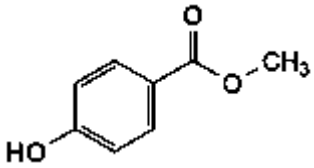
Methyl Hydroxybenzoate[1]

General Notices

Methylparaben

(Methyl Parahydroxybenzoate, Ph. Eur. monograph 0409)



$C_8H_8O_3$ 152.1 *99-76-3*

Action and use

Antimicrobial preservative.

Ph Eur

DEFINITION

Methyl 4-hydroxybenzoate.

Content

98.0 per cent to 102.0 per cent.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent) and in methanol.♦

IDENTIFICATION

First identification: A, B.

◊ *Second identification: A, C.*◊

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A. Melting point (2.2.14): 125 °C to 128 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison methyl parahydroxybenzoate CRS.

◊ C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.10 g of the substance to be examined in acetone R and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with acetone R.

Reference solution (a) Dissolve 10 mg of methyl parahydroxybenzoate CRS in acetone R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of ethyl parahydroxybenzoate CRS in 1 mL of test solution (a) and dilute to 10 mL with acetone R.

Plate TLC octadecylsilyl silica gel F_{254} plate R.

Mobile phase glacial acetic acid R, water R, methanol R (1:30:70 *V/V/V*).

Application 2 µL of test solution (b) and reference solutions (a) and (b).

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).◊

TESTS

Solution S

Dissolve 1.0 g in ethanol (96 per cent) R and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Acidity

To 2 mL of solution S add 3 mL of ethanol (96 per cent) R, 5 mL of carbon dioxide-free water R and 0.1 mL of bromocresol green solution R. Not more than 0.1 mL of 0.1 M sodium hydroxide is required to change the colour of the indicator to blue.

Related substances

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Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of *methanol R* and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *4-hydroxybenzoic acid R* (impurity A) and 5 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50.0 mg of *methyl parahydroxybenzoate CRS* in 2.5 mL of *methanol R* and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 6.8 g/L solution of *potassium dihydrogen phosphate R*, *methanol R* (35:65 *V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 5 times the retention time of methyl parahydroxybenzoate.

Relative retention With reference to methyl parahydroxybenzoate (retention time = about 2.3 min): impurity A = about 0.6.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity A and methyl parahydroxybenzoate.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

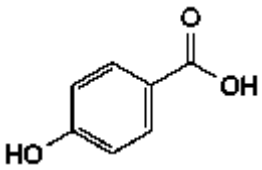
Injection Test solution and reference solution (b).

Calculate the percentage content of $C_8H_8O_3$ from the declared content of *methyl parahydroxybenzoate CRS*.

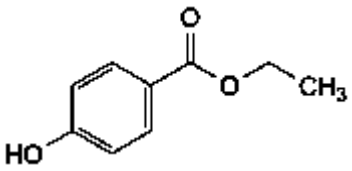
IMPURITIES

Specified impurities *A.*

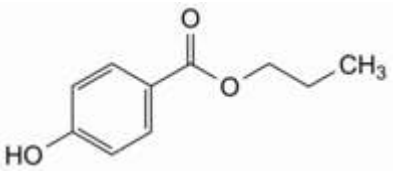
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D.*



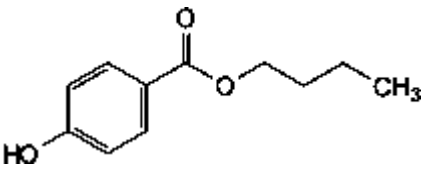
A. 4-hydroxybenzoic acid,



B. ethyl 4-hydroxybenzoate (ethyl parahydroxybenzoate),



C. propyl 4-hydroxybenzoate (propyl parahydroxybenzoate),



D. butyl 4-hydroxybenzoate (butyl parahydroxybenzoate).

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

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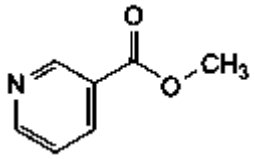
Methyl Nicotinate

General Notices

(Ph. Eur. monograph 2129)



$C_7H_7NO_2$ 137.1 *93-60-7*

Action and use

Vasodilator.

Ph Eur

DEFINITION

Methyl pyridine-3-carboxylate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 40 °C to 42 °C.

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B. Infrared absorption spectrophotometry (2.2.24).

Comparison methyl nicotinate CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 2 mL with the same solvent.

Reference solution Dissolve 10 mg of methyl nicotinate CRS in methanol R and dilute to 2 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase methanol R, toluene R (10:90 *V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 0.5 g add 0.1 g of citric acid monohydrate R and 0.2 mL of acetic anhydride R. Heat cautiously for 1 min. A yellow colour is produced which turns first to orange, then to red and then to violet.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25 mg of nicotinic acid R in the mobile phase and dilute to 25.0 mL with the mobile phase. To 0.5 mL of this solution add 0.5 mL of the test solution and dilute to 100 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm,

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase acetic acid R, water R, acetonitrile R (1:29:70 *V/V/V*).

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Flow rate 1 mL/min.

Detection Spectrophotometer at 261 nm.

Injection 20 µL.

Run time 3 times the retention time of methyl nicotinate.

Retention time Methyl nicotinate = about 3.3 min.

System suitability Reference solution (a):

— *resolution*: minimum 2 between the peaks due to impurity A and methyl nicotinate.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.25 g in *water R* and dilute to 15 mL with the same solvent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 2.000 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.120 g in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 13.71 mg of $C_7H_7NO_2$.

STORAGE

Protected from light.

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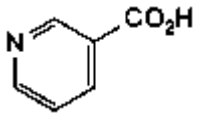
IMPURITIES

Specified impurities *A.*



A. pyridine-3-carboxylic acid (nicotinic acid).

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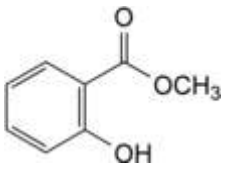
Methyl Salicylate

General Notices

(Ph. Eur. monograph 0230)



$C_8H_8O_3$ 152.1 *119-36-8*

Action and use

Counter-irritant.

Preparations

Kaolin Poultice

Methyl Salicylate Liniment

Methyl Salicylate Ointment

Surgical Spirit

Ph Eur

DEFINITION

Methyl 2-hydroxybenzoate.

Content

99.0 per cent *m/m* to 101.0 per cent *m/m*.

CHARACTERS

Appearance

Colourless or slightly yellow liquid.

Solubility

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Very slightly soluble in water, miscible with ethanol (96 per cent) and with fatty and essential oils.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *methyl salicylate CRS*.

B. Heat 0.25 mL with 2 mL of *dilute sodium hydroxide solution R* on a water-bath for 5 min. Add 3 mL of *dilute sulfuric acid R*. A crystalline precipitate is formed. Filter. The precipitate, washed with *water R* and dried at 100-105 °C, melts (*2.2.14*) at 156 °C to 161 °C.

C. To 10 mL of a saturated solution add 0.05 mL of *ferric chloride solution R1*. A violet colour develops.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

To 2 mL add 10 mL of *ethanol (96 per cent) R*.

Acidity

Dissolve 5.0 g in a mixture of 0.2 mL of *bromocresol green solution R* and 50 mL of *ethanol (96 per cent) R* previously neutralised to a blue colour by addition of *0.1 M sodium hydroxide*. Not more than 0.4 mL of *0.1 M sodium hydroxide* is required to restore the blue colour.

Relative density (*2.2.5*)

1.182 to 1.188.

Refractive index (*2.2.6*)

1.535 to 1.538.

Related substances

Gas chromatography (*2.2.28*).

Test solution The substance to be examined.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *acetone R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetone R*.

Reference solution (b) Dissolve 59.0 mg of *phenol R* (impurity B) in *acetone R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *acetone R*.

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Reference solution (c) Dissolve 5 mg of *methyl 2-methoxybenzoate R* (impurity M) and 5 mg of *methyl 4-methoxybenzoate R* (impurity D) in *acetone R* and dilute to 100 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 5.0 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 32.5	100 → 230
	32.5 - 40.5	230
Injection port		200
Detector		250

Detection Flame ionisation.

Injection 0.5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and M.

Relative retention With reference to methyl salicylate (retention time = about 9 min): methanol = about 0.15; anisole = about 0.37; impurity B = about 0.47; impurity M = about 1.56; impurity D = about 1.59.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities M and D.

Calculation of contents:

— for impurity B, use the concentration of impurity B in reference solution (b);

— for impurities other than B, use the concentration of methyl salicylate in reference solution (a).

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Limits:

— *impurity B*: maximum 50 ppm;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent, except for impurity B; disregard the peaks due to anisole and methanol.

ASSAY

Dissolve 0.500 g in 25 mL of *ethanol (96 per cent) R*. Add 0.05 mL of *phenol red solution R* and neutralise with *0.1 M sodium hydroxide*. To the neutralised solution add 50.0 mL of *0.1 M sodium hydroxide* and heat under a reflux condenser on a water-bath for 30 min. Cool and titrate with *0.1 M hydrochloric acid*. Calculate the volume of *0.1 M sodium hydroxide* used in the saponification. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 15.21 mg of $C_8H_8O_3$.

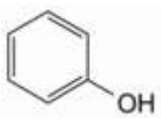
STORAGE

Protected from light.

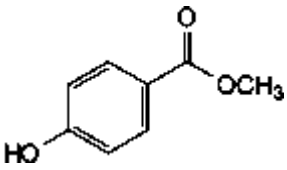
IMPURITIES

Specified impurities B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E, F, I, J, K, L, M.



B. phenol,



C. methyl 4-hydroxybenzoate (methyl parahydroxybenzoate),

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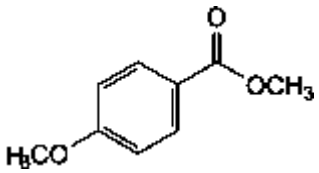
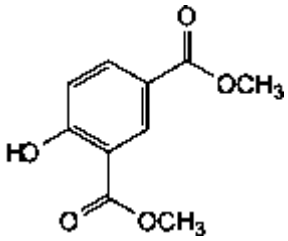
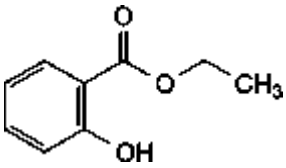


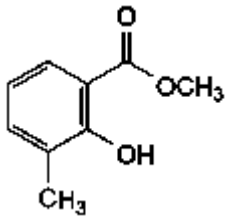
D. methyl 4-methoxybenzoate,



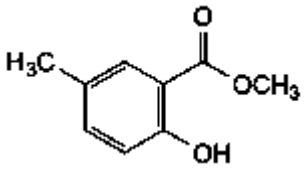
E. dimethyl 4-hydroxybenzene-1,3-dicarboxylate,



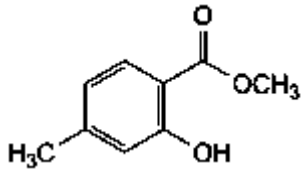
F. ethyl 2-hydroxybenzoate,



I. methyl 2-hydroxy-3-methylbenzoate,



J. methyl 2-hydroxy-5-methylbenzoate,



K. methyl 2-hydroxy-4-methylbenzoate,

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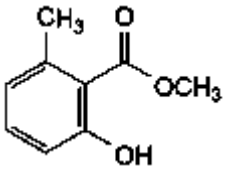
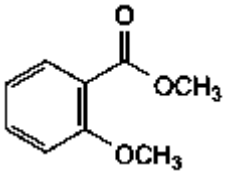


L. methyl 2-hydroxy-6-methylbenzoate,



M. methyl 2-methoxybenzoate.

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Methyl Salicylate Liniment

General Notices

Methyl Salicylate Cutaneous Emulsion

DEFINITION

Methyl Salicylate is a *cutaneous emulsion*. It contains 25% v/v of Methyl Salicylate in Arachis Oil or other suitable fixed oil.

The liniment complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of methyl salicylate, $C_8H_8O_3$

23.0 to 26.5% v/v.

CHARACTERISTICS

The liniment has a characteristic odour.

IDENTIFICATION

In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as that due to methyl salicylate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B. using the following solutions in *petroleum spirit (boiling range, 80° to 100°)*.

(1) 4% w/v of the preparation being examined and 1% w/v of *benzyl alcohol* (internal standard).

(2) 4% w/v of the preparation being examined.

(3) 1% w/v of *benzyl alcohol* (internal standard) and 1% w/v of *methyl salicylate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *diatomaceous support* (60 to 80 mesh) coated with 10% w/w of polyethylene glycol 1540.

(b) Use *helium* as the carrier gas.

(c) Use isothermal conditions maintained at 110°.

(d) Use an inlet temperature of 110°.

(e) Use a flame ionisation detector at a temperature of 110°.

(f) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

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Determine the *weight per mL* of the liniment, Appendix V G, and calculate the content of $C_8H_8O_3$, volume in volume, taking the content of $C_8H_8O_3$ in *methyl salicylate* to be 100.0% and its *weight per mL* to be 1.18 g.

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Methyl Salicylate Ointment

General Notices

Strong Methyl Salicylate Ointment

DEFINITION

Methyl Salicylate Ointment contains 50% w/w of Methyl Salicylate in a suitable water-emulsifying basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of methyl salicylate, $C_8H_8O_3$

45.0 to 52.5% w/w.

CHARACTERISTICS

The ointment has a characteristic odour.

IDENTIFICATION

In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as that due to methyl salicylate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B, using three solutions in *petroleum spirit* *(boiling range, 80° to 100°)* containing (1) 1% w/v of *benzyl alcohol* (internal standard) and 1% w/v of *methyl salicylate*, (2) 2% w/v of the ointment and (3) 2% w/v of the ointment and 1% w/v of the internal standard.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *diatomaceous support* (60 to 80 mesh) coated with 10% w/w of polyethylene glycol 1540 and maintained at 110°.

Calculate the content of $C_8H_8O_3$ taking 100.0% as the content of $C_8H_8O_3$ in *methyl salicylate*.

STORAGE

Certain plastic containers, such as those made from polystyrene, are unsuitable for Methyl Salicylate Ointment.

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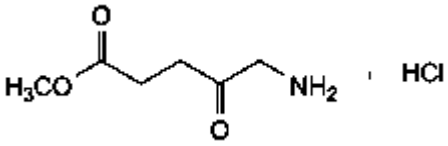
Methylaminolevulinate Hydrochloride

General Notices

(Ph. Eur. monograph 3073)



$C_6H_{12}ClNO_3$ 181.6 *79416-27-6*

Ph Eur

DEFINITION

Methyl 5-amino-4-oxopentanoate hydrochloride.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow powder, hygroscopic.

Solubility

Very soluble in water, slightly soluble in anhydrous ethanol, very slightly soluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *methylaminolevulinate hydrochloride CRS*.

B. Dissolve 25 mg in 5 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Impurity A

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Thin-layer chromatography (2.2.27).

Test solution Dissolve 50.0 mg of the substance to be examined in water R and dilute to 2.0 mL with the same solvent.

Reference solution Dissolve 22.0 mg of 1,3-diaminopropan-2-one dihydrochloride monohydrate R (impurity A) in water R and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with water R.

Plate TLC silica gel plate R.

Mobile phase acetic acid R, water R, acetone R, butanol R (10:20:35:35 *V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Spray with ninhydrin solution R3 and heat at 105 °C for 5 min.

Retardation factors Impurity A = about 0.03; methylaminolevulinate = about 0.5.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with the reference solution (0.8 per cent).

Related substances

Liquid chromatography (2.2.29).

Carry out the test protected from light. Store the solutions at 2-8 °C.

Solvent mixture methanol R, water R (10:90 *V/V*).

Solution A Dissolve 0.23 g of ammonium acetate R1 in 950 mL of water R, adjust to pH 2.5 with phosphoric acid R and dilute to 1000 mL with water R.

Test solution (a) Dissolve 75.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dissolve 75.0 mg of the substance to be examined in solution A and dilute to 25.0 mL with solution A.

Test solution (c) Dilute 1.0 mL of test solution (a) to 5.0 mL with the solvent mixture.

Reference solution (a) Dissolve 12.0 mg of methylaminolevulinate impurity B CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 12.0 mg of methylaminolevulinate impurity C CRS in 1 mL of tetrahydrofuran R and dilute to 100.0 mL with solution A. Dilute 5.0 mL of the solution to 200.0 mL with solution A.

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Reference solution (d) Dissolve 30.0 mg of *methylaminolevulinate hydrochloride CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (e) Dissolve 50 mg of *benzoic acid R* (impurity I) and 50 mg of *hippuric acid R* (impurity H) in solution A and dilute to 100 mL with solution A. Dilute 1 mL of the solution to 10 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.77 g of *ammonium acetate R1* in 950 mL of *water for chromatography R*, adjust to pH 5.5 with *glacial acetic acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	100	0
1 - 19	100 → 10	0 → 90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Autosampler Set at 5 °C.

Injection 30 µL of test solutions (a) and (b) and reference solutions (a), (b), (c) and (e).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (e) to identify the peaks due to impurities H and I.

Relative retention With reference to methylaminolevulinate (retention time = about 6 min): impurity B = about 0.5; impurity I = about 1.8; impurity H = about 1.9; impurity C = about 2.9.

System suitability:

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (b);

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— *resolution*: minimum 1.5 between the peaks due to impurities I and H in the chromatogram obtained with reference solution (e).

Calculation of percentage contents:

— for impurity B, use test solution (a) and the concentration of impurity B in reference solution (a);

— for impurities other than B, use test solution (b) and the concentration of impurity C in reference solution (c).

Limits:

— *impurity B*: maximum 1.8 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total (excluding impurity B)*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification:

Injection Test solution (c) and reference solution (d).

Calculate the percentage content of $C_6H_{12}ClNO_3$ taking into account the assigned content of *methylaminolevulinate hydrochloride CRS*.

STORAGE

In an airtight container at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, G, H, I.*

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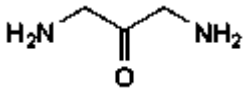
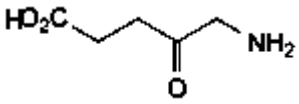
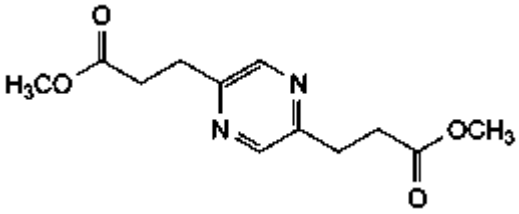


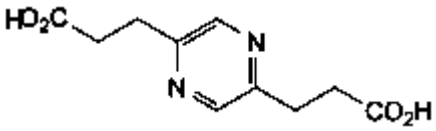
A. 1,3-diaminopropan-2-one,



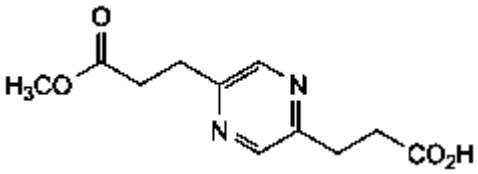
B. 5-amino-4-oxopentanoic acid (5-aminolevulinic acid),



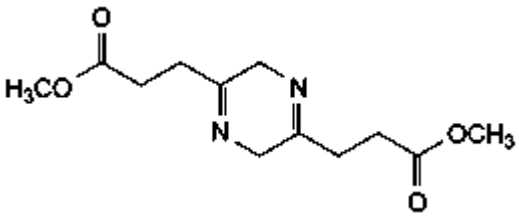
C. dimethyl 3,3′-(pyrazine-2,5-diyl)dipropanoate,



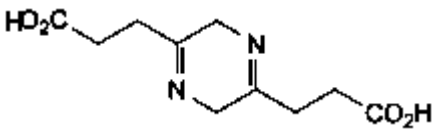
D. 3,3′-(pyrazine-2,5-diyl)dipropanoic acid,



E. 3-[5-(3-methoxy-3-oxopropyl)pyrazin-2-yl]propanoic acid,



F. dimethyl 3,3′-(3,6-dihydropyrazine-2,5-diyl)dipropanoate,



G. 3,3′-(3,6-dihydropyrazine-2,5-diyl)dipropanoic acid,

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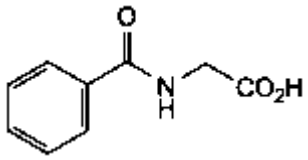
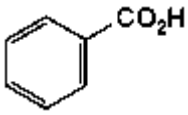


H. benzamidoacetic acid (hippuric acid),



I. benzoic acid.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Methylcellulose[1]

General Notices

(Ph. Eur. monograph 0345)

9004-67-5

Action and use

Bulk-forming laxative; excipient.

Preparation

Methylcellulose Tablets

Ph Eur

DEFINITION

Partly *O*-methylated cellulose. Methyl ether of cellulose.

Content

26.0 per cent to 33.0 per cent of methoxy groups (-OCH_3; M_r 31.03) (dried substance).

♦ CHARACTERS

Appearance

White, yellowish-white or greyish-white powder or granules, hygroscopic after drying.

Solubility

Practically insoluble in hot water, in acetone, in anhydrous ethanol and in toluene. It dissolves in cold water giving a colloidal solution.♦

IDENTIFICATION

A. Evenly distribute 1.0 g onto the surface of 100 mL of *water R* in a beaker, tapping the top of the beaker gently if necessary to ensure a uniform layer on the surface. Allow to stand for 1-2 min: the powdered material aggregates on the surface.

B. Evenly distribute 1.0 g into 100 mL of boiling *water R*, and stir the mixture using a magnetic stirrer with a bar 25 mm long: a slurry is formed and the particles do not dissolve. Allow the slurry to cool to 5 °C and stir using a magnetic stirrer: a clear or slightly turbid solution

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occurs with its thickness dependent on the viscosity grade.

C. To 0.1 mL of the solution obtained in identification test B add 9 mL of a 90 per cent *V/V* solution of *sulfuric acid R*, shake, heat on a water-bath for exactly 3 min, immediately cool in an ice-bath, carefully add 0.6 mL of a 20 g/L solution of *ninhydrin R*, shake and allow to stand at 25 °C: a red colour develops and does not change to purple within 100 min.

D. Place 2-3 mL of the solution obtained in identification test B on a glass slide as a thin film and allow the water to evaporate: a coherent, clear film forms on the glass slide.

E. Add 50.0 mL of the solution obtained in identification test B to 50.0 mL of *water R* in a beaker. Insert a thermometer into the solution. Stir the solution on a magnetic stirrer/hot plate and begin heating, increasing the temperature at a rate of 2-5 °C per minute. Determine the temperature at which a turbidity increase begins to occur and designate the temperature as the flocculation temperature: the flocculation temperature is higher than 50 °C.

TESTS

◊ Appearance of solution

The solution is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

While stirring, introduce a quantity of the substance to be examined equivalent to 1.0 g of the dried substance into 50 g of *carbon dioxide-free water R* heated to 90 °C. Allow to cool, adjust the mass of the solution to 100 g with *carbon dioxide-free water R* and stir until dissolution is complete. Allow to stand at 2-8 °C for 1 h before carrying out the test.◊

pH (*2.2.3*)

5.0 to 8.0 for the solution prepared as described under Viscosity.

Read the pH after the probe has been immersed for 5 ± 0.5 min.

Viscosity

80 per cent to 120 per cent of the nominal value for samples with a viscosity of less than 600 mPa·s (Method 1); 75 per cent to 140 per cent of the nominal value for samples with a viscosity of 600 mPa·s or higher (Method 2).

Method 1, to be applied to samples with a viscosity of less than 600 mPa·s Weigh a quantity of the substance to be examined equivalent to 4.000 g of the dried substance. Transfer into a wide-mouthed bottle, and adjust the total mass of the sample and the water to 200.0 g with hot *water R* (90-99 °C). Capping the bottle, stir by mechanical means at 400 ± 50 r/min for 10-20 min until the particles are thoroughly dispersed and wetted. Scrape down the insides of the bottle with a spatula if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water-bath maintained at a temperature below 5 °C for another 20-40 min. Adjust the solution mass if necessary to 200.0 g using cold *water R*. Centrifuge the solution if necessary to expel any entrapped air bubbles. Using a spatula, remove any foam. Determine the kinematic viscosity (ν) of this solution using the capillary viscometer method (*2.2.9*). Separately, determine the density (ρ) (*2.2.5*) of the solution and calculate the dynamic viscosity (η), as $\eta = \rho\nu$.

Method 2, to be applied to samples with a viscosity of 600 mPa·s or higher Weigh a quantity of the substance to be examined equivalent to 10.00 g of the dried substance. Transfer into a wide-mouthed bottle, and adjust the total mass of the sample and the water to 500.0 g

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with hot *water R* (90-99 °C). Capping the bottle, stir by mechanical means at 400 ± 50 r/min for 10-20 min until the particles are thoroughly dispersed and wetted. Scrape down the insides of the bottle with a spatula if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water-bath maintained at a temperature below 5 °C for another 20-40 min. Adjust the solution mass if necessary to 500.0 g using cold *water R*. Centrifuge the solution if necessary to expel any entrapped air bubbles. Using a spatula, remove any foam. Determine the viscosity (*2.2.10*) of this solution at 20 ± 0.1 °C using a rotating viscometer.

Apparatus Single-cylinder type spindle viscometer.

Rotor number, revolution and calculation multiplier Apply the conditions specified in Table 0345.-1.

Table 0345.-1.

Nominal viscosity* (mPa·s)	Rotor number	Revolution (r/min)	Calculation multiplier
600 to less than 1400	3	60	20
1400 to less than 3500	3	12	100
3500 to less than 9500	4	60	100
9500 to less than 99 500	4	6	1000
99 500 or more	4	3	2000

*the nominal viscosity is based on the manufacturer's specifications.

Allow the spindle to rotate for 2 min before taking the measurement. Allow a rest period of at least 2 min between subsequent measurements. Repeat the measurement twice and determine the mean of the 3 readings.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (*2.4.14*)

Maximum 1.5 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*).

Apparatus:

— *reaction vial*: a 5 mL pressure-tight vial, 50 mm in height, 20 mm in external diameter and 13 mm in internal diameter at the mouth, equipped with a pressure-tight butyl rubber membrane stopper coated with polytetrafluoroethylene and secured with an aluminium crimp cap or another sealing system providing a sufficient air-tightness;

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— *heater*: a heating module with a square aluminium block having holes 20 mm in diameter and 32 mm in depth, so that the reaction vials fit; mixing of the contents of the vial is effected using a magnetic stirrer equipped in the heating module or using a reciprocal shaker that performs approximately 100 cycles/min.

Internal standard solution 30 g/L solution of *octane R* in *o-xylene R*.

Test solution Weigh 65.0 mg of the substance to be examined, place in a reaction vial, add 0.06-0.10 g of *adipic acid R*, 2.0 mL of the internal standard solution and 2.0 mL of *hydriodic acid R*, immediately cap and seal the vial, and weigh accurately. Mix the contents of the vial continuously for 60 min while heating the block so that the temperature of the contents is maintained at 130 ± 2 °C. If a reciprocal shaker or magnetic stirrer cannot be used, shake the vial thoroughly by hand at 5 min intervals during the initial 30 min of the heating time. Allow the vial to cool, and again weigh accurately. If the loss of mass is less than 26 mg and there is no evidence of a leak, use the upper layer of the mixture as the test solution.

Reference solution Place 0.06-0.10 g of *adipic acid R*, 2.0 mL of the internal standard solution and 2.0 mL of *hydriodic acid R* in another reaction vial, cap and seal the vial, and weigh accurately. Add 45 µL of *methyl iodide R* through the septum with a syringe, and weigh accurately. Shake the reaction vial thoroughly and use the upper layer as the reference solution.

Use a precolumn if needed.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *methylpolysiloxane R* (3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 4.3 mL/min.

Split ratio 1:40.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3	50
	3 - 8	50 → 100
	8 - 12.3	100 → 250
	12.3 - 20.3	250
Injection port		250
Detector		280

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Detection Flame ionisation or thermal conductivity.

Injection 1-2 µL.

Relative retention With reference to octane (retention time = about 10 min): methyl iodide = about 0.4.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to methyl iodide and octane;

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the ratio of the area of the peak due to methyl iodide to that due to octane, determined on 6 injections.

Calculate the ratio (Q) of the area of the peak due to methyl iodide to the area of the peak due to the internal standard in the chromatogram obtained with the test solution, and the ratio (Q_1) of the area of the peak due to methyl iodide to the area of the peak due to the internal standard in the chromatogram obtained with the reference solution.

Calculate the percentage content of methoxy groups using the following expression:

$$\frac{Q \times m_1}{Q_1 \times m} \times 21.864$$

m_1 = mass of methyl iodide in the reference solution, in milligrams;

m = mass of the sample (dried substance), in milligrams.

LABELLING

The label states the viscosity in millipascal seconds.

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for methylcellulose used as binder, viscosity-enhancing agent or film former.

Viscosity

See Tests.

Degree of substitution

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See Assay.◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Methylcellulose Tablets

General Notices

DEFINITION

Methylcellulose Tablets contain Methylcellulose 450 in a suitable flavoured basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

IDENTIFICATION

A. Whilst stirring, introduce a quantity of the powdered tablets containing 1.0 g of Methylcellulose 450 into 50 mL of *carbon dioxide-free water* heated at 90°. Allow to cool, dilute to 100 mL with the same solvent and continue stirring until solution is complete (solution A). Heat 10 mL of solution A in a water bath, with stirring. At temperatures above 50° either the solution becomes cloudy or a flocculent precipitate is produced. The solution becomes clear on cooling.

B. Mix thoroughly a quantity of the powdered tablets containing 1 g of Methylcellulose 450 with 2 g of finely powdered *manganese(II) sulfate* in a test-tube about 16 cm long. Impregnate a strip of filter paper with a freshly prepared mixture of 1 volume of a 20% v/v solution of *diethanolamine* and 11 volumes of a 5% w/v solution of *sodium nitroprusside* adjusted to pH 9.8 with 1M *hydrochloric acid*. Insert the strip to a depth of 2 cm into the upper part of the tube, immerse the tube to a depth of 8 cm in a silicone oil bath and heat at 190° to 200°. The filter paper does not become blue within 10 minutes. Carry out a blank test.

TESTS

Kinematic viscosity

For tablets containing 500 mg of Methylcellulose 450, at 20°, 350 to 550 $mm^2 s^{-1}$, when determined by the following method. Place 2.6 g of the powdered tablets in a wide-mouthed bottle, add 100 mL of *water* heated to 85° to 90°, close the bottle with a stopper fitted with a stirrer and stir for 10 minutes. Cool in ice and continue stirring until the solution is of uniform consistence. Remove the ice and allow the solution to attain room temperature. Determine the *kinematic viscosity* of the solution, Appendix V H, Method II, using a suspended-level viscometer (size 3).

Disintegration

The requirement for Disintegration does not apply to Methylcellulose Tablets.

LABELLING

The label states that the tablets should be broken in the mouth before swallowing.

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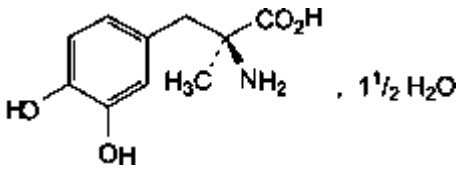
Methyldopa

General Notices

(Ph. Eur. monograph 0045)



$C_{10}H_{13}NO_4,1½H_2O$ 238.2 *41372-08-1*

Action and use

Alpha$_2$-adrenoceptor agonist; treatment of hypertension.

Preparation

Methyldopa Tablets

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid sesquihydrate (L-methyldopa sesquihydrate).

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder or colourless or almost colourless crystals.

Solubility

Slightly soluble in water, very slightly soluble in ethanol (96 per cent). It is freely soluble in dilute mineral acids.

IDENTIFICATION

Carry out either tests A, B or tests A, C.

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison methyldopa CRS.

B. Enantiomeric purity (see Tests).

C. Specific optical rotation (2.2.7): -28.0 to -25.0.

Dissolve a quantity equivalent to 2.20 g of the anhydrous substance in aluminium chloride solution R and dilute to 50.0 mL with the same solution.

TESTS

Appearance of solution

Dissolve 1.0 g in 1 M hydrochloric acid and dilute to 25 mL with the same solvent. The solution is not more intensely coloured than reference solution BY_6 or B_6 (2.2.2, Method II).

Acidity

Dissolve 1.0 g with heating in 100 mL of carbon dioxide-free water R. Add 0.1 mL of methyl red solution R. Not more than 0.5 mL of 0.1 M sodium hydroxide is required to produce the pure yellow colour of the indicator.

Absorbance (2.2.25)

Test solution Dissolve 40.0 mg in 0.1 M hydrochloric acid and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of the solution to 100.0 mL with 0.1 M hydrochloric acid.

Spectral range 230-350 nm.

Absorption maximum At 280 nm.

Specific absorbance at the absorption maximum 122 to 137 (anhydrous substance).

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of racemic methyldopa CRS in the mobile phase and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: spherical end-capped octadecylsilyl silica gel for chromatography R (5 µm).

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Mobile phase Dissolve separately 0.200 g of *copper acetate R* and 0.387 g of *N,N-dimethyl-L-phenylalanine R* in *water R*; mix the 2 solutions and adjust immediately to pH 4.3 with *acetic acid R*; add 50 mL of *methanol R* and dilute to 1000 mL with *water R*; mix and filter.

Equilibrate the column with the mobile phase for about 2 h.

If necessary, decrease the concentration of *methanol R* so the peak corresponding to D-methyldopa is clearly separated from the negative system peak that appears at about 6 min.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time Twice the retention time of L-methyldopa.

Relative retention With reference to L-methyldopa (retention time = about 14 min): D-methyldopa = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to D-methyldopa and L-methyldopa.

Limit:

— *D-methyldopa (impurity D)*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.100 g of the substance to be examined in *0.1 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with *0.1 M hydrochloric acid*. Dilute 5.0 mL of this solution to 100.0 mL with *0.1 M hydrochloric acid*.

Reference solution (b) Dissolve the contents of a vial of *methyldopa for system suitability CRS* (containing impurities A, B and C) in 1.0 mL of *0.1 M hydrochloric acid*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *di-isobutyloctadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 8 nm.

Mobile phase *methanol R*, 0.1 M phosphate buffer solution pH 3.0 R (15:85 *V/V*).

Flow rate 1 mL/min.

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Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 6 times the retention time of methyldopa.

Identification of impurities Use the chromatogram supplied with *methyldopa for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to methyldopa (retention time = about 5 min): impurity A = about 1.9; impurity B = about 4.3; impurity C = about 4.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities B and C.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 2.6; impurity C = 1.3;

— *impurities A, B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Water (*2.5.12*)

10.0 per cent to 13.0 per cent, determined on 0.20 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g, heating if necessary, in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 21.12 mg of $C_{10}H_{13}NO_4$.

STORAGE

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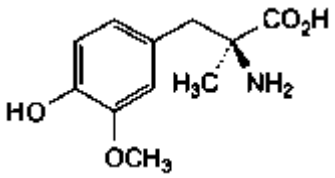
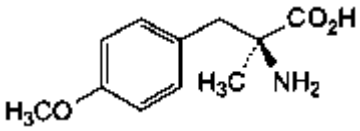
Protected from light.

IMPURITIES

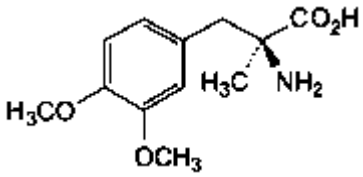
Specified impurities *A, B, C, D.*



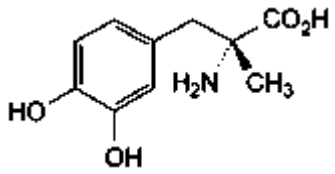
A. (2*S*)-2-amino-3-(4-hydroxy-3-methoxyphenyl)-2-methylpropanoic acid (3-methoxymethyldopa),



B. (2*S*)-2-amino-3-(4-methoxyphenyl)-2-methylpropanoic acid,



C. (2*S*)-2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid,



D. (2*R*)-2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid (D-methyldopa).

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Methyldopa Tablets

General Notices

Action and use

Alpha$_2$-adrenoceptor agonist; treatment of hypertension.

DEFINITION

Methyldopa Tablets contain Methyldopa. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous methyldopa, $C_{10}H_{13}NO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove the coating from a suitable number of tablets by washing with *chloroform*. To a quantity of the powdered tablet cores containing the equivalent of 5 g of anhydrous methyldopa add 35 mL of a mixture of equal volumes of *chloroform* and *methanol* and shake for 3 minutes. Centrifuge and discard the supernatant liquid. Repeat the operation with a further 35 mL of a mixture of equal volumes of *chloroform* and *methanol*. Dry the residue in a current of nitrogen, add 20 mL of *methanol* and 15 mL of 2M *hydrochloric acid*, shake for 2 minutes and filter. Adjust the pH of the filtrate to 4.9 with 5M *ammonia*, allow to stand for several hours at 2° to 8° and filter. Wash the precipitate with 15 mL of *water* and dry it at 50° at a pressure not exceeding 0.7 kPa for 3 hours. Reserve a portion of the residue for the test for Optical rotation. The remainder of the residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of methyldopa *(RS 223)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using *microcrystalline cellulose* as the coating substance and a mixture of 50 volumes of *butan-1-ol*, 25 volumes of *glacial acetic acid* and 25 volumes of *water* as the mobile phase. Apply separately to the plate 5 µL of each of two solutions in 1M *hydrochloric acid* containing (1) 1% w/v of the residue and (2) 1% w/v of *methyldopa BPCRS*. After removal of the plate, dry it in a current of warm air and spray with a freshly prepared mixture of equal volumes of a 10% w/v solution of *iron(III) chloride hexahydrate* and a 5% w/v solution of *potassium hexacyanoferrate*(III). The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. Add 0.1 mL of *iron(III) chloride solution R1* to 5 mL of a 0.4% w/v solution in 0.1M *hydrochloric acid*; a green colour is produced. To half of the solution add an excess of 5M *ammonia*; a purple colour is produced. To the remainder of the solution add an excess of 5M *sodium hydroxide*; a red colour is produced.

Optical rotation

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Determine the content of $C_{10}H_{13}NO_4$ in the residue reserved in the test for Identification by carrying out Method I for *non-aqueous titration*, Appendix VIII A, using 0.2 g of the residue and *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 21.12 mg of $C_{10}H_{13}NO_4$. Dissolve a quantity of the residue containing 0.39 g of $C_{10}H_{13}NO_4$ in sufficient *aluminium chloride solution* to produce 10 mL. The *optical rotation* of the resulting solution at 25° is –0.98° to –1.09°, Appendix V F.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing the equivalent of 0.1 g of anhydrous methyldopa as completely as possible in sufficient 0.05M *sulfuric acid* to produce 100 mL and filter. To 5 mL of the filtrate add 2 mL of *iron(II) sulfate–citrate solution*, 8 mL of *glycine buffer solution* and sufficient *water* to produce 100 mL. Measure the *absorbance* of the resulting solution at the maximum at 545 nm, Appendix II B. Repeat the procedure using 5 mL of a 0.10% w/v solution of *methyldopa BPCRS* in place of 5 mL of the filtrate, beginning at the words 'add 2 mL of…'. Calculate the content of $C_{10}H_{13}NO_4$ using the declared content of $C_{10}H_{13}NO_4$ in *methyldopa BPCRS*.

STORAGE

Methyldopa Tablets should be protected from light.

LABELLING

The quantity of active ingredient is expressed in terms of the equivalent amount of anhydrous methyldopa.

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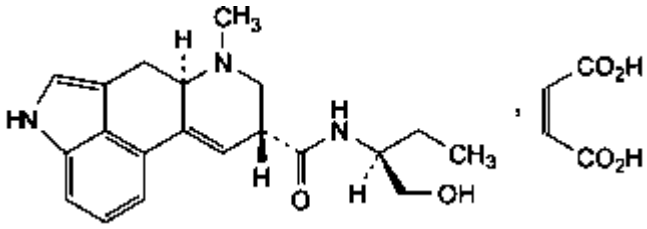
Methylergometrine Maleate

General Notices

(Ph. Eur. monograph 1788)



$C_{24}H_{29}N_3O_6$ 455.5 *57432-61-8*

Action and use

Oxytocic.

Ph Eur

DEFINITION

(6a*R*,9*R*)-*N*-[(1*S*)-1-(Hydroxymethyl)propyl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (*Z*)-butenedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Soluble in water, slightly soluble in anhydrous ethanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *methylergometrine maleate CRS*.

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TESTS

Solution S

Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

pH (2.2.3)

4.4 to 5.2.

Dilute 2.0 mL of solution S to 50.0 mL with *carbon dioxide-free water R*.

Specific optical rotation (2.2.7)

+ 44.0 to + 50.0 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 25 mg of the substance to be examined in 15 mL of mobile phase B and dilute to 50.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve the contents of a vial of *methylergometrine for system suitability CRS* (containing impurities A, B, C, D, E, F, G, H and I) in 1.0 mL of a mixture of 30 volumes of mobile phase B and 70 volumes of *water R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: 2 g/L solution of *ammonium carbamate R*;

— *mobile phase B*: *acetonitrile R*, *water R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 7	85 → 65	15 → 35
7 - 12	65	35
12 - 17	65 → 20	35 → 80

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
17 - 19	20	80

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 310 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *methylergometrine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E, F, G, H and I.

Relative retention With reference to methylergometrine (retention time = about 12 min): impurity A = about 0.2; impurity B = about 0.5; impurity C = about 0.6; impurity D = about 0.7; impurity I = about 1.10; impurity E = about 1.14; impurity F = about 1.2; impurity G = about 1.3; impurity H = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to methylergometrine and impurity I; minimum 1.5 between the peaks due to impurities I and E.

Limits:

— *impurity I*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities A, B, D, E, F, G, H*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.300 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

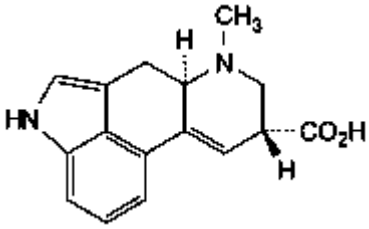
1 mL of *0.1 M perchloric acid* is equivalent to 45.55 mg of $C_{24}H_{29}N_3O_6$.

STORAGE

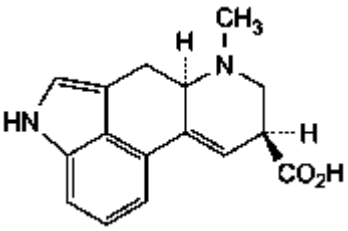
In an airtight container, protected from light.

IMPURITIES

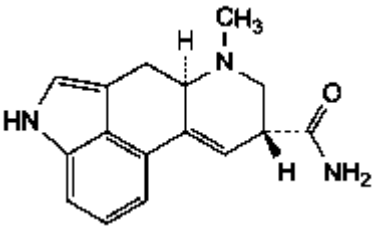
Specified impurities *A, B, C, D, E, F, G, H, I.*



A. (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid,



B. (6a*R*,9*S*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid,



C. (6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide,

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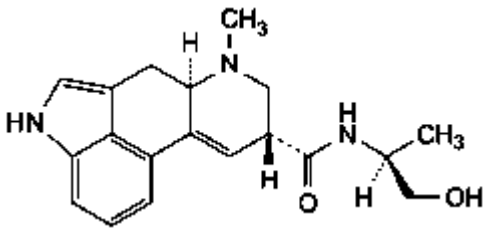
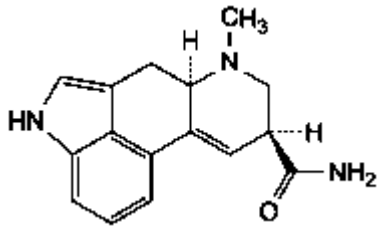
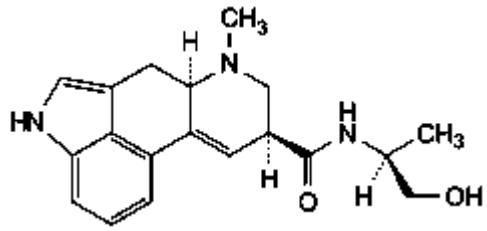


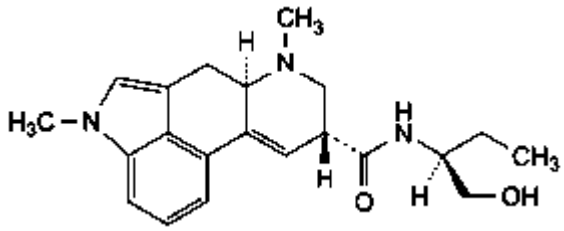
D. (6a*R*,9*R*)-*N*-[(1*S*)-2-hydroxy-1-methylethyl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergometrine),



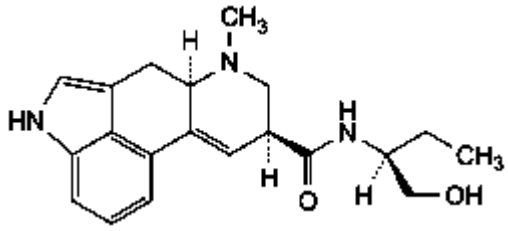
E. (6a*R*,9*S*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide,



F. (6a*R*,9*S*)-*N*-[(1*S*)-2-hydroxy-1-methylethyl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergometrinine),



G. (6a*R*,9*R*)-*N*-[(1*S*)-1-(hydroxymethyl)propyl]-4,7-dimethyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (methysergide),



H. (6a*R*,9*S*)-*N*-[(1*S*)-1-(hydroxymethyl)propyl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (methylergometrinine),

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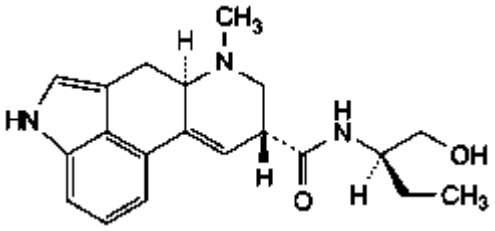

I. (6a*R*,9*R*)-*N*-[(1*R*)-1-(hydroxymethyl)propyl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (1′-*epi*-methylergometrine).

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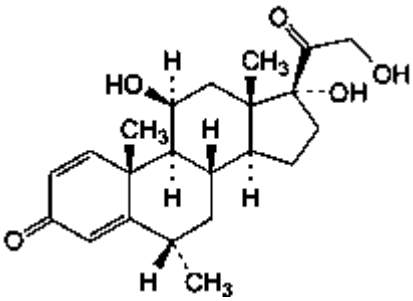
Methylprednisolone

General Notices

(Ph. Eur. monograph 0561)



$C_{22}H_{30}O_5$ 374.5 *83-43-2*

Action and use

Glucocorticoid.

Preparation

Methylprednisolone Tablets

Ph Eur

DEFINITION

11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent), slightly soluble in acetone and in methylene chloride.

It shows polymorphism (*5.9*).

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IDENTIFICATION

First identification: A, B.

Second identification: C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison methylprednisolone CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of acetone R, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 10 mg of methylprednisolone CRS in the mobile phase and dilute to 10.0 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase methanol R, methylene chloride R (10:90 *V/V*).

Application 10 µL; the volume may be adapted based on the type of plate used.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of 2,4-dihydroxybenzaldehyde R in glacial acetic acid R, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of sulfuric acid R and 37.5 mL of glacial acetic acid R; heat the plate at 90 °C for 35 min or until the spots appear and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Add about 2 mg to 2 mL of sulfuric acid R and shake to dissolve. Within 5 min, an intense red colour develops. When examined in ultraviolet light at 365 nm, brownish-red fluorescence is seen. Add this solution to 10 mL of water R and mix. The colour fades and there is a faint yellowish-green fluorescence in ultraviolet light at 365 nm.

TESTS

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Specific optical rotation (2.2.7)

+ 97.0 to + 103.0 (dried substance).

Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *phosphoric acid R*, *acetonitrile R*, *water R* (0.1:50:50 *V/V/V*).

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 3 mg of *methylprednisolone for system suitability A CRS* (containing impurities A, B, C, D, E, F, G, H and I) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 30.0 mg of *methylprednisolone CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *tetrahydrofuran R*, *acetonitrile for chromatography R*, *water for chromatography R* (0.1:1.5:10:90 *V/V/V/V*);

— *mobile phase B*: *phosphoric acid R*, *tetrahydrofuran R*, *acetonitrile for chromatography R* (0.1:1.5:100 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	83	17
14 - 30	83 → 52	17 → 48

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 247 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

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Identification of impurities Use the chromatogram supplied with *methylprednisolone for system suitability A CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, F, G, H and I.

Relative retention With reference to methylprednisolone (retention time = about 12 min): impurity B = about 0.85; impurity H = about 0.88; impurity A = about 0.92; impurity F = about 1.1; impurities G and I = about 1.54; impurity C = about 1.7; impurity E = about 1.9; impurity D (isomer 1) = about 2.10; impurity D (isomer 2) = about 2.2.

System suitability Reference solution (a):

— *resolution*: minimum 1.7 between the peaks due to impurity A and methylprednisolone;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to methylprednisolone.

Limits:

— *impurity D*: for the sum of the areas of the 2 isomer peaks, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity A*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *sum of impurities G and I*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities B, H*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities C, E, F*: for each impurity, not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

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Calculate the percentage content of $C_{22}H_{30}O_5$ taking into account the assigned content of *methylprednisolone CRS*.

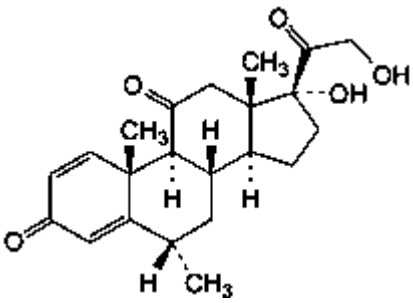
STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

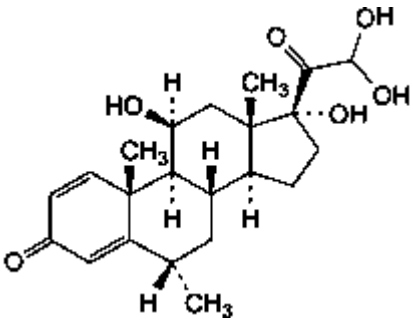
IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I.*

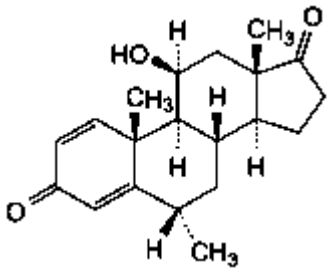
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *J, K, L.*



A. 17,21-dihydroxy-6α-methylpregna-1,4-diene-3,11,20-trione,



B. 11β,17,21,21-tetrahydroxy-6α-methylpregna-1,4-diene-3,20-dione,



C. 11β-hydroxy-6α-methylandrosta-1,4-diene-3,17-dione,

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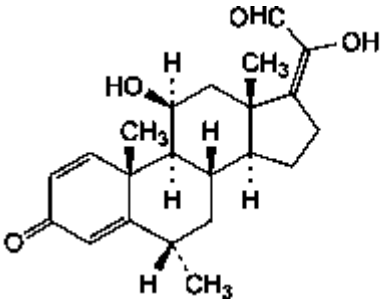
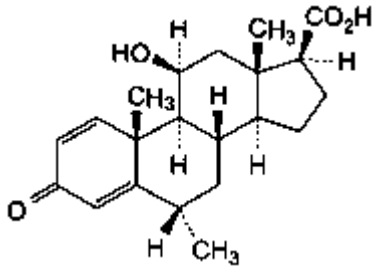
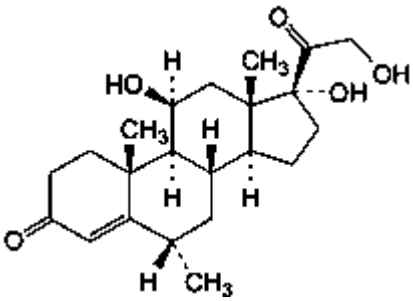


and (*Z*)-isomer

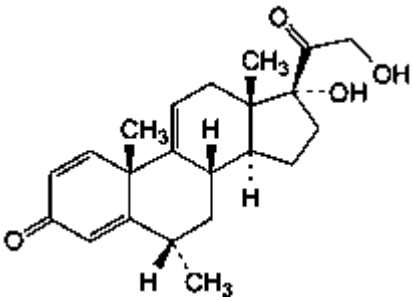
D. (17*EZ*)-11β,20-dihydroxy-6α-methylpregna-1,4,17(20)-triene-3,21-dione,



E. 11β-hydroxy-6α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid,



F. 11β,17,21-trihydroxy-6α-methylpregn-4-ene-3,20-dione,



G. 17,21-dihydroxy-6α-methylpregna-1,4,9(11)-triene-3,20-dione,

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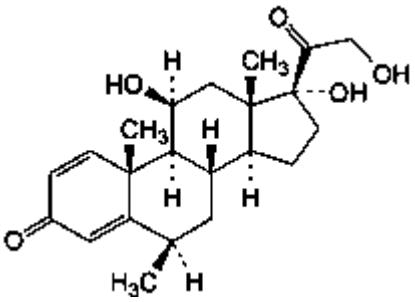
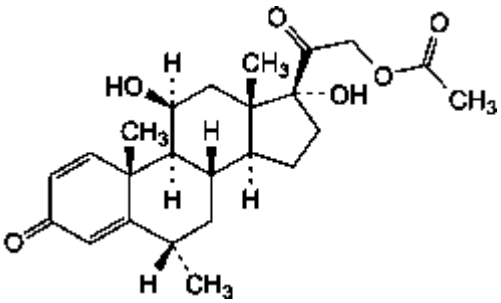
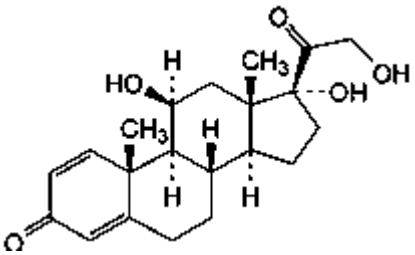


H. 11β,17,21-trihydroxy-6β-methylpregna-1,4-diene-3,20-dione,

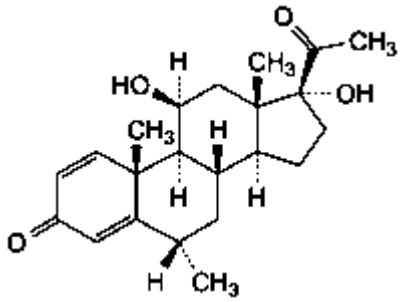
I. unknown structure,



J. 11β,17-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (methylprednisolone acetate),



K. 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (prednisolone),



L. 11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

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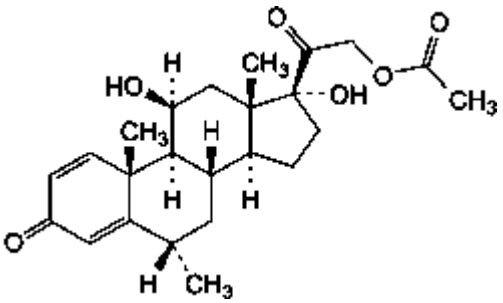
Methylprednisolone Acetate

General Notices

(Ph. Eur. monograph 0933)



$C_{24}H_{32}O_6$ 416.5 *53-36-1*

Action and use

Glucocorticoid.

Preparation

Methylprednisolone Acetate Injection

Ph Eur

DEFINITION

11β,17-Dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone and in ethanol (96 per cent).

It shows polymorphism (*5.9*).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison methylprednisolone acetate CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of acetone R, evaporate to dryness and record new spectra using the residues.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

TESTS

Specific optical rotation (2.2.7)

+ 107 to + 113 (dried substance).

Dissolve 0.250 g in ethanol (96 per cent) R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Buffer solution Mix 20 mL of a 103 g/L solution of hydrochloric acid R, 50 mL of a 68 g/L solution of sodium acetate R and 150 mL of a 37.3 g/L solution of potassium chloride R and dilute to 1.0 L with water R.

Solvent mixture acetonitrile R, buffer solution (50:50 *V/V*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of methylprednisolone acetate for system suitability CRS (containing impurities E, G and J) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of methylprednisolone acetate for peak identification CRS (impurities A and K) in 1.0 mL of the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of methylprednisolone acetate CRS in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

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— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water for chromatography R* (28:72 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	95	5
15 - 25	95 → 50	5 → 50
25 - 28	50	50

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *methylprednisolone acetate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities E, G and J; use the chromatogram supplied with *methylprednisolone acetate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and K.

Relative retention With reference to methylprednisolone acetate (retention time = about 15 min): impurity A = about 0.4; impurity E = about 0.6; impurity J = about 0.9; impurity G = about 1.1; impurity K = about 1.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to methylprednisolone acetate.

Calculation of percentage contents:

— for each impurity, use the concentration of methylprednisolone acetate in reference solution (b).

Limits:

— *impurity J*: maximum 0.3 per cent;

— *impurities A, G*: for each impurity, maximum 0.2 per cent;

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— *impurities E, K*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase *acetonitrile R*, *water for chromatography R* (32:68 *V/V*).

Injection Test solution (b) and reference solution (d).

Run time 1.5 times the retention time of methylprednisolone acetate.

Retention time Methylprednisolone acetate = about 15 min.

Calculate the percentage content of $C_{24}H_{32}O_6$ taking into account the assigned content of *methylprednisolone acetate CRS*.

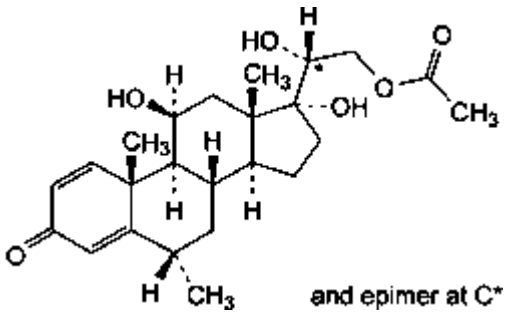
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, E, G, J, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, F, H, I.*



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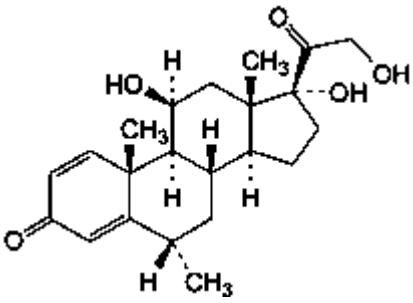
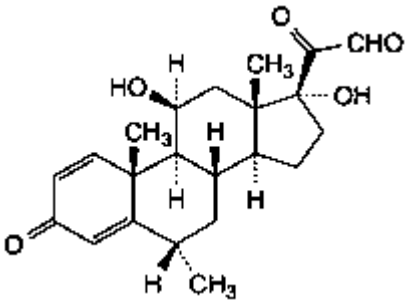
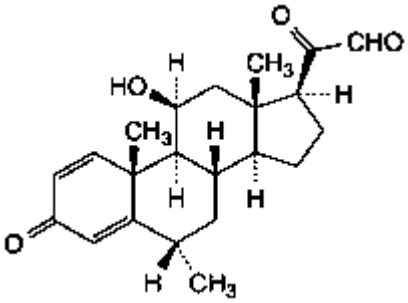
A. (20*RS*)-11β,17,20-trihydroxy-6α-methyl-3-oxopregna-1,4-dien-21-yl acetate,



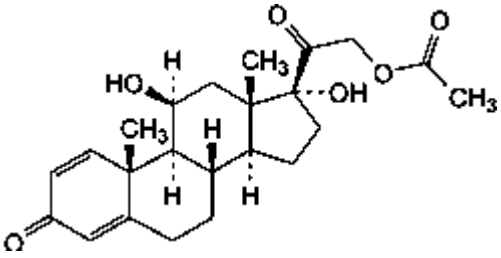
B. 11β,17,21-trihydroxy-6α-methylpregna-1,4-diene-3,20-dione (methylprednisolone),



C. 11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20,21-trione,



D. 11β-hydroxy-6α-methylpregna-1,4-diene-3,20,21-trione,



E. 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate (prednisolone acetate),

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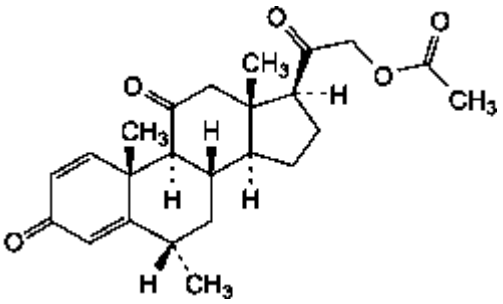
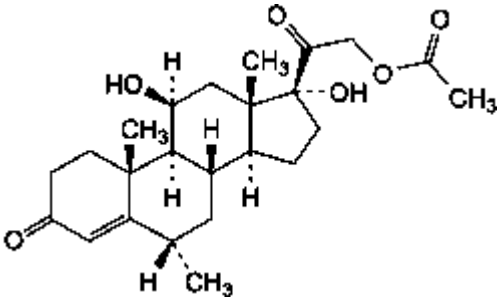
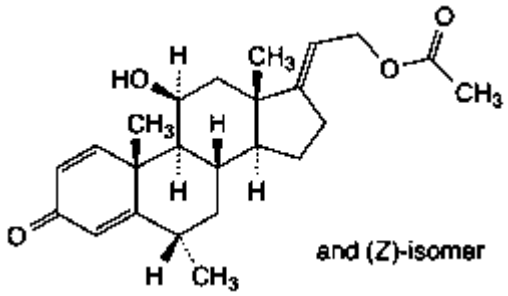


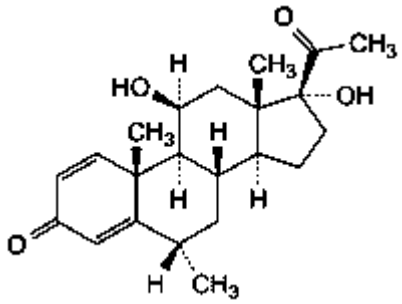
F. 6α-methyl-3,11,20-trioxopregna-1,4-dien-21-yl acetate,



G. 11β,17-dihydroxy-6α-methyl-3,20-dioxopregn-4-en-21-yl acetate,



H. (*EZ*)-11β-hydroxy-6α-methyl-3-oxopregna-1,4,17(20)-trien-21-yl acetate,



I. 11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione,

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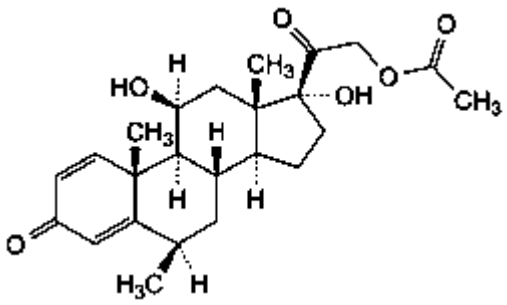
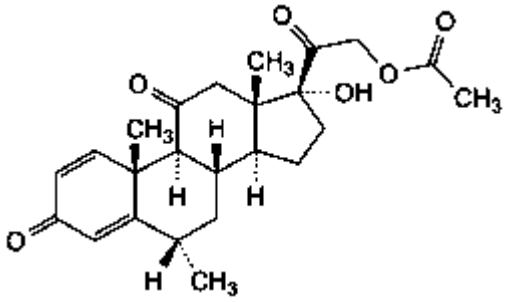


J. 11β,17-dihydroxy-6β-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate,



K. 17-hydroxy-6α-methyl-3,11,20-trioxopregna-1,4-dien-21-yl acetate.

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Methylprednisolone Acetate Injection

General Notices

Action and use

Glucocorticoid.

DEFINITION

Methylprednisolone Acetate Injection is a sterile suspension of Methylprednisolone Acetate in Water for Injections. It is prepared using aseptic technique.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of methylprednisolone acetate, $C_{24}H_{32}O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Dilute a volume containing 0.1 g of Methylprednisolone Acetate to 5 mL with *water*, centrifuge and discard the supernatant liquid. Wash the residue with five 5 mL quantities of *water*, resuspending the residue in the *water* each time, centrifuging and discarding the washings. The residue, after drying at 105° for 3 hours, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of methylprednisolone acetate *(RS 226)*.

B. Complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase A*.

TESTS

Acidity or alkalinity

pH, 3.5 to 7.0, Appendix V L.

ASSAY

Mix 0.12 g of *prednisone BPCRS* (internal standard) with 0.6 mL of *glacial acetic acid*, slowly add *chloroform* with the aid of ultrasound, shake to dissolve and dilute with sufficient *chloroform* to produce 20 mL (solution A).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 10 mL of solution A to a quantity of the injection containing 40 mg of Methylprednisolone Acetate, add sufficient *chloroform* to produce 25 mL and shake for 15 minutes or until the aqueous layer is clear; to 4 mL of the chloroform layer, add 30 mL of *chloroform* and

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0.4 g of *anhydrous sodium sulfate*, shake for 5 minutes, centrifuge and use the supernatant solution.

(2) Dissolve 20 mg of *methylprednisolone acetate BPCRS* in 5 mL of solution A and add sufficient *chloroform* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *silica gel for chromatography* (5 to 10 µm).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *glacial acetic acid*, 35 volumes of *methanol*, 70 volumes of *tetrahydrofuran*, 475 volumes of water-saturated *1-chlorobutane* and 475 volumes of *1-chlorobutane*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to methylprednisolone acetate and the internal standard is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{32}O_6$ in the injection using the declared content of $C_{24}H_{32}O_6$ in *methylprednisolone acetate BPCRS*.

STORAGE

Methylprednisolone Acetate Injection should be protected from light and stored at a temperature not exceeding 30°. It should not be allowed to freeze.

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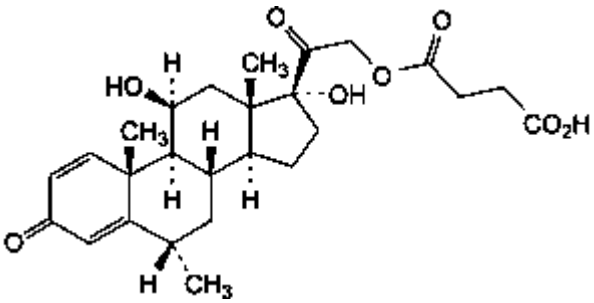
Methylprednisolone Hydrogen Succinate

General Notices

(Ph. Eur. monograph 1131)



$C_{26}H_{34}O_8$ 474.5 *2921-57-5*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

4-[(11β,17-Dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-21-yl)oxy]-4-oxobutanoic acid.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Practically insoluble in water, slightly soluble in acetone and in anhydrous ethanol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *methylprednisolone hydrogen succinate CRS*.

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B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (e).

TESTS

Appearance of solution

The solution is clear (*2.2.1*).

Dissolve 0.100 g in 5 mL of *sodium hydrogen carbonate solution R*.

Specific optical rotation (*2.2.7*)

+ 97 to + 104 (dried substance).

Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in 1 mL of *tetrahydrofuran R* and dilute to 20.0 mL with the mobile phase.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *methylprednisolone hydrogen succinate for performance test CRS* (containing impurity D) in 0.25 mL of *tetrahydrofuran R* and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *methylprednisolone hydrogen succinate for peak identification CRS* (containing impurity F) in 0.25 mL of *tetrahydrofuran R* and dilute to 5.0 mL with the mobile phase.

Reference solution (d) Dissolve 5 mg of *methylprednisolone R* (impurity A) in 0.25 mL of *tetrahydrofuran R* and dilute to 5.0 mL with the mobile phase.

Reference solution (e) Dissolve 20.0 mg of *methylprednisolone hydrogen succinate CRS* in 1 mL of *tetrahydrofuran R* and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

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Mobile phase *glacial acetic acid R*, *acetonitrile R*, *water R* (2:31:67 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b), (c) and (d).

Run time Twice the retention time of methylprednisolone hydrogen succinate.

Identification of impurities Use the chromatogram supplied with *methylprednisolone hydrogen succinate for performance test CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity D; use the chromatogram supplied with *methylprednisolone hydrogen succinate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity F; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention With reference to methylprednisolone hydrogen succinate (retention time = about 21 min): impurity A = about 0.5; impurity F = about 0.9; impurity D = about 1.1.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to methylprednisolone hydrogen succinate.

Calculation of percentage contents:

— for each impurity, use the concentration of methylprednisolone hydrogen succinate in reference solution (b).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *impurity F*: maximum 0.2 per cent;

— *impurity D*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (e).

Calculate the percentage content of $C_{26}H_{34}O_8$ taking into account the assigned content of *methylprednisolone hydrogen succinate CRS*.

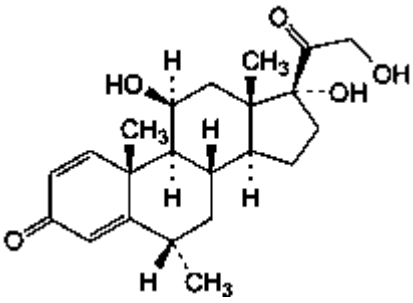
STORAGE

In an airtight container, protected from light.

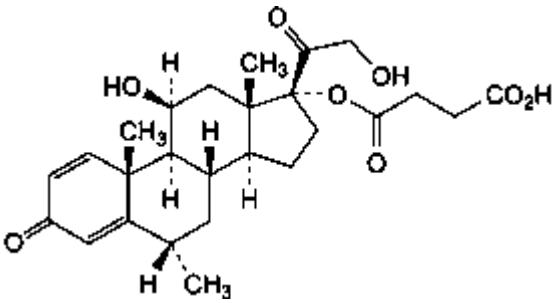
IMPURITIES

Specified impurities *A, D, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, E, G.*



A. 11β,17,21-trihydroxy-6α-methylpregna-1,4-diene-3,20-dione (methylprednisolone),



B. 4-[(11β,21-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-17-yl)oxy]-4-oxobutanoic acid (methylprednisolone 17-(hydrogen succinate)),

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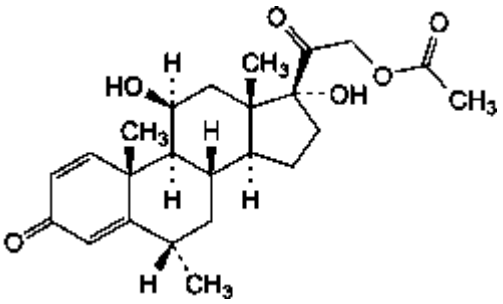
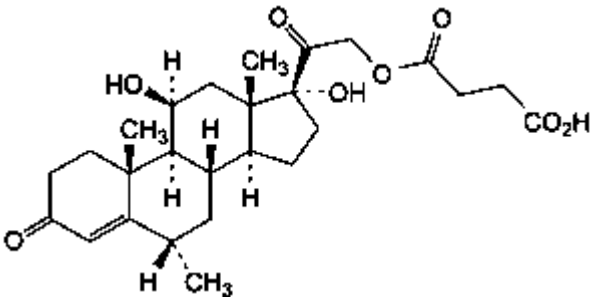
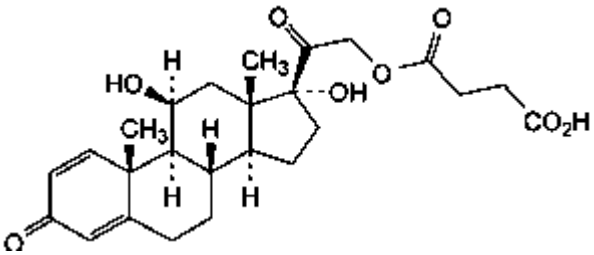


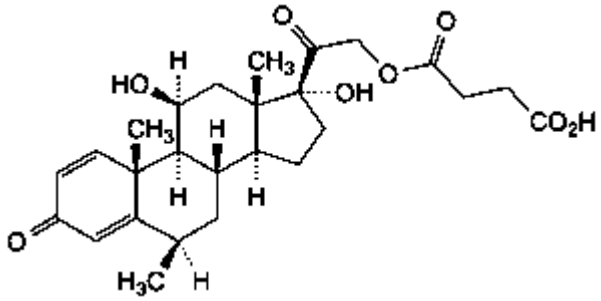
C. 11β,17-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (methylprednisolone acetate),



D. 4-[(11β,17-dihydroxy-6α-methyl-3,20-dioxopregn-4-en-21-yl)oxy]-4-oxobutanoic acid (methylhydrocortisone 21-(hydrogen succinate)),



E. 4-[(11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl)oxy]-4-oxobutanoic acid,



F. 4-[(11β,17-dihydroxy-6β-methyl-3,20-dioxopregna-1,4-dien-21-yl)oxy]-4-oxobutanoic acid,

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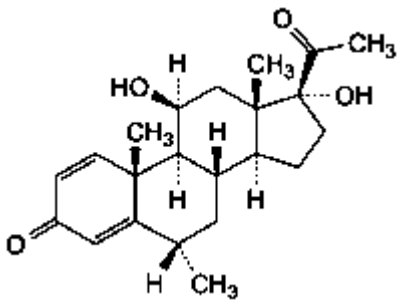

G. 11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

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Methylprednisolone Tablets

General Notices

Action and use

Glucocorticoid.

DEFINITION

Methylprednisolone Tablets contain Methylprednisolone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of methylprednisolone, $C_{22}H_{30}O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 50 mg with 100 mL of *chloroform*, filter and evaporate the filtrate to dryness. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of methylprednisolone *(RS 225)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 10 mg of methylprednisolone in a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane* and dilute to 10 mL with the same solvent; centrifuge and use the supernatant liquid.

(2) Dissolve 20 mg of *methylprednisolone BPCRS* in a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane* and dilute to 20 mL with the same solvent mixture.

(3) Dissolve 10 mg of *hydrocortisone BPCRS* in solution (2) and dilute to 10 mL with solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After the first development carry out the second development, dry in air and examine under *ultraviolet light (254nm)*. Spray with *alcoholic solution of sulfuric acid*, heat at 120 °C for 10 minutes or until the spots appear. Allow to cool. Examine in daylight and under *ultraviolet light (365 nm)*.

MOBILE PHASE

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For the first development Add a mixture of 1.2 volumes of *water* and 8 volumes of *methanol* to a mixture of 15 volumes of *ether* and 77 volumes of *dichloromethane*.

For the second development *Butanol* saturated with a mixture of 5 volumes of *water*, 15 volumes of *toluene* and 80 volumes of *ether*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 256 nm, Appendix II B using *water* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of methylprednisolone, $C_{22}H_{30}O_5$, in the medium taking 400 as the value of *A* (1%, 1 cm) at the maximum at 256 nm.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Methylprednisolone for 15 minutes with 2 mL of a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of Solution (1) to 50 volumes with a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*.

(3) Dilute 1 volume of solution (2) to 4 volumes with a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*.

(4) For solution (4) dissolve 1 mg of *hydrocortisone* in a mixture of 0.1 mL of solution (1) and 0.9 mL of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel F_{254} plates are suitable).

(b) Use the mobile phase as described below.

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(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two principal spots that are close together but separated.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (2%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Weigh and powder 20 tablets. Suspend a quantity of the powder containing 10 mg of Methylprednisolone in 10 mL of *water* and extract with successive quantities of 100, 50, 50 and 40 mL of *chloroform*. Wash each extract with the same 10 mL quantity of *water*, filter and dilute the combined filtrates to 250 mL with *chloroform*. Evaporate 25 mL just to dryness, dissolve the residue in sufficient *aldehyde-free ethanol (96%)* to produce a solution containing between 390 and 410 µg of Methylprednisolone in 10 mL and complete the *tetrazolium assay of steroids*, Appendix VIII J, beginning at the words ‘Transfer 10 mL…’.

Dissolve a quantity of *methylprednisolone BPCRS* in sufficient *aldehyde-free ethanol (96%)* to produce a solution containing between 390 and 410 µg in 10 mL and complete the tetrazolium assay beginning at the words ‘Transfer 10 mL…’. From the *absorbances* so obtained, and using the declared content of $C_{22}H_{30}O_5$ in *methylprednisolone BPCRS,* calculate the content of $C_{22}H_{30}O_5$ in the tablets.

STORAGE

Methylprednisolone Tablets should be stored protected from light.

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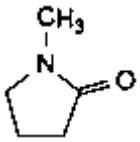
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Methylpyrrolidone

General Notices

(N-Methylpyrrolidone, Ph. Eur. monograph 1675)



C_5H_9NO 99.1 *872-50-4*

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DEFINITION

1-Methylpyrrolidin-2-one.

CHARACTERS

Appearance

Clear, colourless liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

bp

About 204 °C.

Relative density

About 1.034.

Refractive index

About 1.469.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Preparation Films.

Comparison Ph. Eur. reference spectrum of N-methylpyrrolidone.

TESTS

Appearance

The substance to be examined is clear (2.2.1) and colourless (2.2.2, Method II).

Alkalinity

Dissolve 50 mL of the substance to be examined in 50 mL of water R previously adjusted with 0.02 M potassium hydroxide or 0.02 M hydrochloric acid until a yellow colour is obtained using 0.5 mL of bromothymol blue solution R1 as indicator. Titrate with 0.02 M hydrochloric acid to the initial coloration. Not more than 8.0 mL of 0.02 M hydrochloric acid is required.

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution The substance to be examined.

Reference solution To 1 mL of the substance to be examined, add 1 mL of 2-pyrrolidone R and dilute to 20 mL with methylene chloride R.

Column:

— *material*: fused silica,

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: methylpolysiloxane R (5 µm).

Carrier gas nitrogen for chromatography R.

Linear velocity 20 cm/s.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0	100
	0 - 23.3	100 → 170
	23.3 - 53	170
Injection port		280

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Detector	Time (min)	Temperature (°C)
		280

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to *N*-methylpyrrolidone and impurity G.

Limits:

— *any impurity*: maximum 0.1 per cent,

— *total*: maximum 0.3 per cent,

— *disregard limit*: 0.02 per cent.

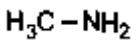
Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.000 g.

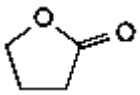
STORAGE

Protected from light.

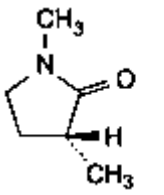
IMPURITIES



A. methanamine (methylamine),



B. dihydrofuran-2(3*H*)-one (γ-butyrolactone),



and enantiomer

C. (3*RS*)-1,3-dimethylpyrrolidin-2-one,

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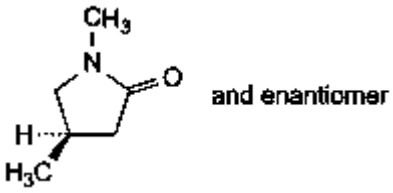
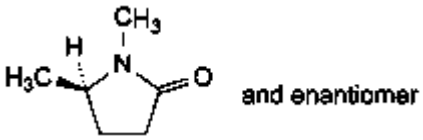


and enantiomer

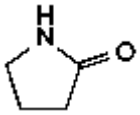
D. (4*RS*)-1,4-dimethylpyrrolidin-2-one,



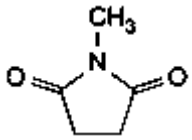
and enantiomer

E. (5*RS*)-1,5-dimethylpyrrolidin-2-one,

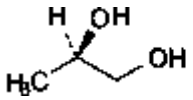
F. butane-1,4-diol,



G. pyrrolidin-2-one (2-pyrrolidone),



H. 1-methylpyrrolidine-2,5-dione (*N*-methylsuccinimide),



and enantiomer

I. (*RS*)-propane-1,2-diol (propylene glycol).

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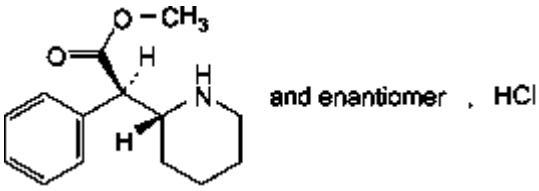
Methylphenidate Hydrochloride

General Notices

(Ph. Eur. monograph 2235)



$C_{14}H_{20}ClNO_2$ 269.8 *298-59-9*

Action and use

Narcolepsy; hyperactivity disorder in children.

Preparations

Methylphenidate Prolonged-release Capsules

Methylphenidate Tablets

Ph Eur

DEFINITION

Methyl (2*RS*)-phenyl[(2*RS*)-piperidin-2-yl]acetate hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, fine, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

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First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *methylphenidate hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in 1.0 mL of *methanol R*.

Reference solution Dissolve 5 mg of *methylphenidate hydrochloride CRS* in 1.0 mL of *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (1:4:95 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 60 °C for 5 min.

Detection Spray with a freshly prepared 5 g/L solution of *fast blue B salt R*; heat to 60 °C for 1 min.

Result The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mix 20 volumes of *acetonitrile R1* and 80 volumes of a solution prepared as follows: dissolve 1.36 g of *sodium octanesulfonate R* in 950 mL of *water for chromatography R*, add 1.0 mL of *triethylamine R2*, adjust to pH 2.7 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *methylphenidate impurity C CRS* in 100.0 mL of the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *methylphenidate impurity mixture CRS* (impurities A and B) in 1.0 mL of reference solution (a).

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Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 2.16 g of *sodium octanesulfonate R* in 950 mL of *water for chromatography R*, add 1.0 mL of *triethylamine R2*, adjust to pH 2.7 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	80	20
15 - 35	80 → 60	20 → 40

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *methylphenidate impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to methylphenidate (retention time = about 20 min): impurity A = about 0.35; impurity C = about 0.40; impurity B = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and C.

Limits:

— *impurities A, B*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

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— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of ethanol (96 per cent) R and add 5.0 mL of 0.01 M hydrochloric acid. Carry out a potentiometric titration (2.2.20) using 0.1 M sodium hydroxide and an electrode for non-aqueous acid-base titrations. Read the volume added between the 2 points of inflexion.

1 mL of 0.1 M sodium hydroxide is equivalent to 26.98 mg of $C_{14}H_{20}ClNO_2$.

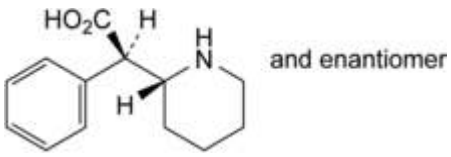
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E, F.



and enantiomer

A. (2*RS*)-phenyl[(2*RS*)-piperidin-2-yl]acetic acid,

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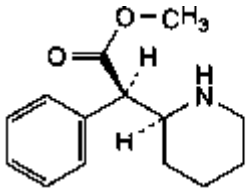
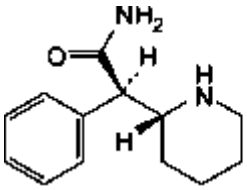


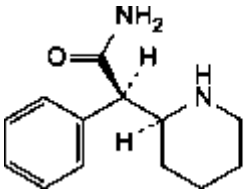
and enantiomer

B. methyl (2*RS*)-phenyl[(2*SR*)-piperidin-2-yl]acetate,



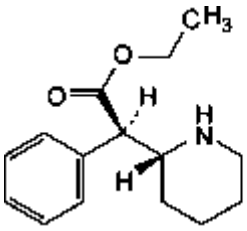
and enantiomer

C. (2*RS*)-2-phenyl-2-[(2*RS*)-piperidin-2-yl]acetamide,



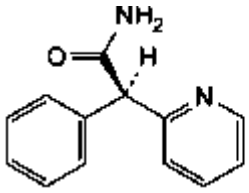
and enantiomer

D. (2*RS*)-2-phenyl-2-[(2*SR*)-piperidin-2-yl]acetamide,



and enantiomer

E. ethyl (2*RS*)-phenyl[(2*RS*)-piperidin-2-yl]acetate,



and enantiomer

F. (2*RS*)-2-phenyl-2-(pyridin-2-yl)acetamide.

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Methylphenidate Prolonged-release Capsules

General Notices

Methylphenidate Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Narcolepsy; attention deficit/hyperactivity disorder (ADHD).

DEFINITION

Methylphenidate Prolonged-release Capsules contain Methylphenidate Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Methylphenidate Hydrochloride. The dissolution profile reflects the in vivo performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

Content of methylphenidate hydrochloride, $C_{14}H_{19}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of mixed capsule contents containing 50 mg of Methylphenidate Hydrochloride with 20 mL of *dichloromethane*, centrifuge and filter. Evaporate the filtrate to about 5 mL and add *ether* slowly until crystals form. Filter, wash the crystals with *ether* and dry at 80° for 30 minutes. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of methylphenidate hydrochloride *(RS 485)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

4 volumes of *methanol* and 11 volumes of a solution of 0.273% w/v of *potassium dihydrogen phosphate*, previously adjusted to pH 4.0 with *glacial acetic acid* (solution A).

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(1) To a quantity of the mixed capsule contents containing 60 mg of Methylphenidate Hydrochloride, add 20 mL of *acetone* and mix with the aid of ultrasound for about 15 minutes. Add 100 mL of solution A and shake vigorously on a mechanically shaker for at least 30 minutes. Dilute to 250 mL with solution A, filter through a 0.45-µm PTFE filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes with solution A.

(3) 0.002% w/v of *methylphenidate impurity mixture EPCRS* and 0.0001% w/v of *methylphenidate impurity C EPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 2.16 g of *sodium octanesulfonate* in 950 mL of *water*, add 1.0 mL of *triethylamine*, adjust to pH 2.7 with *orthophosphoric acid* and dilute to 1000 mL with *water*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	80	20	isocratic
15-35	80→60	20→40	linear gradient
35-36	60→80	40→20	linear gradient
36-45	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methylphenidate (retention time about 20 minutes) are: impurity A, about 0.35; impurity C, about 0.4 and impurity B, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity C is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

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the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

4 volumes of *methanol* and 11 volumes of a solution of 0.273% w/v of*potassium dihydrogen phosphate*, previously adjusted to pH 4.0 with *glacial acetic acid* (solution A).

(1) To a quantity of the mixed capsule contents containing 60 mg of Methylphenidate Hydrochloride, add 20 mL of *acetone* and mix with the aid of ultrasound for about 15 minutes. Add 100 mL of solution A and shake vigorously on a mechanically shaker for at least 30 minutes. Dilute to 250 mL with solution A and filter through a 0.45-µm PTFE filter. Dilute 2 volumes of the filtrate to 5 volumes with the mobile phase.
(2) 0.0096% w/v of *methylphenidate hydrochloride BPCRS* in the mobile phase.
(3) 0.015% w/v each of *methylphenidate hydrochloride BPCRS* and *phenylephrine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

300 volumes of a 0.16% w/v solution of *anhydrous sodium acetate* pH adjusted to 4.0 with *glacial acetic acid*, 300 volumes of *acetonitrile R1* and 400 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of methylphenidate is about 4 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to phenylephrine and methylphenidate is not less than 2.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{14}H_{19}NO_2$,HCl, in the capsules using the declared content of $C_{14}H_{19}NO_2$,HCl in *methylphenidate hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Methylphenidate Hydrochloride*.

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Methylphenidate Tablets

General Notices

Action and use

Narcolepsy; attention deficit/hyperactivity disorder (ADHD).

DEFINITION

Methylphenidate Tablets contain Methylphenidate Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of methylphenidate hydrochloride, $C_{14}H_{19}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Methylphenidate Hydrochloride with 10 mL of *absolute ethanol*, centrifuge and filter (a 0.45-µm PTFE filter is suitable). Evaporate the filtrate to dryness at 80°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of methylphenidate hydrochloride *(RS 485)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, and rotate the basket at 100 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, expected to contain 0.00056% w/v of Methylphenidate Hydrochloride.

(2) 0.00056% w/v of *methylphenidate hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

300 volumes of a 0.16% w/v solution of *anhydrous sodium acetate* pH adjusted to 4.0 with *acetic acid*, 300 volumes of *acetonitrile R1* and 400 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the total content of methylphenidate hydrochloride, $C_{14}H_{19}NO_2$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{14}H_{19}NO_2$,HCl in *methylphenidate hydrochloride BPCRS*.

LIMITS

The amount of methylphenidate hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A 20 volumes of *acetonitrile R1* and 80 volumes of a solution prepared as follows: dissolve 1.36 g of *sodium octanesulfonate* in 950 mL of *water*, add 1.0 mL of *triethylamine*, adjust to pH 2.7 with *orthophosphoric acid* and dilute to 1000 mL with *water*.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 25 mg of Methylphenidate Hydrochloride in 40 mL of solution A, dilute to 50 mL with the same solvent, and filter through a 0.45-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with solution A.

(3) 0.0001% w/v of *methylphenidate impurity C EPCRS* and 0.002% w/v of *methylphenidate impurity mixture EPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 2.16 g of *sodium octanesulfonate* in 950 mL of *water*, add 1.0 mL of *triethylamine*, adjust to pH 2.7 with *orthophosphoric acid* and dilute to 1000 mL with *water*.

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Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	80	20	isocratic
15-35	80→60	20→40	linear gradient
35-36	60→80	40→20	linear gradient
36-40	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methylphenidate (retention time about 20 minutes) are: impurity A, about 0.35; impurity C, about 0.4 and impurity B, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity C is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks*, excluding impurity A, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 20 mg of Methylphenidate Hydrochloride in 75 mL, dilute to 100 mL and filter through a 0.45-µm filter.

(2) 0.02% w/v of *methylphenidate hydrochloride BPCRS*.

(3) 0.015% w/v each of *methylphenidate hydrochloride BPCRS* and *phenylephrine hydrochloride BPCRS*.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to phenylephrine and methylphenidate is not less than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{19}NO_2$,HCl, in the tablets using the declared content of $C_{14}H_{19}NO_2$,HCl in *methylphenidate hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Methylphenidate Hydrochloride.

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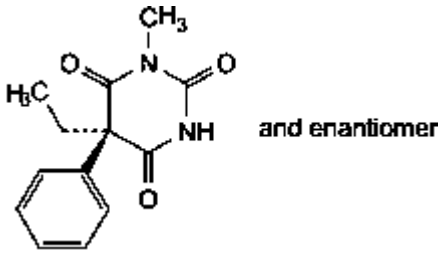
Methylphenobarbital

General Notices

(Ph. Eur. monograph 0189)



and enantiomer

$C_{13}H_{14}N_2O_3$ 246.3 *115-38-8*

Action and use

Barbiturate.

Ph Eur

DEFINITION

(5*RS*)-5-Ethyl-1-methyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, very slightly soluble in ethanol (96 per cent).

It forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

IDENTIFICATION

First identification: A, B.

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Second identification: A, C, D.

A. Determine the melting point (2.2.14) of the substance to be examined. Mix equal parts of the substance to be examined and *methylphenobarbital CRS* and determine the melting point of the mixture. The difference between the melting points (which are about 178 °C) is not greater than 2 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *methylphenobarbital CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *methylphenobarbital CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *concentrated ammonia R*, *ethanol (96 per cent) R*, *methylene chloride R* (5:15:80 *V/V/V*); use the lower layer.

Application 10 µL.

Development Over 2/3 of the plate.

Detection Examine immediately in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. To about 10 mg add 0.2 mL of *sulfuric acid R* and 0.1 mL of *nitric acid R*. Heat on a water-bath for 10 min. Cool in iced water and add 5 mL of *water R* and 5 mL of *strong sodium hydroxide solution R*. Add 5 mL of *acetone R*, shake and allow to stand. A dark-red colour develops in the upper layer.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 1.0 g, with gentle heating, in a mixture of 4 mL of *dilute sodium hydroxide solution R* and 6 mL of *water R*.

Acidity

Boil 1.0 g with 50 mL of *water R* for 2 min, allow to cool and filter. To 10 mL of the filtrate add 0.15 mL of *methyl red solution R*. The solution is orange-yellow. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to produce a pure yellow colour.

Related substances

Liquid chromatography (2.2.29).

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Test solution Dissolve 50 mg of the substance to be examined in 10.0 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *phenobarbital CRS* (impurity A) in 1.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 6.60 g of *sodium acetate R* in 900 mL of *water R*, add 3 mL of *glacial acetic acid R*, adjust to pH 4.5 with *glacial acetic acid R* and dilute to 1000 mL with *water R*. Mix 40 volumes of this solution with 60 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 3.5 times the retention time of methylphenobarbital.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to methylphenobarbital (retention time = about 7 min): impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and methylphenobarbital.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 1.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

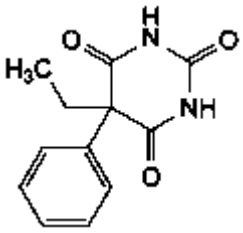
ASSAY

Dissolve 0.100 g in 70 mL of *ethanol (96 per cent) R* and add 20 mL of *water R*. Stir with a mechanical stirrer for about 30 min and sonicate to achieve complete dissolution. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 24.63 mg of $C_{13}H_{14}N_2O_3$.

IMPURITIES

Specified impurities *A.*



A. 5-ethyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (phenobarbital).

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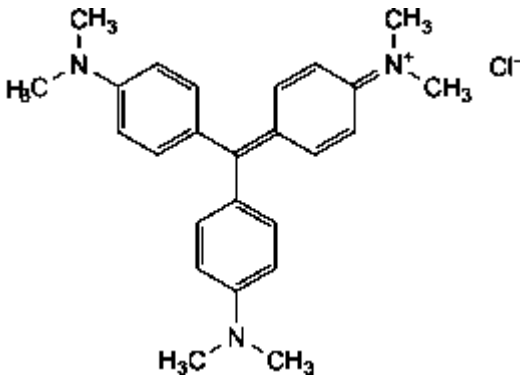
Methylrosanilinium Chloride

General Notices

(Ph. Eur. monograph 1990)



$C_{25}H_{30}ClN_3$ 408.0 *548-62-9*

Action and use

Antiseptic dye (gentian violet).

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DEFINITION

4-[Bis[4-(dimethylamino)phenyl]methylidene]-*N*,*N*-dimethylcyclohexa-2,5-dien-1-iminium chloride (hexamethyl-*p*-rosanilinium chloride). It is also known as crystal violet or gentian violet.

Content

95.0 per cent to 103.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Dark green, shiny powder, hygroscopic.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

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First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *methylrosanilinium chloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *methylrosanilinium chloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (17:17:66 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution. In the chromatogram obtained with the test solution, a secondary spot may be observed.

C. Dissolve 50 mg in *water R* and dilute to 5 mL with the same solvent; add 3 mL of *dilute sulfuric acid R*, 1 g of *zinc powder R* and heat gently. The mixture decolourises. Filter. To 3 mL of the filtrate add 0.5 mL of *silver nitrate solution R1*. A white turbidity is produced which slowly forms a dark, coagulating precipitate.

TESTS

N,*N*-Dimethylaniline (*2.4.26, Method A*)

Maximum 100 ppm.

Test solution Dissolve in a ground-glass-stoppered tube 0.50 g of the substance to be examined in 30.0 mL of *water R*. Add 1.0 mL of the internal standard solution. Adjust the solution to 26-28 °C. Add 1.0 mL of *strong sodium hydroxide solution R* and mix for 2 min. Add 2.0 mL of *trimethylpentane R*. Shake for 2 min and centrifuge. Use the upper layer.

Reference solution Dissolve 50.0 mg of *N,N-dimethylaniline R* in 4.0 mL of *0.1 M hydrochloric acid* and dilute to 50.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*. To 0.50 g of the substance to be examined add 5.0 mL of this solution and dilute to 30.0 mL with *water R*. Add 1.0 mL of the internal standard solution and 1.0 mL of *strong sodium hydroxide solution R*. Add 2.0 mL of *trimethylpentane R*. Shake for 2 min and centrifuge. Use the upper layer.

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Limit:

— calculate the ratio (*R*) of the area of the peak due to *N*,*N*-dimethylaniline to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the area of the peak due to *N*,*N*-dimethylaniline to the area of the peak due to the internal standard: this ratio is not greater than 0.5 *R*.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 30.0 mg of the substance to be examined in ethanol (96 per cent) R and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 3 mg of methylrosanilinium for system suitability CRS (containing impurities A and B) in ethanol (96 per cent) R and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with ethanol (96 per cent) R. Dilute 1.0 mL of this solution to 100.0 mL with ethanol (96 per cent) R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: spherical base-deactivated end-capped octylsilyl silica gel for chromatography R (5 µm).

Mobile phase glacial acetic acid R, water for chromatography R, methanol R (10:190:800 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 589 nm.

Injection 20 µL.

Run time 2.5 times the retention time of methylrosanilinium.

Identification of impurities Use the chromatogram supplied with methylrosanilinium for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B.

Relative retention With reference to methylrosanilinium (retention time = about 23 min): impurity A = about 0.71; impurity B = about 0.85.

System suitability Reference solution (a):

— resolution: minimum 1.5 between the peaks due to impurity B and methylrosanilinium.

Limits:

— *impurity B*: maximum 10.0 per cent;

— *impurity A*: maximum 1.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

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— *sum of impurities other than A and B*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent (peak due to methylrosanilinium in the chromatogram obtained with reference solution (b)).

Substances insoluble in ethanol (90 per cent *V/V*)

Maximum 0.5 per cent.

In a conical flask introduce 1.0 g and add 50 mL of *ethanol (90 per cent V/V) R*. Boil under a reflux condenser for 1 h. Filter the warm liquid through a weighed sintered glass filter (16) (*2.1.2*) previously dried at 100-105 °C. Wash with hot *ethanol (90 per cent V/V) R* until a colourless filtrate is obtained. Dry at 100-105 °C until constant weight.

Water (*2.5.12*)

Maximum 10.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 1.5 per cent, determined on 1.0 g.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 250.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the maximum at 589 nm.

Calculate the content of $C_{25}H_{30}ClN_3$ taking the specific absorbance to be 2605.

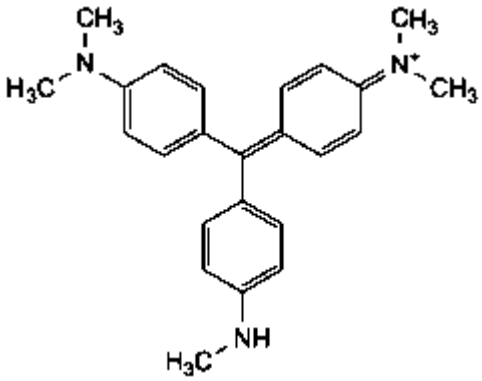
STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A, B.*

A. unknown structure,



B. 4-[[4-(dimethylamino)phenyl][4-(methylamino)phenyl]methylidene]-*N,N*-dimethylcyclohexa-2,5-dien-1-iminium.

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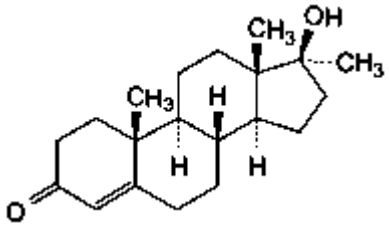
Methyltestosterone

General Notices

(Ph. Eur. monograph 0410)



$C_{20}H_{30}O_2$ 302.5 *58-18-4*

Action and use

Anabolic steroid.

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DEFINITION

17β-Hydroxy-17-methylandrost-4-en-3-one.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish-white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *methyltestosterone CRS*.

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TESTS

Specific optical rotation (2.2.7)

+ 79 to + 85 (dried substance).

Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 0.5 mL of the test solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *methyltestosterone for system suitability CRS* (containing impurity A) in *methanol R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	30	70
15 - 45	30 → 0	70 → 100
45 - 50	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *methyltestosterone for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

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Relative retention With reference to methyltestosterone (retention time = about 8 min): impurity A = about 1.5.

System suitability Reference solution (b):

— *resolution*: minimum 5 between the peaks due to methyltestosterone and impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 2.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 2 h.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*. Dilute 10.0 mL of this solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (2.2.25) at the absorption maximum at 241 nm.

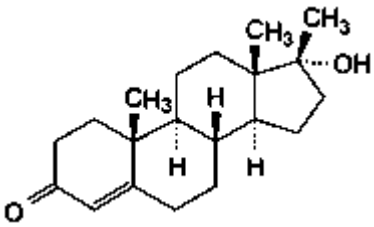
Calculate the content of $C_{20}H_{30}O_2$ taking the specific absorbance to be 540.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A*.



A. 17α-hydroxy-17-methylandrost-4-en-3-one.

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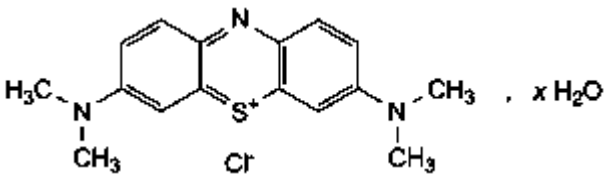
Methylthioninium Chloride Hydrate

General Notices

Methylthioninium Chloride

(Ph. Eur. monograph 1132)



$C_{16}H_{18}ClN_3S,xH_2O$ 319.9 (anhydrous substance) *122965-43-9*

Action and use

Reducing agent; antidote to methaemoglobinaemia.

Preparation

Methylthioninium Injection

Ph Eur

DEFINITION

3,7-Bis(dimethylamino)phenothiazin-5-ylium chloride (methylene blue) hydrate.

Content

93.0 per cent to 102.0 per cent (dried substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

Dark blue or dark green, hygroscopic, crystalline powder with a metallic sheen.

Solubility

Slightly soluble in water and in ethanol (96 per cent).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison methylthioninium chloride CRS.

B. Ignite 50 mg with 0.5 g of anhydrous sodium carbonate R. Cool and dissolve the residue in 10 mL of dilute nitric acid R. Filter. The filtrate, without further addition of dilute nitric acid R, gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, mobile phase A (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Sonicate for 5 min.

Reference solution (a) Dissolve 50.0 mg of methylthioninium chloride CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Sonicate for 5 min.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 10 mg of methylthioninium for system suitability CRS (containing impurity A) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R (3.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of trifluoroacetic acid R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
5 - 25	80 → 30	20 → 70
25 - 32	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 246 nm.

Injection 5 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *methylthioninium for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to methylthioninium (retention time = about 11 min): impurity A = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 3.5 between the peaks due to impurity A and methylthioninium.

Calculation of percentage contents:

— for impurity A, use the concentration of methylthioninium chloride hydrate in reference solution (b);

— for impurities other than A, use the concentration of methylthioninium chloride hydrate in reference solution (d).

Limits:

— *impurity A*: maximum 5.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than A*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Aluminium	100
Cadmium	1
Chromium	100

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Element	Maximum content (ppm)
Copper	300
Iron	200
Lead	10
Manganese	10
Mercury	1
Molybdenum	10
Nickel	10
Tin	10
Zinc	100

Loss on drying (*2.2.32*)

8.0 per cent to 24.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.25 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 3.0 for the principal peak.

Calculate the percentage content of $C_{16}H_{18}ClN_3S$ taking into account the assigned content of *methylthioninium chloride CRS*.

STORAGE

In an airtight container, protected from light, at a temperature not exceeding 30 °C.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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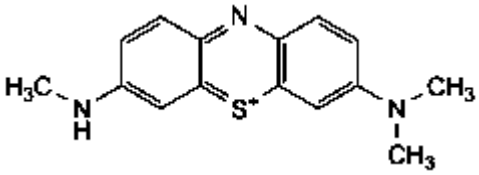
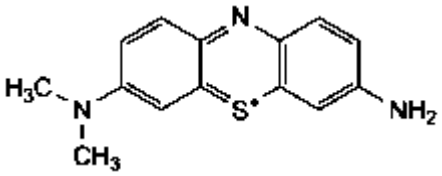
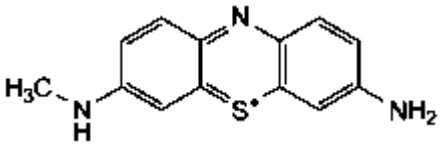
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. 3-(dimethylamino)-7-(methylamino)phenothiazin-5-ylium (azure B),



B. 3-amino-7-(dimethylamino)phenothiazin-5-ylium (azure A),



C. 3-amino-7-(methylamino)phenothiazin-5-ylium (azure C).

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Methylthioninium Injection

General Notices

Action and use

Reducing agent; antidote to methaemoglobinaemia.

DEFINITION

Methylthioninium Injection is a sterile solution of Methylthioninium Chloride Hydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of methylthioninium chloride hydrate, $C_{16}H_{18}ClN_3S,3H_2O$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A blue solution.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 240 to 800 nm of a solution diluted, if necessary, with *dilute hydrochloric acid* to contain 0.0005% w/v of Methylthioninium Chloride Hydrate exhibits maxima at 255 to 260 nm, 285 to 290 nm, 670 to 680 nm and 740 to 750 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) The injection diluted, if necessary, with *methanol* to produce a solution containing 0.01% w/v of Methylthioninium Chloride Hydrate.

(2) 0.01% w/v of *methylthioninium chloride EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air protected from light and examine in daylight.

MOBILE PHASE

20 volumes of anhydrous *formic acid* and 80 volumes of *propan-1-ol*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2). A *secondary spot* may appear above the principal spot in both chromatograms.

TESTS

Acidity

pH, 3.0 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in 30 volumes of *acetonitrile* and 70 volumes of mobile phase A (solution A).

(1) Dilute the injection to produce a solution expected to contain 0.1% w/v of Methylthioninium Chloride Hydrate.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.1% w/v *methylthioninium for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (10 cm × 4.6 mm) packed with *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material)* (3.5 µm) (Waters Xbridge Phenyl is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 246 nm.
(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1% v/v of *trifluoroacetic acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	80	20	isocratic
5-25	80→30	20→70	linear gradient
25-32	30	70	isocratic
32-34	30→80	70→20	linear gradient
34-37	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to methylthioninium (retention time, about 11 minutes) is: impurity A, about 0.8.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and methylthioninium is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks*, excluding impurity A, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing 1% w/v of Methylthioninium Chloride Hydrate (solution A). The endotoxin limit concentration of solution A is 2.5 IU of endotoxin per mL.

ASSAY

To a weighed quantity of the injection containing 0.3 g of Methylthioninium Chloride Hydrate add 50 mL of *potassium dichromate solution R1*, dilute to 100 mL with *water* and allow to stand for 10 minutes. Filter and discard the first 20 mL of the filtrate. To 50 mL of the filtrate add 50 mL of 1M *sulfuric acid* and 8 mL of *potassium iodide solution*. Allow to stand protected from light for 5 minutes. Add 80 mL of *water* and titrate with 0.1M *sodium thiosulfate VS* using 2 mL of starch solution as indicator. Repeat the procedure without the preparation being examined. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 12.45 mg of $C_{16}H_{18}ClN_3S,3H_2O$. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage of $C_{16}H_{18}ClN_3S,3H_2O$, weight in volume.

STORAGE

Methylthioninium Injection should be protected from light. It should not be refrigerated or frozen.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Methylthioninium Chloride Hydrate.

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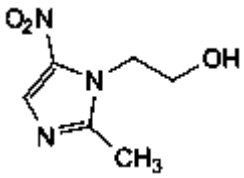
Metronidazole

General Notices

(Ph. Eur. monograph 0675)



$C_6H_9N_3O_3$ 171.2 *443-48-1*

Action and use

Imidazole antibacterial.

Preparations

Metronidazole Gel

Metronidazole Infusion

Metronidazole Suppositories

Metronidazole Tablets

Ph Eur

DEFINITION

2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)ethanol.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

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Solubility

Slightly soluble in water, in acetone, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 159 °C to 163 °C.

B. Dissolve 40.0 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 5.0 mL of the solution to 100.0 mL with *0.1 M hydrochloric acid*. Examined between 230 nm and 350 nm (2.2.25), the solution shows an absorption maximum at 277 nm and a minimum at 240 nm. The specific absorbance at the maximum is 365 to 395.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *metronidazole CRS*.

D. To about 10 mg add about 10 mg of *zinc powder R*, 1 mL of *water R* and 0.25 mL of *dilute hydrochloric acid R*. Heat on a water-bath for 5 min. Cool. The solution gives the reaction of primary aromatic amines (2.3.1).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, *Method II*).

Dissolve 1.0 g in *1 M hydrochloric acid* and dilute to 20 mL with the same acid.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from light*.

Test solution Dissolve 0.05 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase and dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *metronidazole impurity A CRS* in the mobile phase, add 10.0 mL of the test solution and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 30 volumes of *methanol R* and 70 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R*,

Flow rate 1 mL/min.

Detection Spectrophotometer at 315 nm.

Injection 10 µL.

Run time 3 times the retention time of metronidazole.

Relative retention With reference to metronidazole (retention time = about 7 min): impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum of 2.0 between the peaks due to metronidazole and to impurity A.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 17.12 mg of $C_6H_9N_3O_3$.

STORAGE

Protected from light.

IMPURITIES

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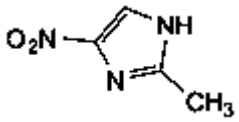
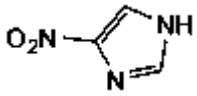
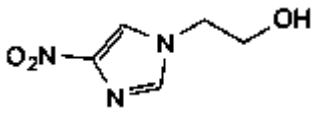


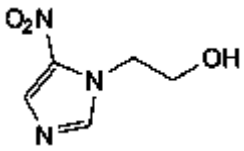
A. 2-methyl-4-nitroimidazole,



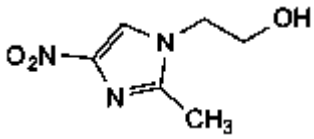
B. 4-nitroimidazole,



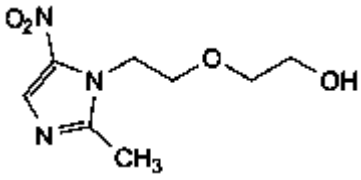
C. 2-(4-nitro-1*H*-imidazol-1-yl)ethanol,



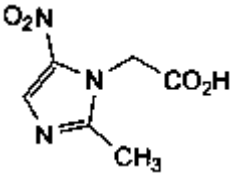
D. 2-(5-nitro-1*H*-imidazol-1-yl)ethanol,



E. 2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)ethanol,



F. 2-[2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethoxy]ethanol,



G. 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetic acid.

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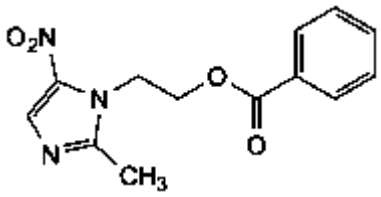
Metronidazole Benzoate

General Notices

(Ph. Eur. monograph 0934)



$C_{13}H_{13}N_3O_4$ 275.3 *13182-89-3*

Action and use

Imidazole antibacterial.

Preparation

Metronidazole Oral Suspension

Ph Eur

DEFINITION

2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)ethyl benzoate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder or flakes.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

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IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 99 °C to 102 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.100 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 1.0 mL of the solution to 100.0 mL with a 103 g/L solution of *hydrochloric acid R*.

Spectral range 220-350 nm.

Absorption maxima At 232 nm and 275 nm.

Specific absorbance at the absorption maximum at 232 nm 525 to 575.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of metronidazole benzoate*.

D. To about 10 mg add about 10 mg of *zinc powder R*, 1 mL of *water R* and 0.3 mL of *hydrochloric acid R*. Heat on a water-bath for 5 min and cool. The solution gives the reaction of primary aromatic amines (2.3.1).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution GY_3 (2.2.2, *Method II*).

Dissolve 1.0 g in *dimethylformamide R* and dilute to 10 mL with the same solvent.

Acidity

Dissolve 2.0 g in a mixture of 20 mL of *dimethylformamide R* and 20 mL of *water R*, previously neutralised with *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* using 0.2 mL of *methyl red solution R*. Not more than 0.25 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase B, mobile phase A (45:55 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of *metronidazole CRS* (impurity A), 5.0 mg of *metronidazole impurity A CRS* (impurity B) and 5.0 mg of *benzoic acid CRS* (impurity C) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *di-isobutyloctadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 180 m^2/g, a pore size of 8 nm and a carbon loading of 10 per cent.

Mobile phase:

— *mobile phase A*: 1.5 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.2 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 15	80 → 55	20 → 45
15 - 40	55	45

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL.

Relative retention With reference to metronidazole benzoate (retention time = about 20 min): impurity B = about 0.17; impurity A = about 0.20; impurity C = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

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— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 80 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

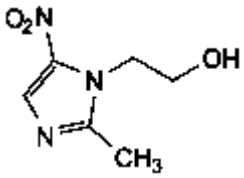
1 mL of *0.1 M perchloric acid* is equivalent to 27.53 mg of $C_{13}H_{13}N_3O_4$.

STORAGE

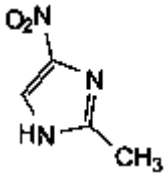
Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol (metronidazole),



B. 2-methyl-4-nitroimidazole,

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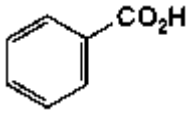

C. benzenecarboxylic acid (benzoic acid).

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Metronidazole Gel

General Notices

Action and use

Imidazole antibacterial.

DEFINITION

Metronidazole Gel contains Metronidazole in a suitable water-soluble basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of metronidazole, $C_6H_9N_3O_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.5 to 6.0, Appendix V L.

Nitrite

Disperse 1.0 g of the gel in sufficient *water* to produce 100 mL. To 40 mL of the solution add 2 mL of *sulfanilic acid solution*, 2 mL of *aminonaphthalenesulfonic acid solution* and sufficient *water* to produce 50 mL. Allow to stand at room temperature for 1 hour. Measure the *absorbance* of the resulting solution at the maximum at 524 nm, Appendix II B, using in the reference cell a solution prepared by treating 40 mL of *water* in the same manner, beginning at the words ‘add 2 mL of *sulfanilic acid* *solution*…’.

The *absorbance* is not greater than that obtained by repeating the procedure using 1 mL of *nitrite standard solution (20 ppm)* diluted to 40 mL with *water* and treated at the same time and in the same manner, beginning at the words ‘add 2 mL of *sulfanilic acid* *solution*…’ (50 ppm, calculated with reference to the gel).

2-Methyl-5-nitroimidazole

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

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(1) Shake for 1 hour a quantity of the gel containing 45 mg of Metronidazole with 150 mL of *methanol*, filter, evaporate the filtrate to dryness and dissolve the residue in 10 mL of a mixture of equal volumes of *dichloromethane* and *methanol*.

(2) 0.0023% w/v of *2-methyl-5-nitroimidazole BPCRS* in a mixture of equal volumes of *dichloromethane* and *methanol*

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*. (Merck silica gel 60 F_{254} plates are suitable)

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*. Spray with *titanium(III) chloride solution* and heat at 110° until the blue-grey colour disappears, cool and spray with a 1% w/v solution of *fast blue B salt* followed by a mixture of 2 volumes of 18 M *ammonia*, 3 volumes of *water* and 5 volumes of *ethanol (96%)*.

MOBILE PHASE

1 volume of *water*, 10 volumes of *ethanol (96%)*, 10 volumes of *diethylamine* and 80 volumes of *dichloromethane*.

LIMITS

Any *secondary spot* corresponding to 2-methyl-5-nitroimidazole in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the gel in *methanol (8%)* to produce a solution containing 0.030% w/v of Metronidazole.

(2) 0.375% w/v of *metronidazole BPCRS* in *methanol (8%)*. Dilute 2 volumes of this solution to 25 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2) is suitable

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 ml per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

3 volumes of *methanol* and 97 volumes of 0.005M *potassium dihydrogen orthophosphate*, the pH of the mixture being adjusted to 4.0 with *orthophosphoric acid*

DETERMINATION OF CONTENT

Calculate the content of $C_6H_9N_3O_3$ in the gel using the declared content of $C_6H_9N_3O_3$ in *metronidazole BPCRS*.

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Metronidazole Infusion

General Notices

Metronidazole Intravenous Infusion

Action and use

Imidazole antibacterial.

DEFINITION

Metronidazole Infusion is a sterile solution containing Metronidazole. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of metronidazole, $C_6H_9N_3O_3$

95.0 to 110.0% of the stated amount.

CHARACTERISTICS

An almost colourless to pale yellow solution.

IDENTIFICATION

Shake a volume of the infusion containing 0.1 g of Metronidazole with 9 g of *sodium chloride* for 5 minutes, add 20 mL of *acetone*, shake for a further 5 minutes and allow to separate. Evaporate the upper layer to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of metronidazole *(RS 229)*.

TESTS

Acidity

pH, 4.5 to 6.0, Appendix V L.

Related substances

Carry out the test described under Metronidazole Tablets but preparing solution (2) in the following manner. Dilute a suitable volume of the infusion with sufficient mobile phase to produce a solution containing 0.1% w/v of Metronidazole.

In the chromatogram obtained with solution (2) the area of any *secondary peak* is not greater than the area of the peak due to 2-methyl-5-nitroimidazole in the chromatogram obtained with solution (1) (0.5%).

Nitrite

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Nitrite

To a volume of the infusion containing 2.5 mg of Metronidazole add 40 mL of *water*, 2 mL of *sulfanilic acid solution*, 2 mL of *aminonaphthalenesulfonic acid solution* and sufficient *water* to produce 50 mL. Allow to stand at room temperature for 1 hour. Measure the *absorbance* of the resulting solution at the maximum at 524 nm, Appendix II B, using in the reference cell a solution prepared by treating 1 mL of *water* in the same manner, beginning at the words 'add 40 mL…'. The *absorbance* is not greater than that obtained by repeating the procedure using 1 mL of *nitrite standard solution (20 ppm)* treated at the same time and in the same manner, beginning at the words 'add 40 mL of *water*…' (0.8%, calculated with reference to the content of metronidazole).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the infusion, if necessary, with *water BET* to give a solution containing 5 mg per mL (solution A). The endotoxin limit concentration of solution A is 3.5 IU per mL.

ASSAY

Dilute a volume of the infusion containing 50 mg of Metronidazole to 100 mL with 0.1M *hydrochloric acid*. Dilute 10 mL of the resulting solution to 250 mL with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at 277 nm, Appendix II B. Calculate the content of $C_6H_9N_3O_3$ taking 375 as the value of A(1%, 1 cm) at the maximum at 277 nm.

STORAGE

Metronidazole Infusion should be protected from light.

LABELLING

The label states that solutions containing visible solid particles must not be used.

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Metronidazole Oral Suspension

General Notices

Action and use

Imidazole antibacterial.

DEFINITION

Metronidazole Oral Suspension is a suspension of Metronidazole Benzoate in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of metronidazole, $C_6H_9N_3O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a volume of the oral suspension containing the equivalent of 200 mg of metronidazole with 20 mL of *water*, filter under partial vacuum and wash the residue with three 10-mL quantities of *water* (Whatman GF/C filter paper is suitable). Dissolve the residue as completely as possible in 10 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue after drying at 60°, Appendix II A, is concordant with the *reference spectrum* of metronidazole benzoate (*RS 408*). Examine as discs prepared using potassium bromide.

TESTS

Acidity

pH, 5.0 to 6.5, Appendix V L.

Metronidazole

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) mix a quantity of the oral suspension containing the equivalent of 200 mg of metronidazole with 150 mL of *methanol*, add sufficient *water*, with mixing and cooling, to produce 250 mL, mix and centrifuge. For solution (2) dissolve 20 mg of *metronidazole BPCRS* in 150 mL of *methanol* and add sufficient *water*, with mixing and cooling, to produce 250 mL. Dilute 1 volume to 10 volumes with *methanol (60%)*.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5µm) (Spherisorb ODS 1 is suitable), (b) as the mobile phase with a flow rate of 1.0 mL per minute a mixture of 40 volumes of a 1.25% w/v solution of *ammonium acetate*, adjusted to pH 7.0 with *dilute acetic acid* or *dilute ammonia R1*, as appropriate, and 60 volumes of *methanol* and (c) a detection wavelength of 310 nm.

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In the chromatogram obtained with solution (1) the area of any peak corresponding to metronidazole is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) mix a quantity of the oral suspension containing the equivalent of 200 mg of metronidazole with 150 mL of *methanol*, add sufficient *water*, with mixing and cooling, to produce 250 mL, mix and centrifuge. Dilute 1 volume to 10 volumes with *methanol (60%)*. For solution (2) dissolve 62.5 mg of *metronidazole benzoate BPCRS* in 1 mL of *dimethylformamide* and 30 mL of *methanol* and add sufficient *water*, with mixing and cooling, to produce 50 mL. Dilute 1 volume to 10 volumes with *methanol (60%)*.

The chromatographic procedure described under the test for Metronidazole may be used.

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_6H_9N_3O_3$, weight in volume, using the declared content of $C_6H_9N_3O_3$ in *metronidazole benzoate BPCRS*.

STORAGE

Metronidazole Oral Suspension should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of metronidazole.

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Metronidazole Suppositories

General Notices

Action and use

Imidazole antibacterial.

DEFINITION

Metronidazole Suppositories contain Metronidazole in a suitable suppository basis.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of metronidazole, $C_6H_9N_3O_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Dissolve a quantity of the suppositories containing 0.5 g of Metronidazole as completely as possible by heating with 30 mL of *petroleum spirit (boiling range, 40° to 60°)* on a water bath. Filter, wash the residue with the same solvent and dry at 100°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Metronidazole. *(RS 229)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Melt a quantity of the suppositories containing 0.25 g of Metronidazole using gentle heat, allow to cool and dissolve as completely as possible in 20 mL of *petroleum spirit (boiling range, 40° to 60°)* by warming on a water bath. Filter, wash the residue with *petroleum spirit (boiling range, 40° to 60°)*, dry in a current of air and dissolve in 250 mL of the mobile phase.

(2) 0.00050% w/v of *2-methyl-5-nitroimidazole BPCRS* in the mobile phase.

(3) 0.00050% w/v of *2-methyl-5-nitroimidazole BPCRS* in solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 315 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *methanol* and 70 volumes of 0.01M *potassium dihydrogen orthophosphate*.

In the chromatogram obtained with solution (3) adjust the sensitivity so that the height of the peak due to 2-methyl-5-nitroimidazole is about 50% of full-scale deflection.

SYSTEM SUITABILITY

Measure the height *(a)* of the peak due to 2-methyl-5-nitroimidazole and the height (*b*) of the lowest part of the curve separating this peak from the principal peak. The test is not valid unless *a* is greater than 10*b*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the peak due to 2-methyl-5-nitroimidazole in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh five suppositories, melt together by warming and allow to cool, stirring continuously until the mass is set. To a quantity containing 0.5 g of Metronidazole add 60 mL of *anhydrous acetic acid*, previously neutralised to *1-naphtholbenzein solution* with *0.1M perchloric acid VS*, warm gently until melted, continue to heat for 30 minutes and shake for 5 minutes. Cool and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 17.12 mg of $C_6H_9N_3O_3$.

STORAGE

Metronidazole Suppositories should be protected from light.

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Metronidazole Tablets

General Notices

Action and use

Imidazole antibacterial.

DEFINITION

Metronidazole Tablets contain Metronidazole.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of metronidazole, $C_6H_9N_3O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Metronidazole with 40 mL of *chloroform* for 15 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of metronidazole *(RS 229)*.

B. Shake a quantity of the powdered tablets containing 0.2 g of Metronidazole with 4 mL of 0.5M *sulfuric acid* and filter. To the filtrate add 10 mL of *picric acid solution R1* and allow to stand. The *melting point* of the precipitate, after washing with *water* and drying at 105°, is about 150°, Appendix V A.

C. Heat a quantity of the powdered tablets containing 10 mg of Metronidazole on a water bath with 10 mg of *zinc powder*, 1 mL of *water* and 0.25 mL of *hydrochloric acid* for 5 minutes, cool in ice, add 0.5 mL of *sodium nitrite solution* and remove the excess of nitrite with *sulfamic acid*. Add 0.5 mL of *2-naphthol solution* and 2 mL of 5M *sodium hydroxide*. An orange-red colour is produced.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.00050% w/v of *2-methyl-5-nitroimidazole BPCRS* in the mobile phase. For solution (2) shake a quantity of the powdered tablets containing 0.2 g of Metronidazole with 100 mL of the mobile phase for 5 minutes, dilute to 200 mL with the mobile phase, filter and use the filtrate. Solution (3) contains 0.00050% w/v of *2-methyl-5-nitroimidazole BPCRS* in solution (2).

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) a mixture of 30 volumes of *methanol* and 70 volumes of 0.01M

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potassium dihydrogen orthophosphate as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 315 nm. Record the chromatograms for 3 times the retention time of the principal peak in the chromatogram obtained with solution (2).

Adjust the sensitivity so that the height of the peak due to 2-methyl-5-nitroimidazole in the chromatogram obtained with solution (3) is about 50% of full-scale deflection. Measure the height (*a*) of the peak due to 2-methyl-5-nitroimidazole and the height (*b*) of the lowest part of the curve separating this peak from the principal peak. The test is not valid unless *a* is greater than 10*b*.

The area of any *secondary peak* in the chromatogram obtained with solution (2) is not greater than the area of the peak due to 2-methyl-5-nitroimidazole in the chromatogram obtained with solution (1).

ASSAY

Weigh and powder 20 tablets. Transfer a quantity of the powder containing 0.2 g of Metronidazole to a sintered-glass crucible and extract with six 10 mL quantities of hot *acetone*. Cool, add to the combined extracts 50 mL of *acetic anhydride* and 0.1 mL of a 1% w/v solution of *brilliant green* in *anhydrous acetic acid* and titrate with *0.1M perchloric acid VS* to a yellowish-green end point. Repeat the operation without the powdered tablets. The difference between the titrations represents the amount of perchloric acid required. Each mL of *0.1M perchloric acid VS* is equivalent to 17.12 mg of $C_6H_9N_3O_3$.

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Mexiletine Capsules

General Notices

Action and use

Class I antiarrhythmic; treatment of myotonia.

DEFINITION

Mexiletine Capsules contain Mexiletine Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of mexiletine hydrochloride, $C_{11}H_{17}NO,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing the 50 mg of Mexiletine Hydrochloride with 10 mL of *methanol* for 15 minutes, filter (Whatman GF/C filter paper is suitable), evaporate to dryness on a rotary evaporator and dry the residue at 105° for 2 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of mexiletine hydrochloride *(RS 233)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 30 minutes withdraw a sample of the medium and filter. Dilute the filtrate with 0.01M *hydrochloric acid*, if necessary, to give a solution expected to contain 0.02% w/v of Mexiletine Hydrochloride. Measure the *absorbance* of this solution, Appendix II B, at the maximum at 260 nm, using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of mexiletine hydrochloride, $C_{11}H_{17}NO,HCl$, in the medium taking 11.6 as the value of A(1%, 1 cm) at the maximum at 260 nm.

LIMITS

The amount of mexiletine hydrochloride released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound, a quantity of the contents of the capsules containing 0.2 g of Mexiletine Hydrochloride with 10 mL of the mobile phase, filter through a 0.4-µm glass microfibre filter (Whatman GF/C is suitable) and use the filtrate.
(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase.
(3) 0.01% w/v of *mexiletine impurity C EPCRS* and 0.08% w/v of *2,6-dimethylphenol* (impurity A) in the mobile phase. Mix 1 volume of this solution with 2 volumes of solution (2) and add sufficient mobile phase to produce 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil 100-5 C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 262 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for 5.5 times the retention time of mexiletine.

MOBILE PHASE

35 volumes of solution A and 65 volumes of *methanol R2*.

Solution A Dissolve 11.5 g of *anhydrous sodium acetate* in 500 mL of *water*, add 3.2 mL of *glacial acetic acid*, mix and allow to cool. Adjust the pH to 4.8 with *glacial acetic acid* and add sufficient *water* to produce 1000 mL.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mexiletine (retention time about 4 minutes) are: impurity C, about 0.7 and impurity A, about 1.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and mexiletine is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 2.5 times the area of the peak due to impurity A in the chromatogram obtained with solution (3) (0.1%);

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the area of any peak corresponding to impurity C is not greater than 20 times the area of the peak due to impurity C in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than half the area of the peak due to mexiletine in the chromatogram obtained with solution (3) (0.1%).

The total impurity content is not greater than 0.5%.

Disregard any peak with an area less than 0.25 times the area of the peak due to mexiletine in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Shake a quantity of capsule contents containing 50 mg of Mexiletine Hydrochloride with 50 mL of 0.01M *hydrochloric acid* for 30 minutes. Dilute to 100 mL with 0.01M *hydrochloric acid* and centrifuge. Measure the *absorbance* of the supernatant liquid at the maximum at 260 nm, Appendix II B. Calculate the content of $C_{11}H_{17}NO,HCl$ taking 11.6 as the value of A(1%, 1 cm) at the maximum at 260 nm.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Mexiletine Hydrochloride.

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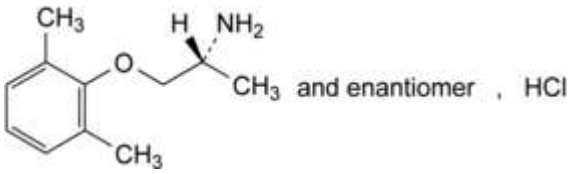
Mexiletine Hydrochloride

General Notices

(Ph. Eur. monograph 1029)



$C_{11}H_{18}ClNO$ 215.7 *5370-01-4*

Action and use

Class I antiarrhythmic.

Preparation

Mexiletine Capsules

Ph Eur

DEFINITION

(2*RS*)-1-(2,6-Dimethylphenoxy)propan-2-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, sparingly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mexiletine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Dilute 1.5 mL of solution S (see Tests) to 15 mL with *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dilute 5 mL of solution S to 10 mL with *water R*.

pH (2.2.3)

4.0 to 5.5 for solution S.

Impurity D Liquid chromatography (2.2.29)

Buffer solution To 1790 mL of *water for chromatography R* add 15 mL of *triethylamine R* and 1 mL of *glacial acetic acid R*.

Solvent mixture *acetonitrile R*, *water R* (20:80 *V/V*).

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5.0 mg of *mexiletine impurity D CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Mix 1 mL of reference solution (a) and 1 mL of the test solution and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, buffer solution (18:82 *V/V*); adjust to pH 11.5 with *triethylamine R*.

Flow rate 2.0 mL/min.

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Detection Spectrophotometer at 262 nm.

Injection 30 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of mexiletine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identifiy the peak due to impurity D.

Relative retention With reference to mexiletine (retention time = about 26 min): impurity D = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity D and mexiletine.

Calculation of percentage content:

— for impurity D, use the concentration of impurity D in reference solution (b).

Limit:

— *impurity D*: maximum 0.10 per cent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.0 mg of *mexiletine impurity C CRS* in the mobile phase and transfer the solution quantitatively to a volumetric flask containing 16.0 mg of *mexiletine impurity A CRS*, then dilute to 20.0 mL with the mobile phase. Mix 1.0 mL of this solution with 2.0 mL of reference solution (a) and dilute the mixture to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 65 volumes of *methanol R2* and 35 volumes of a solution prepared as follows: dissolve 11.5 g of *anhydrous sodium acetate R* in 500 mL of *water for chromatography R*, add 3.2 mL of *glacial acetic acid R*, mix and allow to cool; adjust to pH 4.8 with *glacial acetic acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 262 nm.

Injection 20 µL.

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Run time 5.5 times the retention time of mexiletine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to mexiletine (retention time = about 4 min): impurity C = about 0.7; impurity A = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity C and mexiletine.

Limits:

— *impurity A*: not more than 2.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *impurity C*: not more than 20 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to mexiletine in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 2.5 times the area of the peak due to mexiletine in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the peak due to mexiletine in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of a mixture of equal volumes of *acetic anhydride R* and *anhydrous acetic acid R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*) and completing the titration within 2 min.

1 mL of *0.1 M perchloric acid* is equivalent to 21.57 mg of $C_{11}H_{18}ClNO$.

IMPURITIES

Specified impurities *A, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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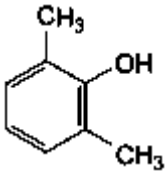
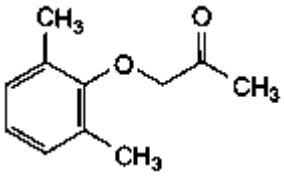
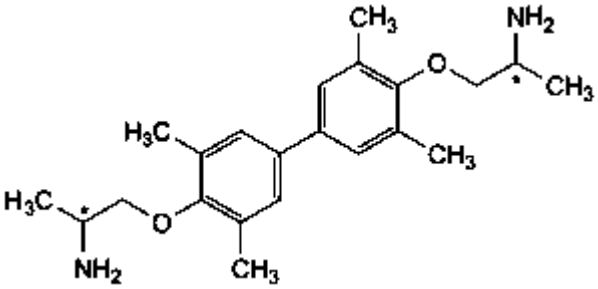
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



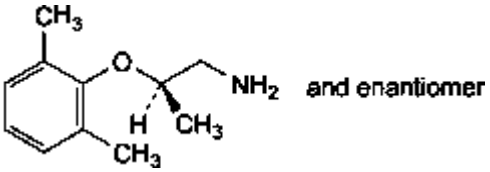
A. 2,6-dimethylphenol,



B. 1-(2,6-dimethylphenoxy)propan-2-one,



C. 1,1′-[(3,3′,5,5′-tetramethyl[1,1′-biphenyl]-4,4′-diyl)bis(oxy)]di(propan-2-amine),



D. (2*RS*)-2-(2,6-dimethylphenoxy)propan-1-amine.

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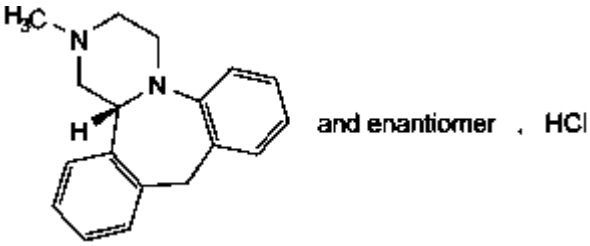
Mianserin Hydrochloride

General Notices

(Ph. Eur. monograph 0846)



$C_{18}H_{21}ClN_2$ 300.8 *21535-47-7*

Action and use

Monoamine reuptake inhibitor; tetracyclic antidepressant.

Preparation

Mianserin Tablets

Ph Eur

DEFINITION

(14b*RS*)-2-Methyl-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrazino[1,2-*a*]azepine hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

Sparingly soluble in water and in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

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First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *water R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *water R*.

Spectral range 230-350 nm.

Absorption maximum At 279 nm.

Specific absorbance at the absorption maximum 64 to 72.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *mianserin hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *mianserin hydrochloride CRS* in *methylene chloride R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *mianserin hydrochloride CRS* and 10 mg of *cyproheptadine hydrochloride CRS* in *methylene chloride R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *diethylamine R*, *ether R*, *cyclohexane R* (5:20:75 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

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TESTS

pH (2.2.3)

4.0 to 5.5.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Buffer solution pH 3.0 Dissolve 5.0 g of *sodium octanesulfonate R* in *water R* and dilute to 350 mL with the same solvent. Stir until complete dissolution. Adjust to pH 3.0 with a mixture of 1 volume of *phosphoric acid R* and 3 volumes of *water R*. Dilute to 400 mL with *water R*.

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *mianserin for system suitability CRS* (containing impurities A, D and E) in 1.0 mL of the mobile phase.

Reference solution (c) Dissolve 5.0 mg of *mianserin impurity B CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Buffer solution pH 3.0, *methanol R* (37:63 *V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Run time Twice the retention time of mianserin.

Identification of impurities Use the chromatogram supplied with *mianserin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, D and E.

Relative retention With reference to mianserin (retention time = about 18 min): impurity B = about 0.2; impurity A = about 0.5; impurity D = about 0.7; impurity E = about 1.1.

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System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to mianserin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.4; impurity D = 2.1;

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities A, D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 65 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 30.08 mg of $C_{18}H_{21}ClN_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, D, E.*

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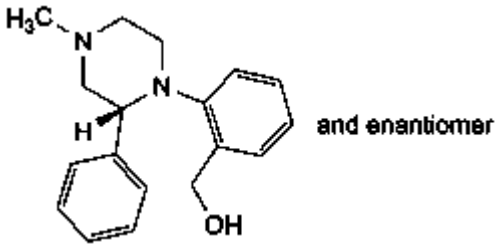
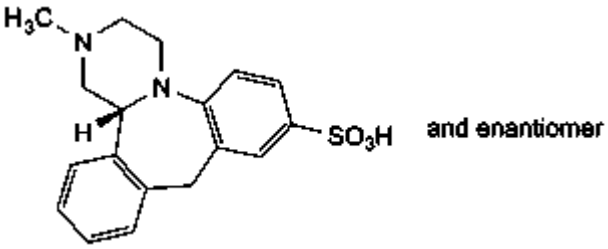
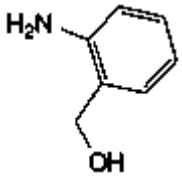
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, F.*



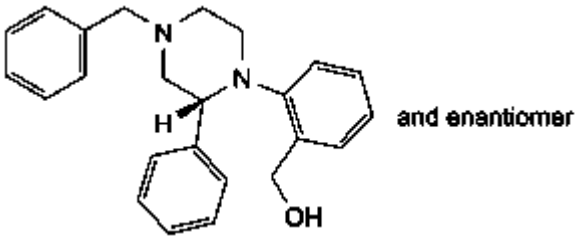
A. [2-[(2*RS*)-4-methyl-2-phenylpiperazin-1-yl]phenyl]methanol,



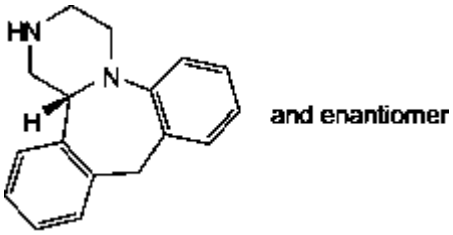
B. (14b*RS*)-2-methyl-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine-8-sulfonic acid,



C. (2-aminophenyl)methanol,



D. [2-[(2*RS*)-4-benzyl-2-phenylpiperazin-1-yl]phenyl]methanol,



E. (14b*RS*)-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine,

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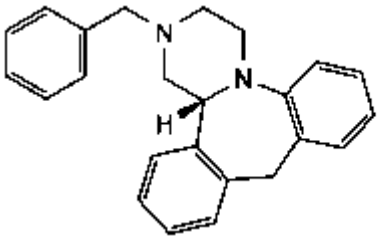

and enantiomer

F. (14b*RS*)-2-benzyl-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine.

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Mianserin Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; tetracyclic antidepressant.

DEFINITION

Mianserin Tablets contain Mianserin Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mianserin hydrochloride, $C_{18}H_{20}N_2,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Mianserin Hydrochloride with 10 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of mianserin hydrochloride *(RS 234)*.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as that due to mianserin in the chromatogram obtained with solution (1).

C. The residue obtained in test A yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared in a mixture of 1 volume of 13.5M *ammonia* and 4 volumes of *methanol*.

(1) Triturate a quantity of the powdered tablets containing 40 mg of Mianserin Hydrochloride with 2 mL of a mixture of 4 volumes of *methanol* and 1 volume of 13.5M *ammonia* and centrifuge. Use the supernatant.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Dilute 2 volumes of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of cold air for 5 minutes and then expose to iodine vapour for 20 minutes.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of *dichloromethane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%) and not more than two such spots are more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

Disregard any spot with an Rf value lower than 0.15.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *gas chromatography*, Appendix III B. Use a 0.2% w/v solution of *triphenylamine* in *toluene* as the internal standard solution.

(1) Shake a quantity of the powdered tablets containing 60 mg of Mianserin Hydrochloride with 30 mL of 0.2M *hydrochloric acid* for 1 hour and filter. To 10 mL of the filtrate add 3 mL of 1M *sodium hydroxide* and 10 mL of internal standard solution, mix for 5 minutes, centrifuge and use the clear upper layer.

(2) Add 3 mL of 1M *sodium hydroxide* and 10 mL of internal standard solution to 10 mL of a solution containing 0.2% w/v of *mianserin hydrochloride BPCRS* in 0.2M *hydrochloric acid*, mix for 5 minutes, centrifuge and use the clear upper layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica column (30 m × 0.32 mm) bonded with a 0.25 µm film of *phenyl(5)methyl(95)polysiloxane* (HP-5 is suitable).

(b) Use *helium* as the carrier gas at 1.0 mL per minute.

(c) Use isothermal conditions maintained at 255°.

(d) Use an inlet temperature of 280°.

(e) Use a flame ionisation detector at a temperature of 300°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:5.

When the chromatograms are recorded under the prescribed conditions the retention time of triphenylamine relative to mianserin (retention time about 5 minutes) is about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to triphenylamine and mianserin is at least 10.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{20}N_2$,HCl in the tablets using the declared content of $C_{18}H_{20}N_2$,HCl in *mianserin hydrochloride BPCRS*.

STORAGE

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Mianserin Tablets should be protected from light.

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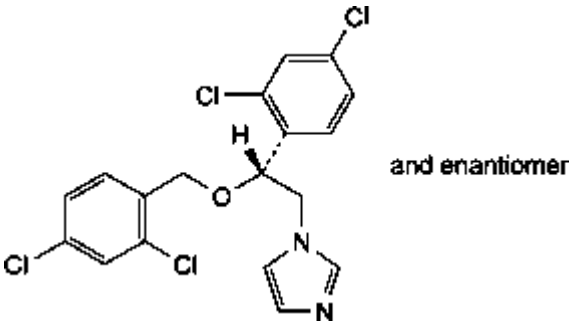
Miconazole

General Notices

(Ph. Eur. monograph 0935)



$C_{18}H_{14}Cl_4N_2O$ 416.1 *22916-47-8*

Action and use

Antifungal azole.

Preparations

Miconazole Oromucosal Gel

Miconazole Eye Drops

Ph Eur

DEFINITION

1-[(2*RS*)-2-(2,4-Dichlorophenyl)-2-[[(2,4-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Very slightly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *miconazole CRS*.

B. Melting point (2.2.14).

Determination A Determine the melting point of the substance to be examined.

Result A 83 °C to 87 °C.

Determination B Mix equal parts of the substance to be examined and *miconazole CRS*, and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

C. To 30 mg in a porcelain crucible add 0.3 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.1 g in *methanol R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution To 0.100 g of the substance to be examined add 3.0 mL of *acetonitrile R* and 3.2 mL of *methanol R*, shake until complete dissolution and dilute to 10.0 mL with a 15.8 g/L solution of *ammonium acetate R*.

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Reference solution (a) Dissolve the contents of a vial of *miconazole impurity G CRS* in 1 mL of the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Dissolve 6.0 g of *ammonium acetate R* in a mixture of 300 mL of *acetonitrile for chromatography R*, 320 mL of *methanol R1* and 380 mL of *water for chromatography R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL.

Run time 1.2 times the retention time of miconazole.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity G.

Relative retention With reference to miconazole (retention time = about 20 min): impurity G = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity G and miconazole.

Calculation of percentage contents:

— for each impurity, use the concentration of miconazole in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Using 0.2 mL of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from orange-yellow to green.

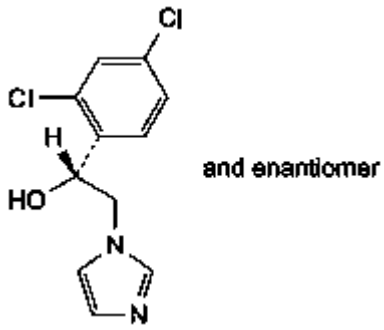
1 mL of *0.1 M perchloric acid* is equivalent to 41.61 mg of $C_{18}H_{14}Cl_4N_2O$.

STORAGE

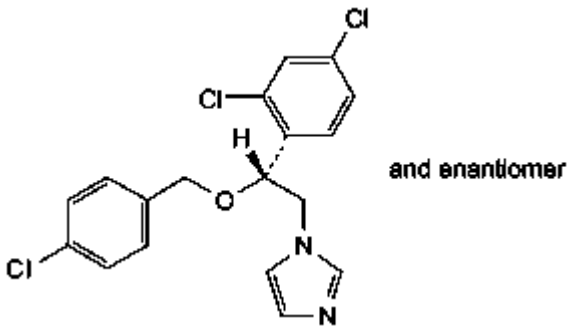
Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I.



A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-ol,



B. 1-[(2*RS*)-2-[[(4-chlorophenyl)methyl]oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole (econazole),

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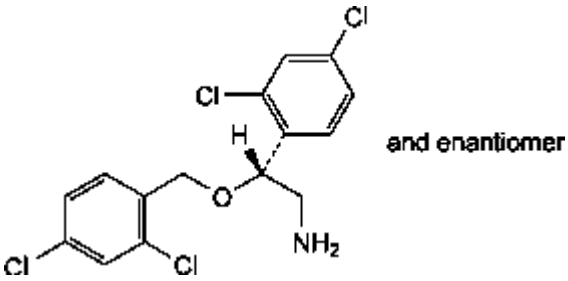
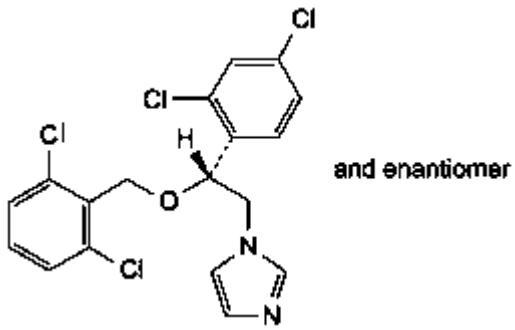
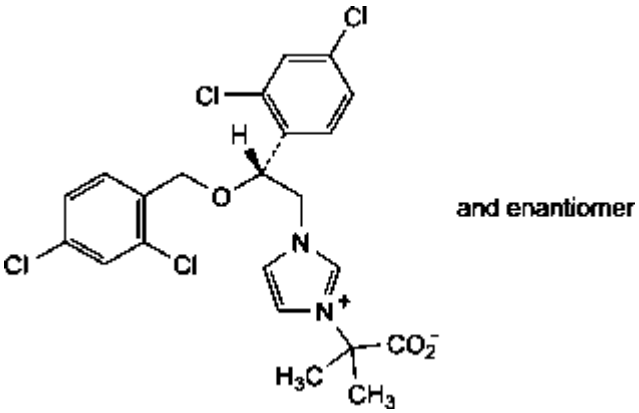


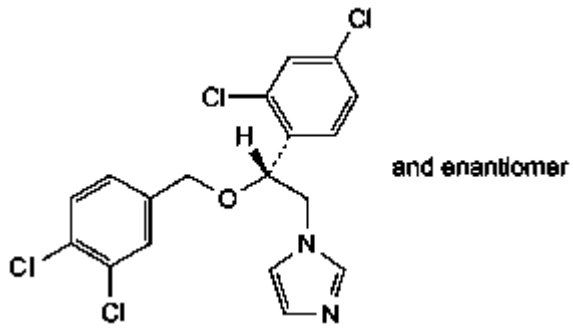
C. (2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,4-dichlorophenyl)methyl]oxy]ethan-1-amine,



D. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,6-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole (isoconazole),



E. 2-[1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,4-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazol-3-ium-3-yl]-2-methylpropanoate,



F. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(3,4-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole,

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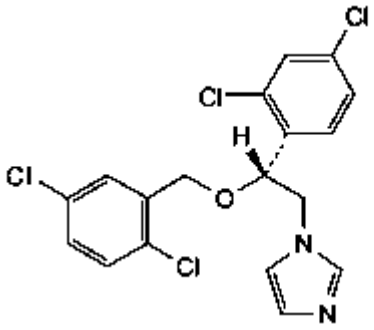
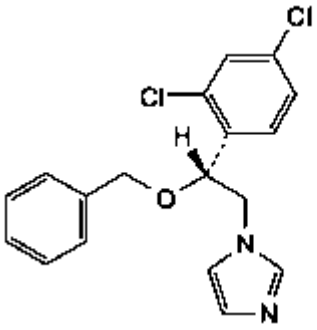


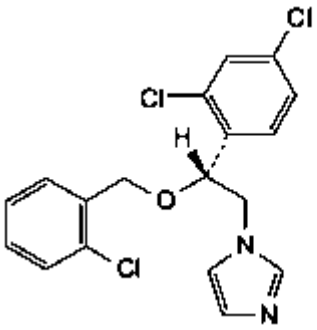
and enantiomer

G. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,5-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole,



and enantiomer

H. 1-[(2*RS*)-2-(benzyloxy)-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,



and enantiomer

I. 1-[(2*RS*)-2-[[(2-chlorophenyl)methyl]oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole.

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Miconazole and Hydrocortisone Acetate Cream

General Notices

Action and use

Antifungal azole.

DEFINITION

Miconazole and Hydrocortisone Acetate Cream contains Miconazole Nitrate and Hydrocortisone Acetate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of miconazole nitrate, $C_{18}H_{14}Cl_4N_2O,HNO_3$

95.0 to 105.0% of the stated amount.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the cream containing 0.15 g of Miconazole Nitrate by shaking with 25 mL of *methanol* for about 30 minutes, dilute to 50 mL with *methanol*, filter and use the filtrate.

(2) 0.3% w/v of *miconazole nitrate BPCRS* in *methanol*.

(3) 0.15% w/v of *hydrocortisone acetate BPCRS* in *methanol*.

(4) 0.15% w/v of *hydrocortisone BPCRS* and 0.15% w/v of *hydrocortisone acetate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, expose to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

20 volumes of *ammonium acetate solution*, 40 volumes of *dioxan* and 40 volumes of *methanol*.

SYSTEM SUITABILITY

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The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay for miconazole nitrate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to miconazole nitrate in the chromatogram obtained with solution (2).

C. In the Assay for hydrocortisone acetate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to hydrocortisone acetate in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a 10% w/v dispersion in *carbon dioxide-free water*, 3.5 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing 25 mg of Miconazole Nitrate with 30 mL of *methanol* for 30 minutes, add sufficient *methanol* to produce 50 mL and filter (Whatman GF/F is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the retention times are: hydrocortisone acetate, about 8 minutes; miconazole, about 18 minutes.

MOBILE PHASE

Mobile phase A 0.01M *ammonium dihydrogen orthophosphate* adjusted to pH 6.0 with *dilute ammonia R1*.

Mobile phase B 10 volumes of *tetrahydrofuran* and 90 volumes of *acetonitrile*.

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Time (minutes)	Mobile phase A % v/v	Mobile phase B % v/v	Comments
0→20	80→20	20→80	linear gradient
20→25	20	80	isocratic
25→27	20→80	80→20	linear gradient
27→32	80	20	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak other than those of hydrocortisone acetate and miconazole is not greater than the area of the miconazole peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak due to nitrate ion and any peak with an area less than 0.2 times the area of the peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For miconazole nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing 50 mg of Miconazole Nitrate with 50 mL of *methanol* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.
(2) 0.050% w/v of *miconazole nitrate BPCRS* in *methanol*.
(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{18}H_{14}Cl_4N_2O$ in the preparation being examined using the declared content of $C_{18}H_{14}Cl_4N_2O.HNO_3$ in *miconazole nitrate BPCRS*.

For hydrocortisone acetate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing 25 mg of Hydrocortisone Acetate with 50 mL of *methanol* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.

(2) 0.025% w/v of *hydrocortisone acetate BPCRS* in *methanol*.

(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4 –dichlorobenzenemethanol* in *methanol*.

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{32}O_6$ in the preparation being examined using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Miconazole Nitrate and the following:

2,4-dichlorobenzenemethanol,

2,4-dichloro-β-[2,4-dichlorophenyl)-methoxy]benzene ethanamine,

N-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)-methoxy]ethyl]formamide.

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Miconazole and Hydrocortisone Cream

General Notices

Action and use

Antifungal azole.

DEFINITION

Miconazole and Hydrocortisone Cream contains Miconazole Nitrate and Hydrocortisone in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of miconazole nitrate, $C_{18}H_{14}Cl_4N_2O,HNO_3$

95.0 to 105.0% of the stated amount.

Content of hydrocortisone, $C_{21}H_{30}O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the cream containing 0.15 g of Miconazole Nitrate by shaking with 25 mL of *methanol* for about 30 minutes, dilute to 50 mL with *methanol*, filter and use the filtrate.

(2) 0.3% w/v of *miconazole nitrate BPCRS* in *methanol*.

(3) 0.15% w/v of *hydrocortisone BPCRS* in *methanol*.

(4) 0.15% w/v of *hydrocortisone BPCRS* and 0.15% w/v of *hydrocortisone acetate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, expose to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

20 volumes of *ammonium acetate solution*, 40 volumes of *dioxan* and 40 volumes of *methanol*.

SYSTEM SUITABILITY

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The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

CONFIRMATION

The principal spots in the chromatogram obtained with solution (1) are similar in position, colour and size to those in the chromatograms obtained with solutions (2) and (3).

B. In the Assay for miconazole nitrate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to miconazole nitrate in the chromatogram obtained with solution (2).

C. In the Assay for hydrocortisone, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a 10% w/v dispersion in *carbon dioxide-free water*, 2.6 to 3.6, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing 25 mg of Miconazole Nitrate with 30 mL of *methanol* for 30 minutes, add sufficient *methanol* to produce 50 mL and filter (Whatman GF/F is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions the retention times are: hydrocortisone, about 8 minutes; miconazole, about 18 minutes.

MOBILE PHASE

Mobile phase A 0.01M *ammonium dihydrogen orthophosphate* adjusted to pH 6.0 with *dilute ammonia R1*.

Mobile phase B 10 volumes of *tetrahydrofuran* and 90 volumes of *acetonitrile*.

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Time (minutes)	Mobile phase A % v/v	Mobile phase B % v/v	Comments
0→20	80→20	20→80	linear gradient
20→25	20	80	isocratic
25→27	20→80	80→20	linear gradient
27→32	80	20	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak other than those due to hydrocortisone and miconazole is not greater than the area of the peak due to miconazole in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak due to nitrate ion and any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For miconazole nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing 50 mg of Miconazole Nitrate with 50 mL of *methanol* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.
(2) 0.050% w/v of *miconazole nitrate BPCRS* in *methanol*.
(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{18}H_{14}Cl_4N_2O$ in the preparation being examined using the declared content of $C_{18}H_{14}Cl_4N_2O.HNO_3$ in *miconazole nitrate BPCRS*.

For hydrocortisone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing 25 mg of Hydrocortisone with 50 mL of *methanol* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.

(2) 0.025% w/v of *hydrocortisone BPCRS* in *methanol*.

(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{30}O_5$ in the preparation being examined using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

STORAGE

Miconazole and Hydrocortisone Cream should be stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Miconazole Nitrate and the following:

2,4-dichlorobenzenemethanol,

2,4-dichloro-β-[2,4-dichlorophenyl)-methoxy]benzene ethanamine,

N-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)-methoxy]ethyl]formamide.

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Miconazole and Hydrocortisone Ointment

General Notices

Action and use

Antifungal azole.

DEFINITION

Miconazole and Hydrocortisone Ointment contains Miconazole Nitrate and Hydrocortisone in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of miconazole nitrate, $C_{18}H_{14}Cl_4N_2O,HNO_3$

95.0 to 105.0% of the stated amount.

Content of hydrocortisone, $C_{21}H_{30}O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ointment containing 0.15 g of Miconazole Nitrate by shaking with 25 mL of *tetrahydrofuran* for about 30 minutes, dilute to 50 mL with *methanol*, filter and use the filtrate.

(2) 0.3% w/v of *miconazole nitrate BPCRS* in equal volumes of *methanol* and *tetrahydrofuran*.

(3) 0.15% w/v of *hydrocortisone BPCRS* in equal volumes of *methanol* and *tetrahydrofuran*.

(4) 0.15% w/v of *hydrocortisone BPCRS* and 0.15% w/v of *hydrocortisone acetate BPCRS* in equal volumes of *methanol* and *tetrahydrofuran*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and expose to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

20 volumes of *ammonium acetate solution*, 40 volumes of *dioxan* and 40 volumes of *methanol*.

SYSTEM SUITABILITY

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The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

CONFIRMATION

The principal spots in the chromatogram obtained with solution (1) are similar in position, colour and size to those in the chromatograms obtained with solutions (2) and (3).

B. In the Assay for miconazole nitrate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to miconazole nitrate in the chromatogram obtained with solution (2).

C. In the Assay for hydrocortisone, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the ointment containing 50 mg of Miconazole Nitrate with 50 mL of *tetrahydrofuran* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter (Whatman GF/F is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the retention times are: hydrocortisone, about 8 minutes; miconazole, about 18 minutes.

MOBILE PHASE

Mobile phase A 0.01M *ammonium dihydrogen orthophosphate* adjusted to pH 6.0 with *dilute ammonia R1*.

Mobile phase B 10 volumes of *tetrahydrofuran* and 90 volumes of *acetonitrile*.

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Time (minutes)	Mobile phase A % v/v	Mobile phase B % v/v	Comments
0→20	80→20	20→80	linear gradient
20→25	20	80	isocratic
25→27	20→80	80→20	linear gradient
27→32	80	20	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak other than those of hydrocortisone and miconazole is not greater than the area of the miconazole peak in the chromatogram obtained with solution (2) (0.5%);

the total area of any such peaks is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak due to nitrate ion and any peak with an area less than 0.2 times the area of the peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For miconazole nitrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the ointment containing 50 mg of Miconazole Nitrate with 50 mL of *tetrahydrofuran* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.

(2) 0.050% w/v of *miconazole nitrate BPCRS* in *methanol*.

(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{18}H_{14}Cl_4N_2O$ in the preparation being examined using the declared contents of $C_{18}H_{14}Cl_4N_2O.HNO_3$ in *miconazole nitrate BPCRS*.

For hydrocortisone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the ointment containing 25 mg of Hydrocortisone with 50 mL of *tetrahydrofuran* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.

(2) 0.025% w/v of *hydrocortisone BPCRS* in *methanol*.

(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{30}O_5$ in the preparation being examined using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Miconazole Nitrate and the following:

2,4-dichlorobenzenemethanol,

2,4-dichloro-β-[2,4-dichlorophenyl)-methoxy]benzene ethanamine,

N-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)-methoxy]ethyl]formamide.

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Miconazole Cream

General Notices

Action and use

Antifungal azole.

DEFINITION

Miconazole Cream contains Miconazole Nitrate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of miconazole nitrate, $C_{18}H_{14}Cl_4N_2O,HNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity containing 40 mg of Miconazole Nitrate with 20 mL of a mixture of 1 volume of 1M *sulfuric acid* and 4 volumes of *methanol* and shake with two 50 mL quantities of *hexane*, discarding the organic layers. Make the aqueous phase alkaline with 2M *ammonia* and extract with two 40 mL quantities of *chloroform*. Combine the chloroform extracts, shake with 5 g of *anhydrous sodium sulfate*, filter and dilute the filtrate to 100 mL with *chloroform*. Evaporate 50 mL to dryness and dissolve the residue in 50 mL of a mixture of 1 volume of 0.1M *hydrochloric acid* and 9 volumes of *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits maxima at 264, 272 and 280 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak due to miconazole in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the cream containing 50 mg of Miconazole Nitrate with 30 mL of a mixture of equal volumes of *methanol* and *tetrahydrofuran* for 30 minutes, add sufficient of the same solvent mixture to produce 50 mL and filter through a glass microfibre filter (Whatman GF/C is suitable). For solution (2) dilute 5 volumes of solution (1) to 100 volumes with a mixture of equal volumes of *methanol* and *tetrahydrofuran* and 5 volumes of the resulting solution to 100 volumes with the same solvent mixture. Solution (3) contains 0.0025% w/v of *miconazole nitrate BPCRS* and 0.0025% w/v of *econazole nitrate BPCRS* in a mixture of equal volumes of *methanol* and *tetrahydrofuran*.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil 3 ODS is suitable), (b) as the mobile phase with a flow rate of 2 mL per minute

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a 0.6% w/v solution of *ammonium acetate* in a mixture of 300 volumes of *acetonitrile*, 320 volumes of *methanol* and 380 volumes of *water* and (c) a detection wavelength of 235 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to miconazole and econazole is at least 10. If necessary adjust the composition of the mobile phase.

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%) and the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the cream containing 50 mg of Miconazole Nitrate with 30 mL of a mixture of equal volumes of *methanol* and *tetrahydrofuran* for 30 minutes, add sufficient of the same solvent mixture to produce 50 mL and filter through a glass microfibre filter (Whatman GF/C is suitable). Solution (2) contains 0.1% w/v of *miconazole nitrate BPCRS* in a mixture of equal volumes of *methanol* and *tetrahydrofuran*. Solution (3) contains 0.0025% w/v of *miconazole nitrate BPCRS* and 0.0025% w/v of *econazole nitrate BPCRS* in a mixture of equal volumes of *methanol* and *tetrahydrofuran*.

The chromatographic procedure described under Related substances may be used.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to miconazole and econazole is at least 10. If necessary adjust the composition of the mobile phase.

Calculate the content of $C_{18}H_{14}Cl_4N_2O,HNO_3$ in the cream using the declared content of $C_{18}H_{14}Cl_4N_2O,HNO_3$ in *miconazole nitrate BPCRS*.

STORAGE

If Miconazole Cream is kept in aluminium tubes, their inner surfaces should be coated with a suitable lacquer.

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Miconazole Eye Drops

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Antifungal azole.

DEFINITION

Miconazole Eye Drops contain Miconazole in a suitable oily vehicle containing Arachis Oil.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of miconazole, $C_{18}H_{14}Cl_4N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin layer chromatography*, Appendix III A, using the following solutions in the mobile phase.

(1) Dilute the eye drops, if necessary, to produce a solution containing 0.6% w/v of Miconazole.

(2) 0.7% w/v of *miconazole nitrate BPCRS*.

(3) 0.7% w/v of *miconazole nitrate BPCRS* and 0.6% w/v of *econazole nitrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC octadecylsilyl silica gel plate*.

(b) Use the mobile phase described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air for 15 minutes and expose to iodine vapour until the spots appear. Examine in daylight.

MOBILE PHASE

20 volumes of *ammonium acetate solution*, 40 volumes of *1,4-dioxan* and 40 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as the retention time of the principal peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the eye drops containing 0.25 g of Miconazole with 50 mL of *methanol* for 2 minutes. Allow the oily phase to settle for at least 5 minutes, filter 8 mL of the cloudy supernatant liquid (discarding the first 3 mL of filtrate) and allow to stand for about 8 hours.
(2) Dissolve 0.3 g of *miconazole nitrate BPCRS* in 25 mL of *methanol*. To 4 mL of this solution add 3.5 g of *arachis oil* and sufficient *methanol* to produce 50 mL; shake for 2 minutes. Allow the oily phase to settle for at least 5 minutes, filter 8 mL of the cloudy supernatant liquid (discarding the first 3 mL of filtrate) and allow to stand for about 8 hours.
(3) 0.08% w/v of each of *miconazole nitrate BPCRS* and *econazole nitrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 200 µL of each solution.
Equilibrate the column with the mobile phase at a flow rate of 0.5 mL per minute for about 8 hours.

MOBILE PHASE

0.1% w/v of *sodium heptanesulfonate* in a mixture of 27 volumes of *water* and 73 volumes of *methanol*, adjusted to pH 4.5 with *orthophosphoric acid* and 2.5M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), there are two clearly separated peaks.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{14}Cl_4N_2O$ in the eye drops using the declared content of $C_{18}H_{14}Cl_4N_2O$ in *miconazole nitrate BPCRS*.

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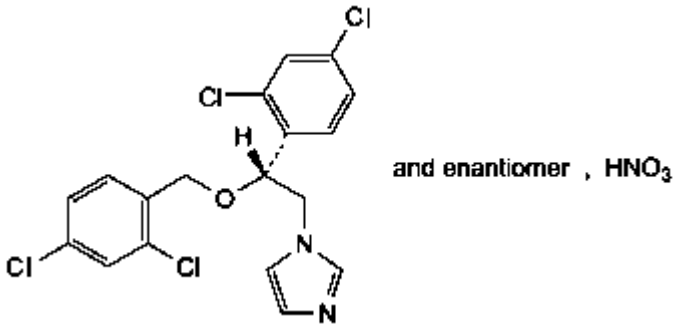
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Miconazole Nitrate

General Notices

(Ph. Eur. monograph 0513)



$C_{18}H_{15}Cl_4N_3O_4$ 479.1 *22832-87-7*

Action and use

Antifungal azole.

Preparations

Miconazole Cream

Miconazole and Hydrocortisone Cream

Miconazole and Hydrocortisone Acetate Cream

Miconazole and Hydrocortisone Ointment

Ph Eur

DEFINITION

1-[(2*RS*)-2-(2,4-Dichlorophenyl)-2-[[(2,4-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole nitrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

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Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *miconazole nitrate CRS*.

B. Melting point (*2.2.14*).

Determination A Determine the melting point of the substance to be examined.

Result A 178 °C to 184 °C.

Determination B Mix equal parts of the substance to be examined and *miconazole nitrate CRS*, and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

C. It gives the reaction of nitrates (*2.3.1*).

TESTS

Solution S

Dissolve 0.1 g in *methanol R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

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Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *miconazole impurity G CRS* in 1 mL of the test solution.

Reference solution (b) Dissolve 10 mg of *miconazole for peak identification CRS* (containing impurities C and F) in the mobile phase and dilute to 1 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Dissolve 6.0 g of *ammonium acetate R* in a mixture of 300 mL of *acetonitrile for chromatography R*, 320 mL of *methanol R1* and 380 mL of *water for chromatography R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL.

Run time 1.2 times the retention time of miconazole.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity G; use the chromatogram supplied with *miconazole for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and F.

Relative retention With reference to miconazole (retention time = about 20 min): nitrate ion = about 0.03; impurity C = about 0.4; impurity F = about 0.82; impurity G = about 0.85.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity G and miconazole.

Calculation of percentage contents:

— for each impurity, use the concentration of miconazole nitrate in reference solution (c).

Limits:

— *impurity C*: maximum 0.2 per cent;

— *sum of impurities F and G*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

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— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to the nitrate ion.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 75 mL of *anhydrous acetic acid R*, with slight heating if necessary. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 47.91 mg of $C_{18}H_{15}Cl_4N_3O_4$.

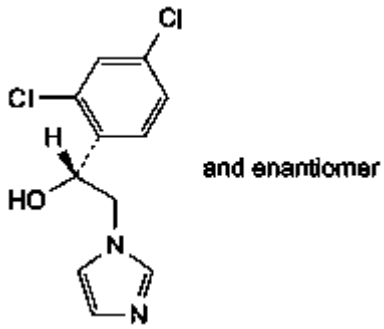
STORAGE

Protected from light.

IMPURITIES

Specified impurities C, F, G.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D, E, H, I.



and enantiomer

A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-ol,

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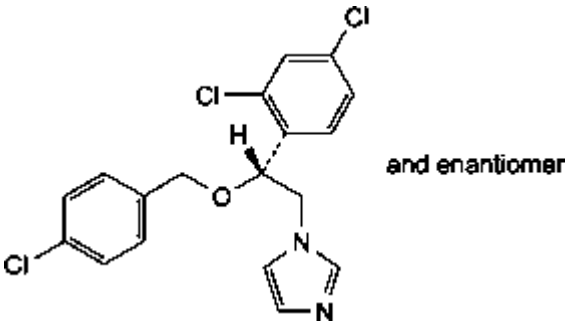
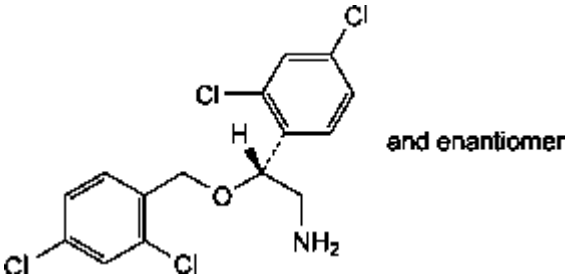
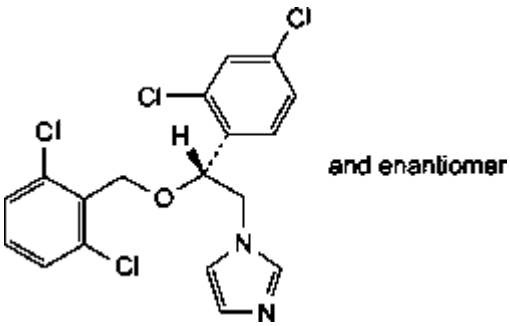


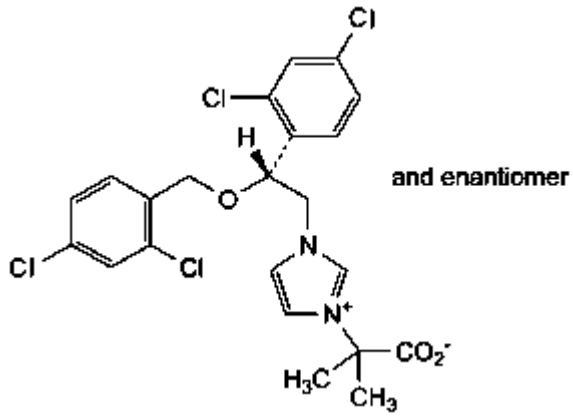
B. 1-[(2*RS*)-2-[[(4-chlorophenyl)methyl]oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole (econazole),



C. (2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,4-dichlorophenyl)methyl]oxy]ethan-1-amine,



D. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,6-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole (isoconazole),



E. 2-[1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,4-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazol-3-ium-3-yl]-2-methylpropanoate,

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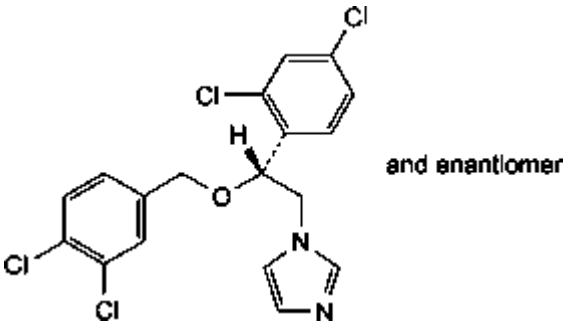
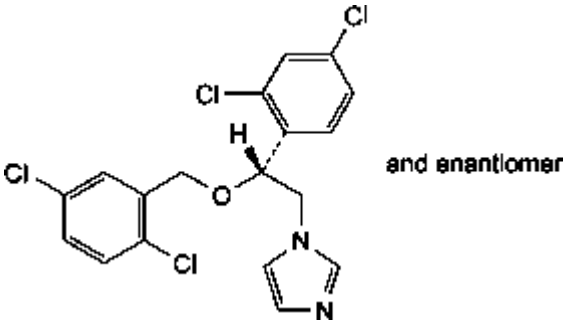
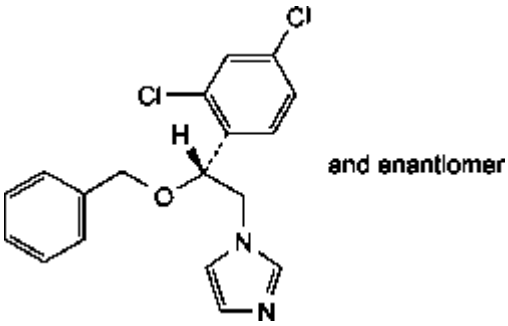


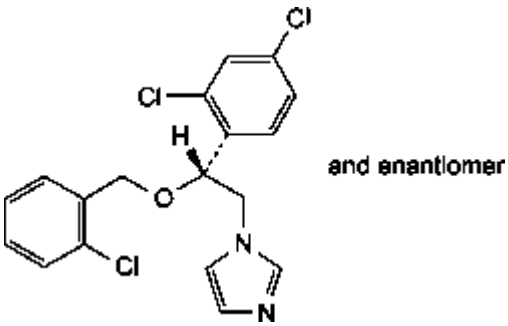
F. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(3,4-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole,



G. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[(2,5-dichlorophenyl)methyl]oxy]ethyl]-1*H*-imidazole,



H. 1-[(2*RS*)-2-(benzyloxy)-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,



I. 1-[(2*RS*)-2-[[(2-chlorophenyl)methyl]oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole.

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Miconazole Oromucosal Gel

General Notices

Action and use

Antifungal azole.

DEFINITION

Miconazole Oromucosal Gel is a suspension of Miconazole, in *very fine powder*, in a suitable water-miscible basis. It may be flavoured.

The oromucosal gel complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of miconazole, $C_{18}H_{14}Cl_4N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the gel containing 20 mg of Miconazole with sufficient *methanol* to produce a 0.05% w/v solution. The *light absorption* of this solution, Appendix II B, in the range 250 to 350 nm exhibits two maxima at 272 and 280 nm and a broad shoulder at about 263 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 4.0 to 7.5 Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the gel containing 50 mg of Miconazole with 25 mL of *methanol* for 30 minutes, add sufficient *methanol* to produce 50 mL and filter through a glass microfibre filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol* and dilute 5 volumes of the resulting solution to 20 volumes with *methanol*.

(3) 0.0025% w/v each of *miconazole nitrate BPCRS* and *econazole nitrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

0.6% w/v solution of *ammonium acetate* in a mixture of 300 volumes of *acetonitrile*, 320 volumes of *methanol* and 380 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to miconazole and econazole is at least 10.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the gel containing 50 mg of Miconazole with 25 mL of *methanol* for 30 minutes, add sufficient *methanol* to produce 50 mL and filter through a glass microfibre filter (Whatman GF/C is suitable).

(2) 0.12% w/v of *miconazole nitrate BPCRS* in *methanol*.

(3) 0.0025% w/v each of *miconazole nitrate BPCRS* and *econazole nitrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to miconazole and econazole is at least 10.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{14}Cl_4N_2O$ in the gel using the declared content of $C_{18}H_{14}Cl_4N_2O$ in *miconazole nitrate BPCRS*.

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STORAGE

Miconazole Oromucosal Gel should be protected from light.

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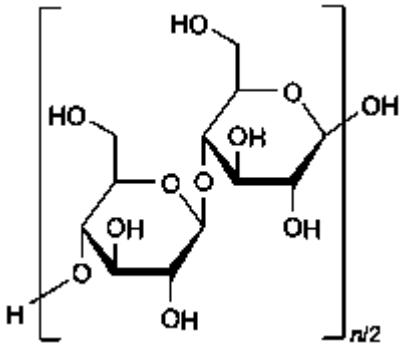
Microcrystalline Cellulose[1]

General Notices

(Ph. Eur. monograph 0316)



$C_{6n}H_{10n+2}O_{5n+1}$

Cellulose *9004-34-6*

Action and use

Excipient.

Ph Eur

DEFINITION

Purified, partly depolymerised cellulose prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

♦ CHARACTERS

Appearance

White or almost white, fine or granular, slightly hygroscopic powder.

Solubility

Practically insoluble in water, in acetone, in anhydrous ethanol, in toluene, in dilute acids and in a 50 g/L solution of sodium hydroxide.♦

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *microcrystalline cellulose CRS*.

Disregard any band between 800 cm^{-1} and 825 cm^{-1} or between 950 cm^{-1} and 1000 cm^{-1}.

B. Place about 10 mg on a watch-glass and disperse in 2 mL of *iodinated zinc chloride solution R*. The substance becomes violet-blue.

C. The degree of polymerisation is not more than 350.

Transfer 1.300 g to a 125 mL conical flask. Add 25.0 mL of *water R* and 25.0 mL of *cupriethylenediamine hydroxide solution R*. Immediately purge the solution with *nitrogen R*, insert the stopper and shake until completely dissolved. Transfer an appropriate volume of the solution to a suitable capillary viscometer (*2.2.9*). Equilibrate the solution at 25 ± 0.1 °C for at least 5 min. Record the flow time (t_1) in seconds between the 2 marks on the viscometer. Calculate the kinematic viscosity (v_1) of the solution using the following expression:

$$t_1\left(k_1\right)$$

k_1 = viscometer constant.

Dilute a suitable volume of *cupriethylenediamine hydroxide solution R* with an equal volume of *water R* and measure the flow time (t_2) using a suitable capillary viscometer. Calculate the kinematic viscosity (v_2) of the solvent using the following expression:

$$t_2\left(k_2\right)$$

k_2 = viscometer constant.

Determine the relative viscosity (η_{rel}) of the substance to be examined using the following expression:

$$v_1 / v_2$$

Determine the intrinsic viscosity ($[\eta]_c$) by interpolation, using the intrinsic viscosity table (Table 0316.-1).

Calculate the degree of polymerisation (P) using the following expression:

$$\frac{95[\eta]_c}{m[(100-b)/100]}$$

m = mass of the substance to be examined, in grams;

b = loss on drying, in per cent.

TESTS

◊ Solubility

Dissolve 50 mg in 10 mL of *ammoniacal solution of copper tetrammine R*. It dissolves completely, leaving no residue.◊

pH (*2.2.3*)

5.0 to 7.5 for the supernatant.

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Shake 5 g with 40 mL of *carbon dioxide-free water R* for 20 min and centrifuge.

Conductivity (*2.2.38*)

The conductivity of the test solution does not exceed the conductivity of the water by more than 75 $\mu S \cdot cm^{-1}$.

Use as test solution the supernatant obtained in the test for pH. Measure the conductivity of the supernatant after a stable reading has been obtained and measure the conductivity of the water used to prepare the test solution.

Ether-soluble substances

Maximum 0.05 per cent (5.0 mg) for the difference between the mass of the residue and the mass obtained from a blank determination.

Place 10.0 g in a chromatography column about 20 mm in internal diameter and pass 50 mL of *peroxide-free ether R* through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish, with the aid of a current of air in a fume cupboard. After all ether has evaporated, dry the residue at 105 °C for 30 min, allow to cool in a desiccator and weigh. Carry out a blank determination.

Water-soluble substances

Maximum 0.25 per cent (12.5 mg) for the difference between the mass of the residue and the mass obtained from a blank determination.

Shake 5.0 g with 80 mL of *water R* for 10 min. Filter through a filter paper with the aid of vacuum into a tared flask. Evaporate to dryness on a water-bath avoiding charring. Dry at 105 °C for 1 h, allow to cool in a desiccator and weigh. Carry out a blank determination.

Table 0316.-1. – *Intrinsic viscosity table*

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}										
	$[\eta]_c$									
η_{rel}	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
1.1	0.098	0.106	0.115	0.125	0.134	0.143	0.152	0.161	0.170	0.180
1.2	0.189	0.198	0.207	0.216	0.225	0.233	0.242	0.250	0.259	0.268
1.3	0.276	0.285	0.293	0.302	0.310	0.318	0.326	0.334	0.342	0.350
1.4	0.358	0.367	0.375	0.383	0.391	0.399	0.407	0.414	0.422	0.430
1.5	0.437	0.445	0.453	0.460	0.468	0.476	0.484	0.491	0.499	0.507
1.6	0.515	0.522	0.529	0.536	0.544	0.551	0.558	0.566	0.573	0.580
1.7	0.587	0.595	0.602	0.608	0.615	0.622	0.629	0.636	0.642	0.649
1.8	0.656	0.663	0.670	0.677	0.683	0.690	0.697	0.704	0.710	0.717
1.9	0.723	0.730	0.736	0.743	0.749	0.756	0.762	0.769	0.775	0.782

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
2.0	0.788	0.795	0.802	0.809	0.815	0.821	0.827	0.833	0.840	0.846
2.1	0.852	0.858	0.864	0.870	0.876	0.882	0.888	0.894	0.900	0.906
2.2	0.912	0.918	0.924	0.929	0.935	0.941	0.948	0.953	0.959	0.965
2.3	0.971	0.976	0.983	0.988	0.994	1.000	1.006	1.011	1.017	1.022
2.4	1.028	1.033	1.039	1.044	1.050	1.056	1.061	1.067	1.072	1.078
2.5	1.083	1.089	1.094	1.100	1.105	1.111	1.116	1.121	1.126	1.131
2.6	1.137	1.142	1.147	1.153	1.158	1.163	1.169	1.174	1.179	1.184
2.7	1.190	1.195	1.200	1.205	1.210	1.215	1.220	1.225	1.230	1.235
2.8	1.240	1.245	1.250	1.255	1.260	1.265	1.270	1.275	1.280	1.285
2.9	1.290	1.295	1.300	1.305	1.310	1.314	1.319	1.324	1.329	1.333
3.0	1.338	1.343	1.348	1.352	1.357	1.362	1.367	1.371	1.376	1.381
3.1	1.386	1.390	1.395	1.400	1.405	1.409	1.414	1.418	1.423	1.427
3.2	1.432	1.436	1.441	1.446	1.450	1.455	1.459	1.464	1.468	1.473
3.3	1.477	1.482	1.486	1.491	1.496	1.500	1.504	1.508	1.513	1.517
3.4	1.521	1.525	1.529	1.533	1.537	1.542	1.546	1.550	1.554	1.558
3.5	1.562	1.566	1.570	1.575	1.579	1.583	1.587	1.591	1.595	1.600
3.6	1.604	1.608	1.612	1.617	1.621	1.625	1.629	1.633	1.637	1.642
3.7	1.646	1.650	1.654	1.658	1.662	1.666	1.671	1.675	1.679	1.683
3.8	1.687	1.691	1.695	1.700	1.704	1.708	1.712	1.715	1.719	1.723
3.9	1.727	1.731	1.735	1.739	1.742	1.746	1.750	1.754	1.758	1.762
4.0	1.765	1.769	1.773	1.777	1.781	1.785	1.789	1.792	1.796	1.800
4.1	1.804	1.808	1.811	1.815	1.819	1.822	1.826	1.830	1.833	1.837

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
4.2	1.841	1.845	1.848	1.852	1.856	1.859	1.863	1.867	1.870	1.874
4.3	1.878	1.882	1.885	1.889	1.893	1.896	1.900	1.904	1.907	1.911
4.4	1.914	1.918	1.921	1.925	1.929	1.932	1.936	1.939	1.943	1.946
4.5	1.950	1.954	1.957	1.961	1.964	1.968	1.971	1.975	1.979	1.982
4.6	1.986	1.989	1.993	1.996	2.000	2.003	2.007	2.010	2.013	2.017
4.7	2.020	2.023	2.027	2.030	2.033	2.037	2.040	2.043	2.047	2.050
4.8	2.053	2.057	2.060	2.063	2.067	2.070	2.073	2.077	2.080	2.083
4.9	2.087	2.090	2.093	2.097	2.100	2.103	2.107	2.110	2.113	2.116
5.0	2.119	2.122	2.125	2.129	2.132	2.135	2.139	2.142	2.145	2.148
5.1	2.151	2.154	2.158	2.160	2.164	2.167	2.170	2.173	2.176	2.180
5.2	2.183	2.186	2.190	2.192	2.195	2.197	2.200	2.203	2.206	2.209
5.3	2.212	2.215	2.218	2.221	2.224	2.227	2.230	2.233	2.236	2.240
5.4	2.243	2.246	2.249	2.252	2.255	2.258	2.261	2.264	2.267	2.270
5.5	2.273	2.276	2.279	2.282	2.285	2.288	2.291	2.294	2.297	2.300
5.6	2.303	2.306	2.309	2.312	2.315	2.318	2.320	2.324	2.326	2.329
5.7	2.332	2.335	2.338	2.341	2.344	2.347	2.350	2.353	2.355	2.358
5.8	2.361	2.364	2.367	2.370	2.373	2.376	2.379	2.382	2.384	2.387
5.9	2.390	2.393	2.396	2.400	2.403	2.405	2.408	2.411	2.414	2.417
6.0	2.419	2.422	2.425	2.428	2.431	2.433	2.436	2.439	2.442	2.444
6.1	2.447	2.450	2.453	2.456	2.458	2.461	2.464	2.467	2.470	2.472
6.2	2.475	2.478	2.481	2.483	2.486	2.489	2.492	2.494	2.497	2.500
6.3	2.503	2.505	2.508	2.511	2.513	2.516	2.518	2.521	2.524	2.526
6.4	2.529	2.532	2.534	2.537	2.540	2.542	2.545	2.547	2.550	2.553

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
6.5	2.555	2.558	2.561	2.563	2.566	2.568	2.571	2.574	2.576	2.579
6.6	2.581	2.584	2.587	2.590	2.592	2.595	2.597	2.600	2.603	2.605
6.7	2.608	2.610	2.613	2.615	2.618	2.620	2.623	2.625	2.627	2.630
6.8	2.633	2.635	2.637	2.640	2.643	2.645	2.648	2.650	2.653	2.655
6.9	2.658	2.660	2.663	2.665	2.668	2.670	2.673	2.675	2.678	2.680
7.0	2.683	2.685	2.687	2.690	2.693	2.695	2.698	2.700	2.702	2.705
7.1	2.707	2.710	2.712	2.714	2.717	2.719	2.721	2.724	2.726	2.729
7.2	2.731	2.733	2.736	2.738	2.740	2.743	2.745	2.748	2.750	2.752
7.3	2.755	2.757	2.760	2.762	2.764	2.767	2.769	2.771	2.774	2.776
7.4	2.779	2.781	2.783	2.786	2.788	2.790	2.793	2.795	2.798	2.800
7.5	2.802	2.805	2.807	2.809	2.812	2.814	2.816	2.819	2.821	2.823
7.6	2.826	2.828	2.830	2.833	2.835	2.837	2.840	2.842	2.844	2.847
7.7	2.849	2.851	2.854	2.856	2.858	2.860	2.863	2.865	2.868	2.870
7.8	2.873	2.875	2.877	2.879	2.881	2.884	2.887	2.889	2.891	2.893
7.9	2.895	2.898	2.900	2.902	2.905	2.907	2.909	2.911	2.913	2.915
8.0	2.918	2.920	2.922	2.924	2.926	2.928	2.931	2.933	2.935	2.937
8.1	2.939	2.942	2.944	2.946	2.948	2.950	2.952	2.955	2.957	2.959
8.2	2.961	2.963	2.966	2.968	2.970	2.972	2.974	2.976	2.979	2.981
8.3	2.983	2.985	2.987	2.990	2.992	2.994	2.996	2.998	3.000	3.002
8.4	3.004	3.006	3.008	3.010	3.012	3.015	3.017	3.019	3.021	3.023
8.5	3.025	3.027	3.029	3.031	3.033	3.035	3.037	3.040	3.042	3.044
8.6	3.046	3.048	3.050	3.052	3.054	3.056	3.058	3.060	3.062	3.064

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
8.7	3.067	3.069	3.071	3.073	3.075	3.077	3.079	3.081	3.083	3.085
8.8	3.087	3.089	3.092	3.094	3.096	3.098	3.100	3.102	3.104	3.106
8.9	3.108	3.110	3.112	3.114	3.116	3.118	3.120	3.122	3.124	3.126
9.0	3.128	3.130	3.132	3.134	3.136	3.138	3.140	3.142	3.144	3.146
9.1	3.148	3.150	3.152	3.154	3.156	3.158	3.160	3.162	3.164	3.166
9.2	3.168	3.170	3.172	3.174	3.176	3.178	3.180	3.182	3.184	3.186
9.3	3.188	3.190	3.192	3.194	3.196	3.198	3.200	3.202	3.204	3.206
9.4	3.208	3.210	3.212	3.214	3.215	3.217	3.219	3.221	3.223	3.225
9.5	3.227	3.229	3.231	3.233	3.235	3.237	3.239	3.241	3.242	3.244
9.6	3.246	3.248	3.250	3.252	3.254	3.256	3.258	3.260	3.262	3.264
9.7	3.266	3.268	3.269	3.271	3.273	3.275	3.277	3.279	3.281	3.283
9.8	3.285	3.287	3.289	3.291	3.293	3.295	3.297	3.298	3.300	3.302
9.9	3.304	3.305	3.307	3.309	3.311	3.313	3.316	3.318	3.320	3.321

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.0**	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
10	3.32	3.34	3.36	3.37	3.39	3.41	3.43	3.45	3.46	3.48
11	3.50	3.52	3.53	3.55	3.56	3.58	3.60	3.61	3.63	3.64
12	3.66	3.68	3.69	3.71	3.72	3.74	3.76	3.77	3.79	3.80
13	3.80	3.83	3.85	3.86	3.88	3.89	3.90	3.92	3.93	3.95
14	3.96	3.97	3.99	4.00	4.02	4.03	4.04	4.06	4.07	4.09
15	4.10	4.11	4.13	4.14	4.15	4.17	4.18	4.19	4.20	4.22

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
16	4.23	4.24	4.25	4.27	4.28	4.29	4.30	4.31	4.33	4.34
17	4.35	4.36	4.37	4.38	4.39	4.41	4.42	4.43	4.44	4.45
18	4.46	4.47	4.48	4.49	4.50	4.52	4.53	4.54	4.55	4.56
19	4.57	4.58	4.59	4.60	4.61	4.62	4.63	4.64	4.65	4.66

Loss on drying (*2.2.32*)

Maximum 7.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Pseudomonas aeruginosa* (*2.6.13*).

Absence of *Staphylococcus aureus* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for microcrystalline cellulose used as binder, diluent or disintegrant.

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Loss on drying

(see Tests).

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

◊

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Microcrystalline Cellulose and Carmellose Sodium

General Notices

(Ph. Eur. monograph 2050)

Action and use

Excipient.

Ph Eur

DEFINITION

Colloid-forming, powdered mixture of *Microcrystalline cellulose (0316)* with 5 per cent to 22 per cent of *Carmellose sodium (0472)*.

Content

75.0 per cent to 125.0 per cent of the nominal content of carmellose sodium (dried substance).

CHARACTERS

Appearance

White or off-white, coarse or fine, hygroscopic powder.

Solubility

Dispersible in water producing a white, opaque colloidal dispersion; practically insoluble in organic solvents and in dilute acids.

IDENTIFICATION

A. Mix 6 g with 300 mL of *water R* and stir at 18 000 r/min for 5 min. A white opaque dispersion is obtained which does not produce a supernatant.

B. Add several drops of the dispersion obtained in identification A to a 100 g/L solution of *aluminium chloride R*. Each drop forms a white, opaque globule which does not disperse on standing.

C. Add 2 mL of *iodinated potassium iodide solution R* to the dispersion obtained in test A. No blue or purplish colour is produced.

D. It complies with the limits of the assay.

TESTS

Solubility

Add 50 mg to 10 mL of *ammoniacal solution of copper tetrammine R* and shake. It dissolves completely, leaving no residue.

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pH (*2.2.3*)

6.0 to 8.0 for the dispersion obtained in identification A.

Loss on drying (*2.2.32*)

Maximum 8.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 7.4 per cent, determined on 2.0 g.

ASSAY

Heat 2.00 g with 75 mL of *anhydrous acetic acid R* under a reflux condenser for 2 h, cool and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 29.6 mg of carmellose sodium.

LABELLING

The label states the nominal content of carmellose sodium in per cent *m/m*.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for microcrystalline cellulose and carmellose sodium used as a suspending agent.

Viscosity (*2.2.10*)

60 per cent to 140 per cent of the nominal value.

Calculate the quantity (*x* g) needed to prepare exactly 600 g of a dispersion of the stated percentage *m/m* (dried substance). To (600 - *x*) g of *water R* at 23-25 °C contained in a 1000 mL high-speed blender bowl, add *x* g of the substance to be examined and stir at reduced speed, taking care to avoid contacting the sides of the bowl with the powder. Continue stirring at low speed for 15 s after the addition of the powder and then stir at 18 000 r/min for exactly 2 min.

Determine the viscosity with a suitable relative rotational viscometer under the following conditions:

— spindle: as appropriate;

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— speed: 20 r/min.

Immerse the spindle into the suspension immediately after preparation, switch on the rotation spindle after 30 s; after a further 30 s, take scale readings and calculate the viscosity according to the viscometer manual.

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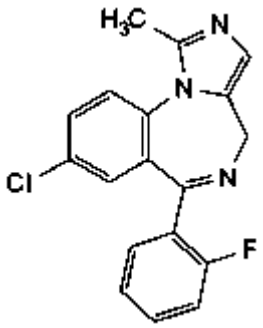
Midazolam

General Notices

(Ph. Eur. monograph 0936)



$C_{18}H_{13}ClFN_3$ 325.8 *59467-70-8*

Action and use

Benzodiazepine.

Preparations

Midazolam Injection

Midazolam Oral Solution

Midazolam Oromucosal Solution

Ph Eur

DEFINITION

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

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Solubility

Practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent), soluble in methanol.

IDENTIFICATION

First identification: B.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 161 °C to 164 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *midazolam CRS*.

C. Examine the chromatograms obtained in the test for impurity C.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (b).

D. Mix 90 mg with 0.30 g of *anhydrous sodium carbonate R* and ignite in a crucible until an almost white residue is obtained (normally in less than 5 min). Allow to cool and dissolve the residue in 5 mL of *dilute nitric acid R*. Filter (the filtrate is also used in identification test E). Add 1.0 mL of the filtrate to a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank solution is red.

E. To 1 mL of the filtrate obtained in identification test D add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 0.1 g in *0.1 M hydrochloric acid* and dilute to 10 mL with the same acid.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve the contents of a vial of *midazolam for system suitability CRS* (containing impurities A, B, E, G and H) in 1.0 mL of *methanol R*.

Column:

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— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Prepare a solution containing 7.7 g/L of *ammonium acetate R* and 10 mL/L of *tetrabutylammonium hydroxide solution (400 g/L) R* and adjust to pH 5.3 with *glacial acetic acid R*. Mix 44 volumes of this solution with 56 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 2.5 times the retention time of midazolam.

Identification of impurities Use the chromatogram supplied with *midazolam for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, E, G and H.

Relative retention With reference to midazolam (retention time = about 17 min): impurity E = about 0.5; impurity A = about 0.9; impurity G = about 1.2; impurity H = about 1.9; impurity B = about 2.2.

System suitability:

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to midazolam in the chromatogram obtained with reference solution (b).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.0; impurity E = 2.0; impurity H = 1.7;

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities A, E, G, H*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity C

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Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.20 g of the substance to be examined in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 50 mL with *ethanol (96 per cent) R*.

Reference solution (a) Dissolve the contents of a vial of *midazolam impurity C CRS* in 1.0 mL of *methanol R*. Dilute 0.5 mL of the solution to 1.0 mL with *methanol R*.

Reference solution (b) Dissolve 8 mg of *midazolam CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (c) Dissolve 40 mg of the substance to be examined in 1 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R*, *ethyl acetate R* (2:15:20:80 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity C*: any spot due to impurity C in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.1 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.120 g in 30 mL of *anhydrous acetic acid R* and add 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid* to the 2nd point of inflexion, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 16.29 mg of $C_{18}H_{13}ClFN_3$.

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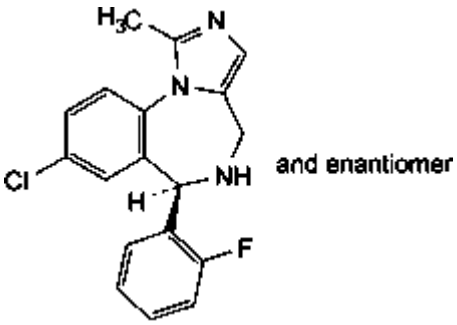
IMPURITIES

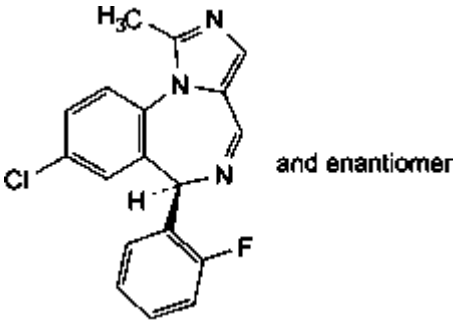
Specified impurities A, B, C, E, G, H.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, F, I, J.



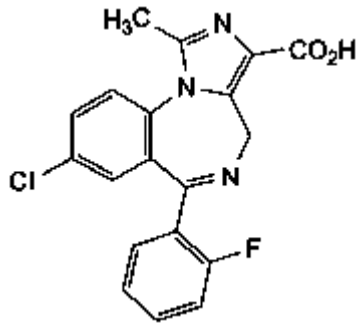
and enantiomer

A. (6*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine,



and enantiomer

B. (6*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine,



C. 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid,

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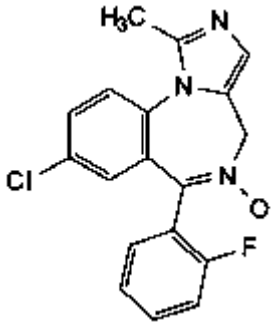
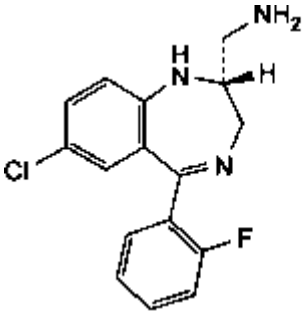
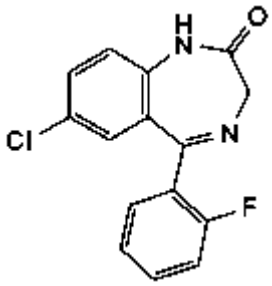


D. 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 5-oxide,

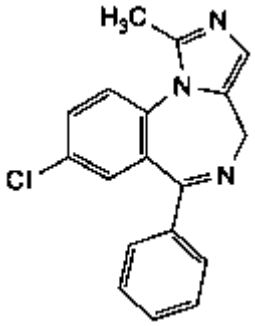


and enantiomer

E. [(2*RS*)-7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-yl]methanamine,



F. 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (1-des[(diethylamino)ethyl]flurazepam),



G. 8-chloro-1-methyl-6-phenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (desfluoromidazolam),

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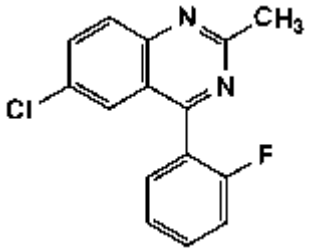
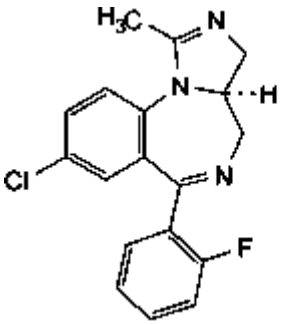
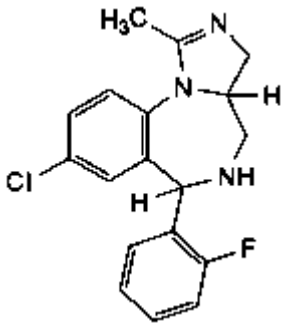


H. 6-chloro-4-(2-fluorophenyl)-2-methylquinazoline,



and enantiomer

I. (3a*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-3a,4-dihydro-3*H*-imidazo[1,5-*a*][1,4]benzodiazepine,



J. 8-chloro-6-(2-fluorophenyl)-1-methyl-3a,4,5,6-tetrahydro-3*H*-imidazo[1,5-*a*][1,4]benzodiazepine.

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Midazolam Injection

General Notices

Action and use

Benzodiazepine.

DEFINITION

Midazolam Injection is a sterile solution of Midazolam in Water for Injections containing Hydrochloric Acid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of midazolam, $C_{18}H_{13}ClFN_3$

95.0% to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume of the injection containing 20 mg of Midazolam add sufficient 5M *ammonia* to make the solution just alkaline, extract with two 10 mL quantities of *dichloromethane*, dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of midazolam *(RS 235)*.

B. In the test for Related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as that due to Midazolam in the chromatogram obtained with solution (3).

TESTS

Acidity

pH, 2.9 to 3.7, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Allow all the solutions to stand protected from light for at least 2 hours before testing.

(1) Dilute a volume of the injection containing 10 mg of Midazolam to 20 mL with the mobile phase.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.001% w/v of each of N-*desalkylflurazepam BPCRS* and *midazolam BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP-18 non-endcapped is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to continue for 3 times the retention time of the principal peak.

MOBILE PHASE

72 volumes of *methanol* and 28 volumes of a solution prepared by mixing equal volumes of 0.1M *orthophosphoric acid* and 0.03M *triethylamine*, and adjust the pH to 3.5 by the addition of 0.1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to midazolam and *N*-desalkylflurazepam is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Allow all the solutions to stand protected from light for at least 2 hours before testing.

(1) Dilute a volume of the injection containing 10 mg of Midazolam to 100 mL with the mobile phase.

(2) 0.01% w/v of *midazolam BPCRS* in the mobile phase.

(3) 0.001% w/v of each of N-*desalkylflurazepam BPCRS* and *midazolam BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to midazolam and *N*-desalkylflurazepam is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{13}ClFN_3$ in the injection using the declared content of $C_{18}H_{13}ClFN_3$ in *midazolam BPCRS*.

STORAGE

Midazolam Injection should be stored protected from light.

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Midazolam Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Benzodiazepine; premedicant sedative.

DEFINITION

Midazolam Oral Solution is a solution of Midazolam in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of midazolam, $C_{18}H_{13}ClFN_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume of the oral solution containing 20 mg of Midazolam add sufficient 5M *ammonia* to make the solution just alkaline, extract with two 10-mL quantities of *dichloromethane*, dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of midazolam *(RS 235)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Allow the solutions to stand protected from light for at least 2 hours before testing.

(1) Dilute a volume of the oral solution containing 10 mg of Midazolam to 20 mL with the mobile phase and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.001% w/v of each of N-*desalkylflurazepam BPCRS* and *midazolam BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP-18 non-endcapped is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3 times the retention time of the principal peak.

MOBILE PHASE

A mixture of 28 volumes of a solution prepared by mixing equal volumes of 0.1M *orthophosphoric acid* and 0.03M *triethylamine*, and adjusting the pH to 3.5 by the addition of 0.1M *sodium hydroxide*, and 72 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to midazolam and *N*-desalkylflurazepam is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Allow the solutions to stand protected from light for at least 2 hours before testing.

(1) Dilute a volume of the oral solution containing 10 mg of Midazolam to 100 mL with the mobile phase and filter (Whatman GF/C is suitable).

(2) 0.01% w/v of *midazolam BPCRS* in the mobile phase.

(3) 0.001% w/v each of N-*desalkylflurazepam BPCRS* and *midazolam BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to midazolam and *N*-desalkylflurazepam is at least 3.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{18}H_{13}ClFN_3$, weight in volume, using the declared content of $C_{18}H_{13}ClFN_3$ in *midazolam BPCRS*.

STORAGE

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Midazolam Oral Solution should be protected from light.

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Midazolam Oromucosal Solution

General Notices

Action and use

Benzodiazepine; premedicant sedative.

DEFINITION

Midazolam Oromucosal Solution is a solution of Midazolam containing hydrochloric acid and/or sodium chloride.

The oromucosal solution complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of midazolam, $C_{18}H_{13}ClFN_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume of the oromucosal solution containing 20 mg of Midazolam add sufficient 5M *ammonia* to make the solution just alkaline, extract with two 10-mL quantities of *dichloromethane*, dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of midazolam *(RS 235)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.9 to 3.7, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase. Allow all of the solutions to stand protected from light for at least 2 hours before testing.

(1) Dilute a volume of the oromucosal solution containing 10 mg of Midazolam to 20 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.001% w/v each of N-*desalkylflurazepam BPCRS* and *midazolam BPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP-18 non-endcapped is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of the principal peak.

MOBILE PHASE

28 volumes of a solution prepared by mixing equal volumes of 0.1M *orthophosphoric acid* and 0.03M *triethylamine*, adjusting the pH to 3.5 with 0.1M *sodium hydroxide*, and 72 volumes of *methanol*.

When the chromatograms are recorded using the prescribed conditions the retention times relative to midazolam (retention time about 6 minutes) are: impurity D = about 0.6; impurity F = about 0.8; impurity B = about 2.1; impurity H = about 2.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to midazolam and *N*-desalkylflurazepam is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. Allow all of the solutions to stand protected from light for at least 2 hours before testing.

(1) Dilute a volume of the oromucosal solution containing 10 mg of Midazolam to 100 mL.

(2) 0.01% w/v of *midazolam BPCRS*.

(3) 0.001% w/v each of N-*desalkylflurazepam BPCRS* and *midazolam BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to midazolam and *N*-desalkylflurazepam is at least 3.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oromucosal solution, Appendix V G, and calculate the content of $C_{18}H_{13}ClFN_3$, weight in volume, using the declared content of $C_{18}H_{13}ClFN_3$ in *midazolam BPCRS*.

STORAGE

Midazolam Oromucosal Solution should be protected from light.

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Minocycline Capsules

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Minocycline Capsules contain Minocycline Hydrochloride Dihydrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of minocycline, $C_{23}H_{27}N_3O_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of the contents of the capsules containing the equivalent of 50 mg of minocycline in 10 mL of *methanol*, filter (0.45-µm nylon filter is suitable), evaporate the filtrate to dryness under a stream of *nitrogen* at 60°. The *infrared absorption spectrum* of the dried residue, Appendix II A. is concordant with the reference spectrum of minocycline (*RS 502*).

TESTS

Dissolution

Comply with the requirements for *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37° as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 348 nm, Appendix II B, using *water* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *minocycline hydrochloride BPCRS* in *water*, using *water* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of minocycline, $C_{23}H_{27}N_3O_7$, in the medium from the chromatograms obtained and using the declared content of $C_{23}H_{27}N_3O_7$,HCl in *minocycline hydrochloride BPCRS*. Each mg of $C_{23}H_{27}N_3O_7$,HCl is equivalent to 0.9261 mg of $C_{23}H_{27}N_3O_7$

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LIMITS

The amount of minocycline released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*, protected from light. Store the solutions at a temperature of 2° to 8° and use within 3 hours of preparation.

(1) Dissolve a quantity of the contents of the capsules containing the equivalent of 50 mg of minocycline with *water*, dilute to 100 mL with the same solvent and filter.
(2) Dilute 1 volume of solution (1) 100 volumes.
(3) Dissolve 2 mg of *minocycline for system suitability EPCRS* in water and dilute to 5 mL.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Sunniest C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of about 40°.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) and solution (3) allow the chromatography to proceed for 3 times the retention time of minocycline.

MOBILE PHASE

8 volumes of *tetrahydrofuran*, 12 volumes of *dimethylformamide*, 78 volumes of solution A.

Solution A 18 volumes of a 0.375% w/v solution of *sodium edetate* and 60 volumes of a 2.83% w/v solution of *ammonium oxalate*. Adjust the pH of the solution to pH 7.2 with *dilute ammonia*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to minocycline (retention time about 11 minutes) are impurity C, about 0.52; impurity H, about 0.55; impurity B, about 0.66; impurity A, about 0.74; impurity G, about 0.8; impurity F, about 0.9 and impurity E, about 2.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3);

the *resolution* between the peaks due to impurity C and impurity H is at least 1.5;

the *resolution* between the peaks due to impurity A and impurity G is at least 1.5;

the *resolution* between the peaks due to impurity F and minocycline is at least 1.5.

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The *signal-to-noise* ratio of the peak in the chromatogram obtained with solution (4) is at least 20

LIMITS

Identify the peaks due to impurity E, impurity F and impurity G using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: impurity E, 1.6; impurity F, 1.6 and impurity G, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity B is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

the area of any peak corresponding to impurity C or impurity E is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity F or impurity G is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity H is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other secondary peaks is not greater than 0.2 times the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any secondary peaks is not greater than 3.5 times the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Loss on drying

When dried at 105° for 2 hours, the contents of the capsules lose not more than 12% of their weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light. Store the solutions at a temperature of 2° to 8° and use within 3 hours of preparation.

(1) Shake a quantity of mixed contents of 20 capsules containing the equivalent of 112 mg of minocycline in *water*, dilute to 200 mL with the same solvent, filter and use the filtrate.
(2) 0.06% w/v of *minocycline hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

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Calculate the content of minocycline, $C_{23}H_{27}N_3O_7$ in the capsules using the declared content of $C_{23}H_{27}N_3O_7$,HCl in *minocycline hydrochloride BPCRS*. Each mg of $C_{23}H_{27}N_3O_7$,HCl is equivalent to 0.9261 mg of $C_{23}H_{27}N_3O_7$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of minocycline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Minocycline Hydrochloride Dihydrate*.

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Minocycline Hydrochloride Dihydrate

General Notices

Minocycline Hydrochloride

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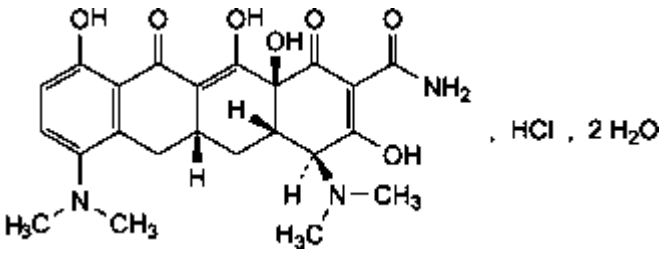

$C_{23}H_{28}ClN_3O_7,2H_2O$ 530.0 *128420-71-3*

Action and use

Tetracycline antibacterial.

Preparations

Minocycline Capsules

Minocycline Prolonged-release Capsules

Minocycline Tablets

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DEFINITION

(4*S*,4a*S*,5a*R*,12a*S*)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride dihydrate.

Semi-synthetic product derived from a fermentation product.

Content

94.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

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Yellow, hygroscopic, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *minocycline hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *minocycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *minocycline hydrochloride CRS* and 5 mg of *oxytetracycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

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Solution S

Dissolve 0.200 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 450 nm using a 1 cm cell is not greater than 0.23.

Dilute 1.0 mL of solution S to 10.0 mL with *water R*.

pH (*2.2.3*)

3.5 to 4.5 for solution S.

Light-absorbing impurities

Carry out the measurement within 1 h of preparing solution S.

The absorbance (*2.2.25*) of solution S measured at 560 nm is not greater than 0.06.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light. Store the solutions at 2-8 °C and use them within 3 h of preparation.*

Solution A Mix 18 volumes of a 3.75 g/L solution of *sodium edetate R* and 60 volumes of a 28.3 g/L solution of *ammonium oxalate R* and adjust to pH 7.2 with *dilute ammonia R2*.

Test solution Dissolve 24.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 2 mg of *minocycline for system suitability CRS* (containing impurities A, B, C, E, F, G and H) in *water R* and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *tetrahydrofuran R*, *dimethylformamide R*, solution A (8:12:78 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

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Run time 3 times the retention time of minocycline.

Identification of impurities Use the chromatogram supplied with *minocycline for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, E, F, G and H.

Relative retention With reference to minocycline (retention time = about 16 min): impurity C = about 0.52; impurity H = about 0.55; impurity B = about 0.66; impurity A = about 0.74; impurity G = about 0.79; impurity F = about 0.92; impurity E = about 2.6.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities C and H; minimum 1.5 between the peaks due to impurities A and G; minimum 1.5 between the peaks due to impurity F and minocycline.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 1.6; impurity F = 1.6; impurity G = 1.4;

— for each impurity, use the concentration of minocycline hydrochloride dihydrate in reference solution (a).

Limits:

— *impurity A*: maximum 1.2 per cent;

— *impurity B*: maximum 0.8 per cent;

— *impurities C, E*: for each impurity, maximum 0.6 per cent;

— *impurities F, G*: for each impurity, maximum 0.5 per cent;

— *impurity H*: maximum 0.3 per cent;

— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 3.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

5.0 per cent to 8.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 1.25 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Test solution Dissolve 30.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 30.0 mg of *minocycline hydrochloride CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Injection Test solution and reference solution.

Calculate the percentage content of $C_{23}H_{28}ClN_3O_7$ taking into account the assigned content of *minocycline hydrochloride CRS*.

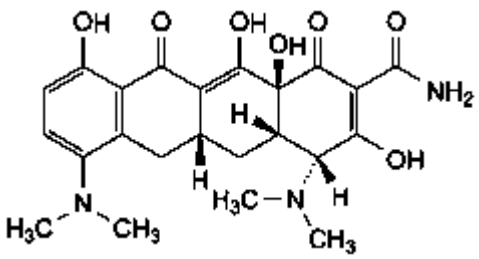
STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

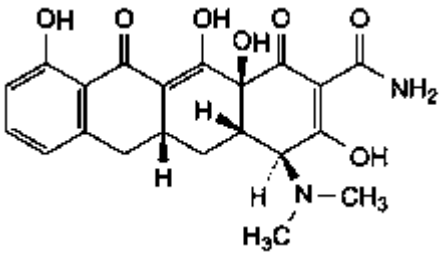
IMPURITIES

Specified impurities *A, B, C, E, F, G, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, I.*



A. (4*R*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epiminocycline),



B. (4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (sancycline),

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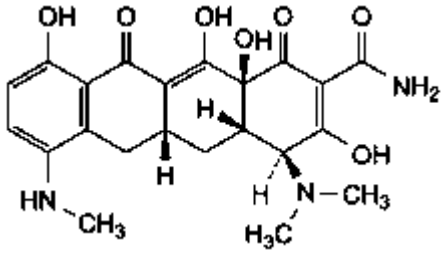
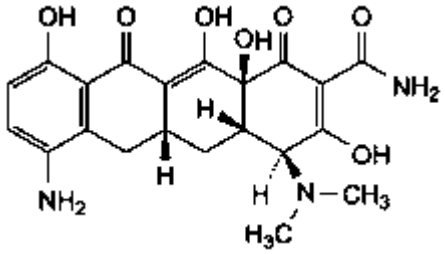
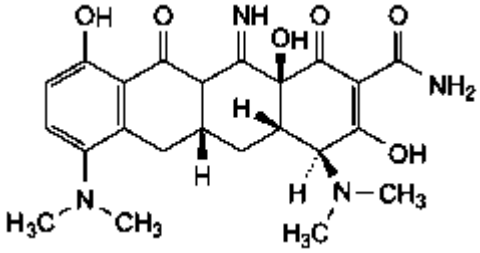


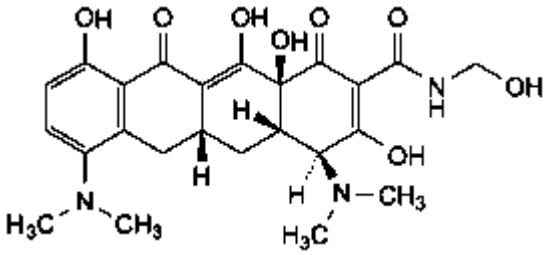
C. (4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-7-(methylamino)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (7-monodemethylminocycline),



D. (4*S*,4a*S*,5a*R*,12a*S*)-7-amino-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (7-aminosancycline),



E. (4*S*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12a-trihydroxy-12-imino-1,11-dioxo-1,4,4a,5,5a,6,11,11a,12,12a-decahydrotetracene-2-carboxamide,



F. (4*S*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-*N*-(hydroxymethyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide,

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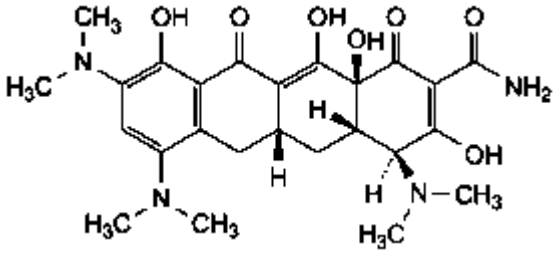
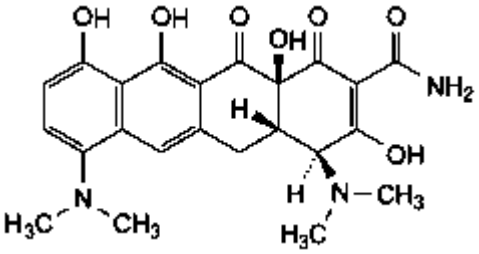
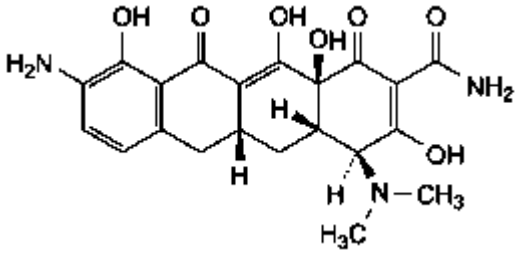


G. (4*S*,4a*S*,5a*R*,12a*S*)-4,7,9-tris(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide,



H. (4*S*,4a*S*,12a*S*)-4,7-bis(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide,



I. (4*S*,4a*S*,5a*R*,12a*S*)-9-amino-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (9-aminosancycline).

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Minocycline Prolonged-Release Capsules

General Notices

Minocycline Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Tetracycline antibacterial.

DEFINITION

Minocycline Prolonged-release Capsules contain Minocycline Hydrochloride Dihydrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Minocycline Hydrochloride Dihydrate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of minocycline, $C_{23}H_{27}N_3O_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of the contents of the capsules containing the equivalent containing 50 mg of minocycline to 10 mL of *methanol*, filter (0.45-µm nylon filter is suitable), evaporate the filtrate to dryness under a stream of *nitrogen* at 60 °. The *infrared absorption* spectrum of the dried residue, *Appendix II A*, is concordant with the reference spectrum of minocycline (*RS 502*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*, protected from light. Store the solutions at a temperature of 2° to 8° and use within 3 hours of preparation.

(1) Dissolve a quantity of the of the contents of the capsules containing the equivalent of 50 mg of minocycline with *water*, dilute to 100 mL with the same solvent and filter.

(2) Dilute 1 volume of solution (1) 100 volumes.

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(3) Dissolve 2 mg of *minocycline for system suitability EPCRS* in *water* and dilute to 5 mL.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Sunniest C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of about 40°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) and solution (3) allow the chromatography to proceed for 3 times the retention time of minocycline.

MOBILE PHASE

8 volumes of *tetrahydrofuran*, 12 volumes of *dimethylformamide*, 78 volumes of solution A.

Solution A 18 volumes of a 0.375% w/v solution of *sodium edetate* and 60 volumes of a 2.83% w/v solution of *ammonium oxalate*. Adjust the pH of the solution to pH 7.2 with *dilute ammonia*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to minocycline (retention time about 11 minutes) are impurity C, about 0.52; impurity H, about 0.55; impurity B, about 0.66; impurity A, about 0.74; impurity G, about 0.8; impurity F, about 0.9 and impurity E, about 2.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity C and impurity H is at least 1.5;

the *resolution* between the peaks due to impurity A and impurity G is at least 1.5;

the *resolution* between the peaks due to impurity F and minocycline is at least 1.5.

The *signal-to-noise* ratio of the peak in the chromatogram obtained with solution (4) is at least 20

LIMITS

Identify the peaks due to impurity E, impurity F and impurity G using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: impurity E, 1.6; impurity F, 1.6 and impurity G, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity B is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

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the area of any peak corresponding to impurity C or impurity E is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity F or impurity G is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity H is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.2 times the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3.5 times the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light. Store the solutions at a temperature of 2° to 8° and use within 3 hours of preparation.

(1) Shake a quantity of mixed contents of 20 capsules containing the equivalent of 112 mg of minocycline in *water*, dilute to 200 mL with the same solvent, filter and use the filtrate.
(2) 0.06% w/v of *minocycline hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of minocycline, $C_{23}H_{27}N_3O_7$ in the tablets using the declared content of $C_{23}H_{27}N_3O_7$,HCl in *minocycline hydrochloride BPCRS*. Each mg of $C_{23}H_{27}N_3O_7$,HCl is equivalent to 0.9261 mg of $C_{23}H_{27}N_3O_7$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of minocycline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Minocycline Hydrochloride Dihydrate.

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Minocycline Tablets

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Minocycline Tablets contain Minocycline Hydrochloride Dihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of minocycline, $C_{23}H_{27}N_3O_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of powdered tablets containing the equivalent of 50 mg of minocycline in 10 mL of *methanol*, filter (0.45-µm nylon filter is suitable) and evaporate the filtrate to dryness under a stream of *nitrogen* at 60°. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the reference spectrum of minocycline (*RS 502*).

TESTS

Dissolution

Comply with the requirements stated under *dissolution test for tablets and capsules*, Appendix XII B.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10-mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with *water* if necessary at the maximum at 348 nm, Appendix II B, using *water* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *minocycline hydrochloride BPCRS* in *water* using *water* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of minocycline, $C_{23}H_{27}N_3O_7$, in the medium from the *absorbance* obtained and using the declared content of $C_{23}H_{27}N_3O_7$,HCl in *minocycline hydrochloride BPCRS*. Each mg of $C_{23}H_{27}N_3O_7$,HCl is equivalent to 0.9261 mg of $C_{23}H_{27}N_3O_7$.

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LIMITS

The amount of minocycline released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*, protected from light. Store the solutions at a temperature of 2° to 8° and use within 3 hours of preparation.

(1) Dissolve a quantity of the powdered tablets containing the equivalent of 50 mg of minocycline with *water*, dilute to 100 mL with the same solvent and filter.
(2) Dilute 1 volume of solution (1) 100 volumes.
(3) Dissolve 2 mg of *minocycline for system suitability EPCRS* in water and dilute to 5 mL.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Sunniest C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of about 40°.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) and solution (3) allow the chromatography to proceed for 3 times the retention time of minocycline.

MOBILE PHASE

8 volumes of *tetrahydrofuran*, 12 volumes of *dimethylformamide*and 78 volumes of solution A.

Solution A 18 volumes of a 0.375% w/v solution of *sodium edetate* and 60 volumes of a 2.83% w/v solution of *ammonium oxalate*. Adjust the pH of the solution to pH 7.2 with *dilute ammonia*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to minocycline (retention time about 11 minutes) are: impurity C, about 0.52; impurity H, about 0.55; impurity B, about 0.66; impurity A, about 0.74; impurity G, about 0.8; impurity F, about 0.9 and impurity E, about 2.1.

SYSTEM SUITABILITY

The test is not valid unless:

In the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity C and impurity H is at least 1.5;

the *resolution* between the peaks due to impurity A and impurity G is at least 1.5;

the *resolution* between the peaks due to impurity F and minocycline is at least 1.5.

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The *signal-to-noise* ratio of the peak in the chromatogram obtained with solution (4) is at least 20

LIMITS

Identify the peaks due to impurity E, impurity F and impurity G using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: impurity E, 1.6; impurity F, 1.6 and impurity G, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity B is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

the area of any peak corresponding to impurity C or impurity E is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity F or impurity G is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity H is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light. Store the solutions at a temperature of 2° to 8° and use within 3 hours of preparation.

(1) Shake a quantity of the powdered tablets containing the equivalent of 112 mg of minocycline in *water*, dilute to 200 mL with the same solvent, filter and use the filtrate.
(2) 0.06% w/v of *minocycline hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of minocycline, $C_{23}H_{27}N_3O_7$ in the tablets using the declared content of $C_{23}H_{27}N_3O_7$,HCl in *minocycline hydrochloride BPCRS*. Each mg of $C_{23}H_{27}N_3O_7$,HCl is equivalent to 0.9261 mg of $C_{23}H_{27}N_3O_7$.

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LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of minocycline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Minocycline Hydrochloride Dihydrate.

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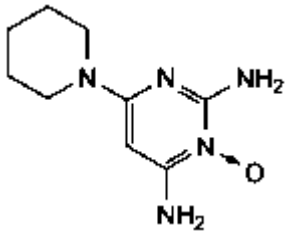
Minoxidil

General Notices

(Ph. Eur. monograph 0937)



$C_9H_{15}N_5O$ 209.3 *38304-91-5*

Action and use

Vasodilator; treatment of hypertension; male pattern baldness.

Preparation

Minoxidil Scalp Application

Ph Eur

DEFINITION

6-(Piperidin-1-yl)pyrimidine-2,4-diamine 3-oxide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, soluble in methanol and in propylene glycol.

IDENTIFICATION

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First identification: B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution (a) Dissolve 20.0 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid (solution A). Dilute 2.0 mL of solution A to 100.0 mL with *0.1 M hydrochloric acid*.

Test solution (b) Dilute 2.0 mL of solution A to 100.0 mL with *0.1 M sodium hydroxide*.

Spectral range 200-350 nm.

Absorption maxima At 230 nm and 281 nm for test solution (a); at 230 nm, 262 nm and 288 nm for test solution (b).

Specific absorbances at the absorption maxima:

— at 230 nm: 1015 to 1120 for test solution (a); 1525 to 1685 for test solution (b);

— at 262 nm: 485 to 535 for test solution (b);

— at 281 nm: 1060 to 1170 for test solution (a);

— at 288 nm: 555 to 605 for test solution (b).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *minoxidil CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *minoxidil CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R* (1.5:100 *V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

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D. Dissolve about 10 mg in 1 mL of *methanol R*. Add 0.1 mL of *copper sulfate solution R*. A green colour develops. The solution becomes greenish-yellow on the addition of 0.1 mL of *dilute hydrochloric acid R*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 12.5 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *minoxidil for system suitability CRS* (containing impurities A, B and E) in the mobile phase and dilute to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (2.6 µm);

— *temperature*: 40 °C.

Mobile phase Solution containing 0.1 per cent *V/V* of *trifluoroacetic acid R* and 2 g/L of *sodium heptanesulfonate R* in a mixture of 45 volumes of *methanol R* and 55 volumes of *water for chromatography R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Run time Twice the retention time of minoxidil.

Identification of impurities Use the chromatogram supplied with *minoxidil for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and E.

Relative retention With reference to minoxidil (retention time = about 5 min): impurity A = about 0.3; impurity B = about 0.4; impurity E = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B; minimum 2.0 between the peaks due to minoxidil and impurity E.

Calculation of percentage contents:

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— for impurity B, multiply the peak area by the correction factor 1.6;

— for each impurity, use the concentration of minoxidil in reference solution (a).

Limits:

— *impurity E*: maximum 0.2 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 20.93 mg of $C_9H_{15}N_5O$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities B, E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.

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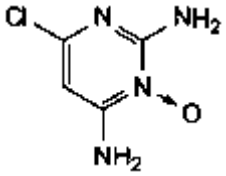
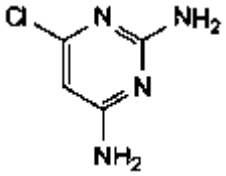
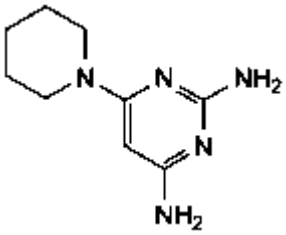


A. 6-chloropyrimidine-2,4-diamine 3-oxide,



B. 6-chloropyrimidine-2,4-diamine,



E. 6-(piperidin-1-yl)pyrimidine-2,4-diamine (deoxyminoxidil).

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Minoxidil Scalp Application

General Notices

Minoxidil Scalp Cutaneous Solution

Action and use

Vasodilator; treatment of hypertension; male pattern baldness.

DEFINITION

Minoxidil Scalp Application is a *cutaneous solution* of Minoxidil in a suitable ethanolic solvent.

The scalp application complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of minoxidil, $C_9H_{15}N_5O$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

Evaporate a volume of the scalp application containing about 50 mg of Minoxidil to dryness at a temperature of about 50° under a stream of nitrogen. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of minoxidil *(RS 376)*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the scalp application with the mobile phase to produce a solution containing 0.025% w/v of Minoxidil.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.
(4) Dissolve 5 mg of *minoxidil for system suitability EPCRS* (containing impurities A, B and E) in the mobile phase and dilute to 20.0 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex XB-C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 10 µL of each solution.

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MOBILE PHASE

0.1% v/v of *trifluoroacetic acid* and 0.01M of *sodium heptanesulfonate* in a mixture of 45 volumes of *methanol* and 55 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5 and the *resolution* between the peaks due to minoxidil and impurity E is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity B using solution (4) and the chromatogram supplied with *minoxidil for system suitability EPCRS* and multiply the area of this peak by a correction factor of 1.6.

the area of any *secondary peak* is not greater than the area of the principal peak obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than 0.5 times that of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.025% w/v of Minoxidil, prepared by serial dilution of the scalp application with the mobile phase.
(2) 0.025% w/v of *minoxidil BPCRS* in the mobile phase.
(3) Dissolve 5 mg of *minoxidil for system suitability EPCRS* (containing impurities A, B and E) in the mobile phase and dilute to 20.0 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under Related substances but with a detection wavelength of 254 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5 and the *resolution* between minoxidil and impurity E is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{15}N_5O$ in the scalp application using the declared content of $C_9H_{15}N_5O$ in *minoxidil BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Minoxidil.

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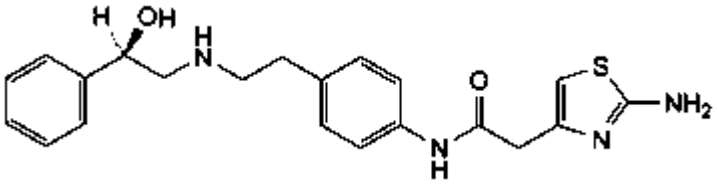
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Mirabegron

General Notices

(Ph. Eur. monograph 3132)



$C_{21}H_{24}N_4O_2S$ 396.5 *223673-61-8*

Action and use

$Beta_3$-adrenoceptor agonist; treatment of overactive bladder syndrome.

Ph Eur

DEFINITION

2-(2-Amino-1,3-thiazol-4-yl)-*N*-[4-[2-[[(2*R*)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]acetamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble to slightly soluble in anhydrous ethanol, very slightly soluble to practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *mirabegron CRS*.

B. It complies with the limit given for impurity A in the test *Enantiomeric purity and impurity B* (see Tests).

TESTS

Enantiomeric purity and impurity B

Liquid chromatography (*2.2.29*). *Store the solutions protected from light*.

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 4 mg of *mirabegron racemate CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *mirabegron impurity B CRS* in the solvent mixture and dilute to 50 mL with the solvent mixture. Dilute 1 mL of this solution and 1 mL of reference solution (b) to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *beta-cyclodextrin derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 50 °C.

Mobile phase Mix 200 volumes of *acetonitrile for chromatography R* and 750 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R*, previously adjusted to pH 4.0 with a 10 per cent *V/V* solution of *phosphoric acid R*.

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of the test solution and reference solutions (a) and (c).

Run time Twice the retention time of mirabegron.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to mirabegron (retention time = about 27 min): impurity B = about 0.7; impurity A = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurity A and mirabegron and minimum 2.0 between the peaks due to impurities A and B.

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Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 1.6;

— for impurities A and B, use the concentration of mirabegron in reference solution (a).

Limits:

— *impurity A ((S)-enantiomer)*: maximum 0.2 per cent;

— *impurity B*: maximum 0.10 per cent;

— *reporting threshold for impurity B*: 0.05 per cent.

Related substances

Liquid chromatography (2.2.29). *Store the solutions at 2-8 °C, protected from light*.

Solvent mixture A acetonitrile R, tetrahydrofuran for chromatography R (33:67 *V/V*).

Solvent mixture B 14 g/L solution of sodium perchlorate R, adjusted to pH 2.0 with perchloric acid R.

Test solution (a) Dissolve 0.100 g of the substance to be examined in solvent mixture A and dilute to 10.0 mL with the same solvent mixture.

Test solution (b) Dilute 2.0 mL of test solution (a) to 20.0 mL with solvent mixture B.

Reference solution (a) Dilute 1.0 mL of test solution (b) to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of mirabegron impurity C CRS in mobile phase A and dilute to 100 mL with mobile phase A. Dilute 3 mL of this solution to 10 mL with mobile phase A. Dilute 1 mL of this solution and 1 mL of test solution (a) to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: encapsulated octadecylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: solvent mixture A, solvent mixture B (10:80 *V/V*);

— *mobile phase B*: acetonitrile R;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 55	100 → 30	0 → 70
55 - 65	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Autosampler Set at 5 °C.

Injection 10 µL of test solution (b) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to mirabegron (retention time = about 12 min): impurity C = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 6.5 between the peaks due to mirabegron and impurity C.

Calculation of percentage contents:

— for each impurity, use the concentration of mirabegron in reference solution (a).

Limits:

— *impurity C*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total, including impurity B* (determined in the test *Enantiomeric purity and impurity B*): maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Impurities E, F, G

Liquid chromatography (2.2.29). *Store the solutions protected from light*.

Solvent mixture Mobile phase B, *water R* (50:50 *V/V*).

Test solution Dissolve 0.300 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution Dissolve 6.1 mg of *4-nitrophenethylamine hydrochloride R* (impurity E), 5.0 mg of *mirabegron impurity F CRS* and 5.0 mg of *mirabegron impurity G CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 3.0 mL of the solution to

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25.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture. Dilute 3.0 mL of the solution obtained to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *encapsulated octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 14 g/L solution of *sodium perchlorate R*, adjusted to pH 2.0 with *perchloric acid R*;

— *mobile phase B*: *acetonitrile R*, *tetrahydrofuran for chromatography R* (33:67 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	85	15
10 - 15	85 → 70	15 → 30
15 - 30	70	30
30 - 40	70 → 35	30 → 65
40 - 50	35	65

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 290 nm.

Injection 15 µL.

Identification of impurities Use the chromatogram obtained with the reference solution to identify the peaks due to impurities E, F and G.

Relative retention With reference to mirabegron (retention time = about 13 min): impurity E = about 0.7; impurity F = about 1.6; impurity G = about 1.7.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 10 for the peaks due to impurities E, F and G;

— *repeatability*: maximum relative standard deviation of 10 per cent for the areas of the peaks due to impurities E, F and G, determined on 6 injections.

Limits:

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— *impurities E, F, G*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (30 ppm).

Impurity I

Gas chromatography (2.2.28).

Solvent mixture *N,N-diisopropylethylamine R*, *dimethylformamide R* (1:1000 *V/V*).

Test solution Dissolve 0.400 g of the substance to be examined in 1.0 mL of solvent mixture, using sonication. Add 9.0 mL of *heptane R* and shake for 45 min. Use the upper layer for injection.

Reference solution Dissolve 24.7 mg of *ethyl[(dimethylamino)propyl]carbodiimide hydrochloride R* (impurity I) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.5 mL of this solution to 25.0 mL with the solvent mixture. Dilute 3.0 mL of this solution to 10.0 mL with the solvent mixture. To 1.0 mL of the solution obtained, add 9.0 mL of *heptane R* and shake for 45 min. Use the upper layer for injection.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *base-deactivated phenyl(5)methyl(95)polysiloxane R* (film thickness 3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 15.0 mL/min.

Split ratio 1:1.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	140
	5 - 10	140 → 240
	10 - 30	240
Injection port		220
Detector		250

Detection Flame ionisation.

Injection 2 µL.

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Retention time Impurity I = about 4 min.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity I;

— *repeatability*: maximum relative standard deviation of 10 per cent determined on 6 injections.

Limit:

— *impurity I*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (30 ppm).

Water (2.5.32)

Maximum 0.2 per cent determined on 0.300 g by direct sample introduction.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29). *Store the solutions at 2-8 °C, protected from light*.

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.5 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution Dissolve 50.0 mg of *mirabegron CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.5 mL of the solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *encapsulated octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 45 °C.

Mobile phase Mix 800 volumes of a 14 g/L solution of *sodium perchlorate R*, previously adjusted to pH 2.0 with *perchloric acid R*, and 100 volumes of a mixture of *acetonitrile R* and *tetrahydrofuran for chromatography R* (33:67 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Autosampler Set at 5 °C.

Injection 10 µL.

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Run time Twice the retention time of mirabegron.

Retention time Mirabegron = about 13 min.

Calculate the percentage content of $C_{21}H_{24}N_4O_2S$ taking into account the assigned content of *mirabegron CRS*.

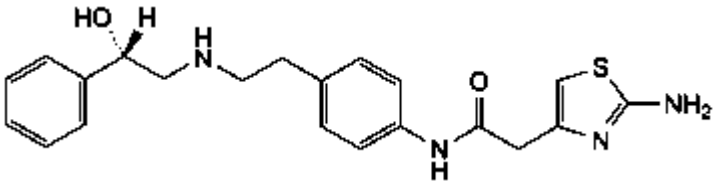
STORAGE

Protected from light.

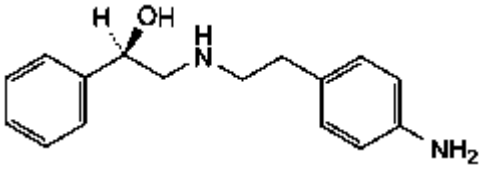
IMPURITIES

Specified impurities *A, B, C, E, F, G, I.*

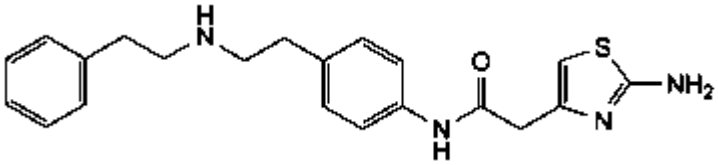
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



A. 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-[2-[[(2*S*)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]acetamide ((*S*)-enantiomer of mirabegron),



B. (1*R*)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethan-1-ol,



C. 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-[2-[(2-phenylethyl)amino]ethyl]phenyl]acetamide,

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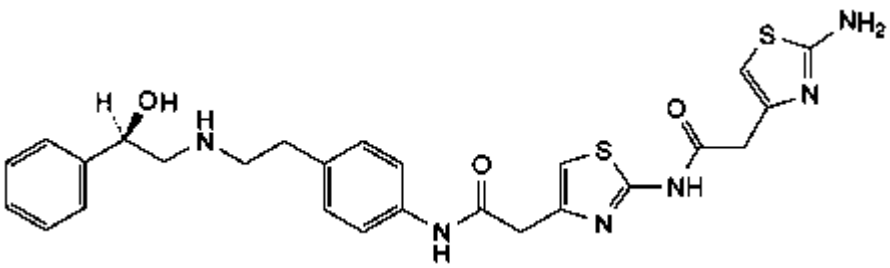
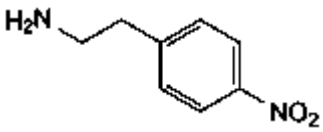
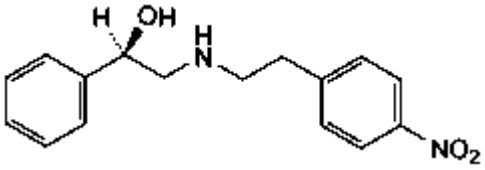


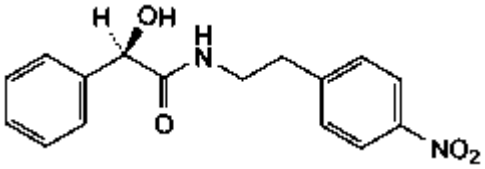
D. 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-[2-[4-[2-[[(2*R*)-2-hydroxy-2-phenylethyl]amino]ethyl]anilino]-2-oxoethyl]-1,3-thiazol-2-yl]acetamide,



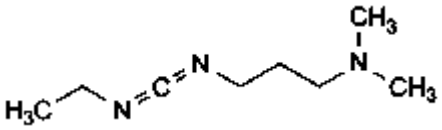
E. 2-(4-nitrophenyl)ethan-1-amine,



F. (1*R*)-2-[[2-(4-nitrophenyl)ethyl]amino]-1-phenylethan-1-ol,



G. (2*R*)-2-hydroxy-*N*-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide,



I. N^1-[(ethylimino)methylidene]-N^3,N^3-dimethylpropan-1,3-diamine.

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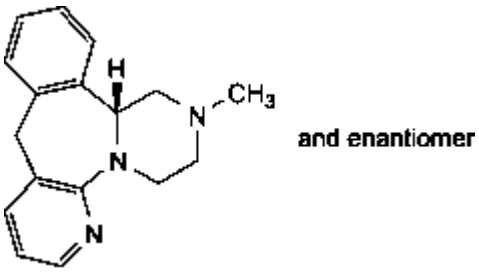
Mirtazapine

General Notices

(Ph. Eur. monograph 2338)



$C_{17}H_{19}N_3$ 265.4 *85650-52-8*

Action and use

Inhibitor of 5HT and noradrenaline reuptake; antidepressant.

Preparations

Mirtazapine Tablets

Mirtazapine Oral Solution

Mirtazapine Orodispersible Tablets

Ph Eur

DEFINITION

(14b*RS*)-2-Methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, slightly hygroscopic to hygroscopic.

Solubility

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Practically insoluble in water, freely soluble in anhydrous ethanol.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison mirtazapine CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in anhydrous ethanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Optical rotation (2.2.7)

-0.10° to + 0.10° (anhydrous substance).

Dissolve 0.250 g in anhydrous ethanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Buffer solution Dissolve 18.0 g of tetramethylammonium hydroxide R in 950 mL of water R. While stirring, adjust to pH 7.4 with phosphoric acid R, then dilute to 1000 mL with water R and mix.

Test solution Dissolve 30 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (a) Dissolve 3 mg of mirtazapine for system suitability CRS (containing impurities A, B, C, D, E and F) in 2 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase tetrahydrofuran for chromatography R, methanol R, acetonitrile R, buffer solution (7.5:12.5:15:65 *V/V/V/V*).

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time Twice the retention time of mirtazapine.

Identification of impurities Use the chromatogram supplied with *mirtazapine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention With reference to mirtazapine (retention time = about 25 min): impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.35; impurity D = about 0.4; impurity E = about 1.3; impurity F = about 1.35.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities E and F in the chromatogram obtained with reference solution (a);

— *symmetry factor*: 0.8 to 2.0 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.3; impurity B = 1.3; impurity F = 0.2;

— *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 3.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 35 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 13.27 mg of $C_{17}H_{19}N_3$.

STORAGE

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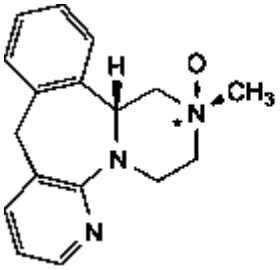
In an airtight container.

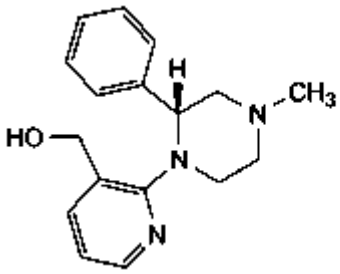
IMPURITIES

Specified impurities *A, B, C, D, E, F.*



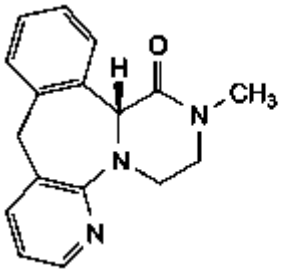
its epimer at N⁺ and their enantiomers

A. (14b*RS*)-2-methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine 2-oxide,



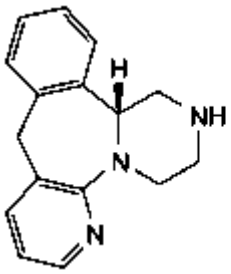
and enantiomer

B. [2-[(2*RS*)-4-methyl-2-phenylpiperazin-1-yl]pyridin-3-yl]methanol,



and enantiomer

C. (14b*RS*)-2-methyl-3,4,10,14b-tetrahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepin-1(2*H*)-one,



and enantiomer

D. (14b*RS*)-1,2,3,4,10,14b-hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine,

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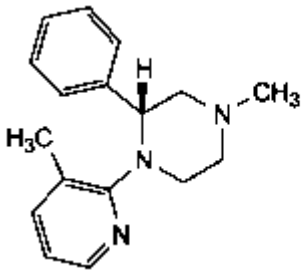
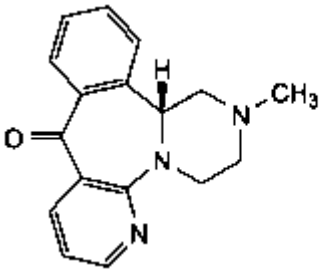


and enantiomer

E. (2*RS*)-4-methyl-1-(3-methylpyridin-2-yl)-2-phenylpiperazine,



and enantiomer

F. (14b*RS*)-2-methyl-1,3,4,14b-tetrahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepin-10(2*H*)-one.

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Mirtazapine Oral Solution

General Notices

Action and use

Inhibitor of 5HT and noradrenaline reuptake; antidepressant.

DEFINITION

Mirtazapine Oral Solution contains Mirtazapine in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of mirtazapine, $C_{17}H_{19}N_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the oral solution containing 50 mg of Mirtazapine with 12.5 mL of *water, add* 12.5 mL of *n-hexane*. Allow to separate, retain and filter the hexane layer and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of mirtazapine *(RS 434)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the oral solution containing 30 mg of Mirtazapine with 10 mL of the solvent mixture, dilute to 20 mL with the same solvent mixture and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

(3) 0.15% w/v of *mirtazapine for system suitability EPCRS* in a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

(4) Dilute 1 volume of solution (2) to 10 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 240 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of mirtazapine.

MOBILE PHASE

75 volumes of *tetrahydrofuran for chromatography*, 125 volumes of *methanol*, 150 volumes of *acetonitrile* and 650 volumes of a solution, previously adjusted to pH 7.4 with *orthophosphoric acid*, containing 1.8% w/v of *tetramethylammonium hydroxide*.

When the chromatograms are recorded using the prescribed conditions the retention time of mirtazapine is about 25 minutes. The retention times relative to mirtazapine are: impurity A, about 0.2; impurity B, about 0.3; impurity C, about 0.35; impurity D, about 0.4; impurity E, about 1.3; impurity F, about 1.35.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities E and F is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B and F using solution (3) and multiply the areas of these peaks by the corresponding correction factors: impurity A, 1.3; impurity B, 1.3; impurity F, 0.2.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity C is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution containing 90 mg of Mirtazapine to 100 mL with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*. Filter the solution and dilute 1 volume of the filtrate to 10 volumes with the same solvent mixture.

(2) 0.009% w/v of *mirtazapine BPCRS* in a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a detection wavelength of 290 nm.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (2) the *symmetry factor* of the peak corresponding to mirtazapine is in the range 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the content of mirtazapine, $C_{17}H_{19}N_3$, in the oral solution from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3$ in *mirtazapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mirtazapine.

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Mirtazapine Orodispersible Tablets

General Notices

Orodispersible Mirtazapine Tablets

Action and use

Inhibitor of 5HT and noradrenaline reuptake; antidepressant.

DEFINITION

Mirtazapine Orodispersible Tablets contain Mirtazapine in a suitable orodispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mirtazapine, $C_{17}H_{19}N_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the orodispersible tablets containing 50 mg of Mirtazapine with 12.5 mL of *water*, *add* 12.5 mL of *n-hexane*. Allow to separate, retain and filter the hexane layer and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of mirtazapine *(RS 434)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the mobile phase if necessary, to produce a solution expected to contain 0.0017% w/v of Mirtazapine.

(2) 0.0017% w/v of *mirtazapine BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 292 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile* and 80 volumes of a solution, previously adjusted to pH 3.0 with *dilute orthophosphoric acid*, containing 2 volumes of *triethylamine* and 1000 volumes of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Calculate the total content of mirtazapine, $C_{17}H_{19}N_3$, in the medium from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3$ in *mirtazapine BPCRS*.

LIMITS

The amount of mirtazapine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake with the aid of ultrasound a quantity of the powdered tablets containing 30 mg of Mirtazapine with 10 mL of a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*, dilute to 20 mL with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water* and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

(3) 0.15% w/v of *mirtazapine for system suitability EPCRS* in a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

(4) Dilute 1 volume of solution (2) to 10 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

75 volumes of *tetrahydrofuran for chromatography*, 125 volumes of *methanol*, 150 volumes of *acetonitrile* and 650 volumes of a solution, previously adjusted to pH 7.4 with *orthophosphoric acid*, containing 1.8% w/v of *tetramethylammonium hydroxide*.

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When the chromatograms are recorded using the prescribed conditions the retention time of mirtazapine is about 25 minutes. The retention times relative to mirtazapine are: impurity A, about 0.2; impurity B, about 0.3; impurity C, about 0.35; impurity D, about 0.4; impurity E, about 1.3; impurity F, about 1.35.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities E and F is at least 1.5;

in the chromatogram obtained with solution (4) the *signal-to-noise ratio* of the principal peak is at least 15.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B and F using solution (3) and multiply the areas of these peaks by the corresponding correction factors; impurity A, 1.3; impurity B, 1.3; impurity F, 0.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not more than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak due to impurity B is not more than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any peak due to impurity F is not more than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not more than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 90 mg of Mirtazapine with 50 mL of a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water* and add sufficient of a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water* to produce 100 mL. Filter the solution and dilute 1 volume of the filtrate to 10 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.
(2) 0.009% w/v of *mirtazapine BPCRS* in a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used with a detection wavelength of 290 nm.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (2) the *symmetry factor* of the peak corresponding to mirtazapine is between 0.8 to 2.0.

DETERMINATION OF CONTENT

Calculate the total content of mirtazapine, $C_{17}H_{19}N_3$, in the tablets from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3$ in *mirtazapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mirtazapine.

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Mirtazapine Tablets

General Notices

Action and use

Inhibitor of 5HT and noradrenaline reuptake; antidepressant.

DEFINITION

Mirtazapine Tablets contain Mirtazapine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mirtazapine, $C_{17}H_{19}N_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the powdered tablets containing 50 mg of Mirtazapine with 12.5 mL of *water*, add 12.5 mL of *n-hexane*, allow to separate, retain and filter the hexane layer and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of mirtazapine *(RS 434)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with mobile phase if necessary, expected to contain 0.0017% w/v of Mirtazapine.

(2) 0.0017% w/v of *mirtazapine BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm x 4 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 292 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile* and 80 volumes of a solution previously adjusted to pH 3.0, with *dilute orthophosphoric acid*, containing 2 volumes of *triethylamine* and 1000 volumes of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Calculate the total content of mirtazapine, $C_{17}H_{19}N_3$, in the medium from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3$ in *mirtazapine BPCRS*.

LIMITS

The amount of mirtazapine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake with the aid of ultrasound a quantity of the powdered tablets containing 30 mg of Mirtazapine with 10 mL of a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*, dilute to 20 mL with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water* and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*

(3) 0.15% w/v of *mirtazapine for system suitability EPCRS* in a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

(4) Dilute 1 volume of solution (2) to 10 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of mirtazapine.

MOBILE PHASE

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75 volumes of *tetrahydrofuran for chromatography*, 125 volumes of *methanol*, 150 volumes of *acetonitrile* and 650 volumes of a solution, previously adjusted to pH 7.4 with *orthophosphoric acid*, containing 1.8% w/v of *tetramethylammonium hydroxide*.

When the chromatograms are recorded using the prescribed conditions the retention time of mirtazapine is about 25 minutes. The retention times relative to mirtazapine are: impurity A, about 0.2; impurity B, about 0.3; impurity C, about 0.35; impurity D, about 0.4; impurity E, about 1.3; impurity F, about 1.35.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities E and F is at least 1.5;

in the chromatogram obtained with solution (4) the *signal-to-noise ratio* of the principal peak is at least 15.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B and F using solution (3) and multiply the areas of these peaks by the corresponding correction factors; impurity A, 1.3; impurity B, 1.3; impurity F, 0.2;

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not more than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak due to impurity B is not more than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any peak due to impurity F is not more than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not more than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 90 mg of Mirtazapine with 50 mL of a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water* and add sufficient of a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water* to produce 100 mL. Filter the solution and dilute 1 volume of the filtrate to 10 volumes with a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.
(2) 0.009% w/v of *mirtazapine BPCRS* in a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic procedure described under Related substances may be used with a detection wavelength of 290 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak corresponding to mirtazapine is between 0.8 to 2.0.

DETERMINATION OF CONTENT

Calculate the content of mirtazapine, $C_{17}H_{19}N_3$, in the tablets from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3$ in *mirtazapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mirtazapine.

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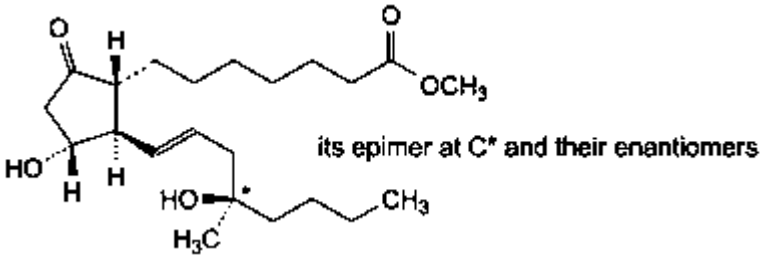
Misoprostol

General Notices

(Ph. Eur. monograph 1731)



$C_{22}H_{38}O_5$ 382.5 *59122-46-2*

Action and use

Prostaglandin (PGE1) analogue.

Ph Eur

DEFINITION

Mixture of methyl 7-[(1*RS*,2*RS*,3*RS*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*RS*,3*RS*)-3-hydroxy-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate.

The 4 stereoisomers are present in approximately equal proportions.

Content

96.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless or yellowish, oily liquid, hygroscopic.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent), sparingly soluble in acetonitrile.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison misoprostol CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions.*

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of misoprostol CRS in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of misoprostol for system suitability CRS (containing impurities A, B and C) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: silica gel for chromatography R (5 µm).

Mobile phase Mix 5 volumes of acetonitrile R1, 215 volumes of dioxan R, 780 volumes of heptane R and sonicate for 10 min.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 1.5 times the retention time of misoprostol.

Identification of impurities Use the chromatogram supplied with misoprostol for system suitability CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

Relative retention With reference to misoprostol (retention time = about 18 min): impurity C = about 0.2; impurity A = about 0.7; impurity B (1^{st} peak) = about 0.85; impurity B (2^{nd} peak) = about 0.91.

System suitability Reference solution (c):

— resolution: minimum 1.2 between the peaks due to impurity B (2^{nd} peak) and misoprostol.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.13;

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— *impurity B* (sum of 1st and 2nd peaks): not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Diastereoisomers

Liquid chromatography (2.2.29). *Use freshly prepared solutions.*

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 20 volumes of *2-propanol R*, 40 volumes of *anhydrous ethanol R*, 940 volumes of *heptane R* and sonicate for 10 min.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL.

Run time 1.5 times the retention time of the 1st peak of misoprostol.

Retention time Misoprostol 1st peak = about 19 min; misoprostol 2nd peak = about 21 min.

System suitability Test solution:

— *resolution*: minimum 2.0 between the 1st and 2nd peaks of misoprostol.

Limit:

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— *1st peak of misoprostol*: 45 per cent to 55 per cent of the sum of the areas of the 2 peaks due to misoprostol.

Water (2.5.32)

Maximum 1.0 per cent.

Use 1.0 mL of a 10 mg/mL solution of the substance to be examined in *methanol R*.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection 20 µL of the test solution and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 3.7 for the peak due to misoprostol.

Calculate the percentage content of $C_{22}H_{38}O_5$ using the declared content of *misoprostol CRS*.

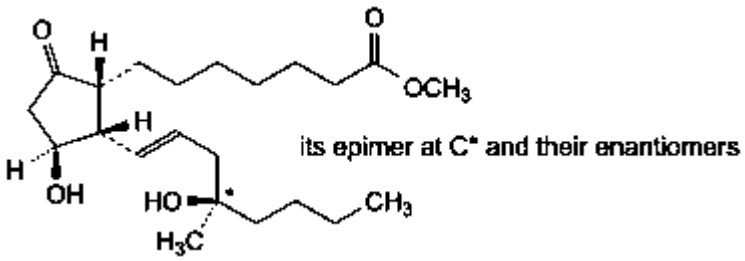
STORAGE

In an airtight container, at -20 °C.

IMPURITIES

Specified impurities *A, B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, F.*



A. mixture of methyl 7-[(1*RS*,2*SR*,3*SR*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*SR*,3*SR*)-3-hydroxy-2-[(1E,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate (8-epimisoprostol),

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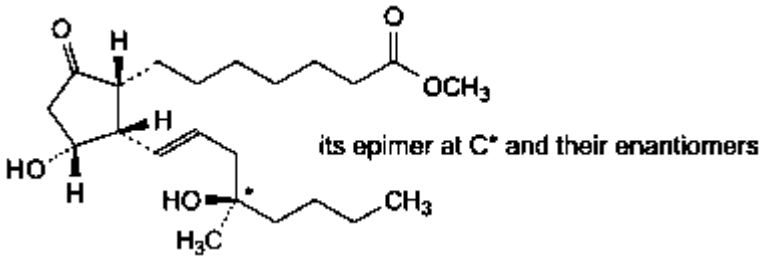
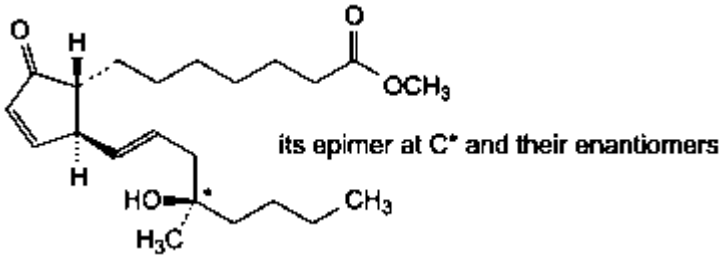
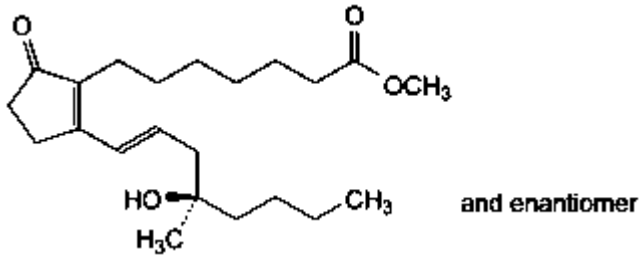


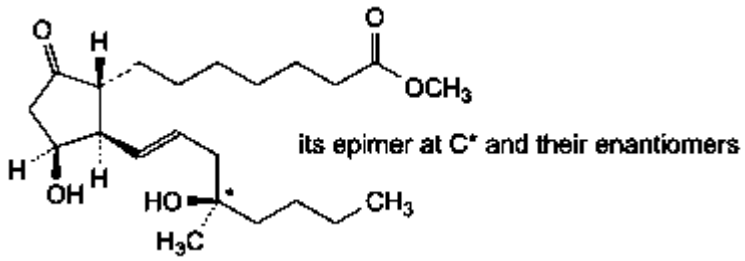
B. mixture of methyl 7-[(1*RS*,2*SR*,3*RS*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*SR*,3*RS*)-3-hydroxy-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate (12-epimisoprostol),



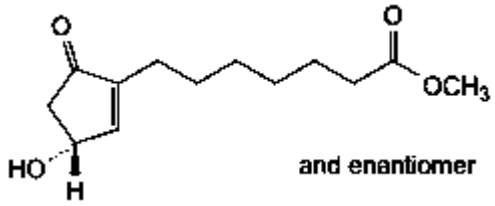
C. mixture of methyl 7-[(1*RS*,2*SR*)-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopent-3-enyl]heptanoate and methyl 7-[(1*RS*,2*SR*)-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopent-3-enyl]heptanoate (misoprostol A),



D. methyl 7-[2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopent-1-enyl]heptanoate (misoprostol B),



E. mixture of methyl 7-[(1*RS*,2*RS*,3*SR*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*RS*,3*SR*)-3-hydroxy-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate (11-epi misoprostol),



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F. methyl 7-[(3*RS*)-3-hydroxy-5-oxocyclopent-1-enyl]heptanoate.

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Mites for Allergen Products

General Notices

(Ph. Eur. monograph 2625)

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DEFINITION

Mites for allergen products are inactivated mite cultures that may consist of faecal particles, mite bodies, mite parts, eggs, larvae and residues from the growth medium. They contain soluble substances, including proteins, whose functional activity is unrelated to any antigenic and allergenic properties they may have.

PRODUCTION

Mites for allergen products are obtained from cultivation techniques. The method of mite cultivation is described and must ensure the quality, homogeneity and traceability of the mites. Critical cultivation parameters such as temperature and humidity are controlled and monitored. Unless otherwise justified, the culture medium is selected to avoid the presence of materials with potential allergenicity. Appropriate measures are taken to avoid contamination by foreign mite cultures. Mite cultures are macroscopically free of moulds.

After cultivation, the mite culture is inactivated by methods whose capability to maintain allergenic properties are qualified.

Certain mite fractions (e.g. mite bodies or mite faeces) may be purified or enriched before the initiation of the active substance manufacture. In these cases, the process must be performed using qualified methods.

Where major changes to the production of the mites take place (e.g. when a new process or supplier of mites is introduced), such changes are qualified.

Microbial contamination of the mite culture may be unavoidable and should be monitored on a representative number of batches of mites according to a justified sampling plan, and each time a new supplier and/or a new process for the mites production is introduced; if a determination of microbial contamination is not applicable, this must be justified. Microbial contamination values and potential increases in microbial contamination are monitored during stability studies, in order to assess this aspect along with the mites for allergen products characteristics upon storage.

Control methods and acceptance criteria relating to identity and purity of the mites are established. The acceptance criteria must ensure the consistency of the mite source material from a qualitative and quantitative point of view. The mite source material is stored under controlled conditions justified by stability data. The collection and production, as well as the handling of the source material, are such that consistent composition is ensured from batch to batch.

MITES FOR ALLERGEN PRODUCTS REFERENCE BATCH

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An appropriate reference batch is established for each species. The nature of the reference batch depends on the testing approach to verify batch-to-batch consistency and to establish acceptable quality. The reference batch may be, for example, an internal reference preparation (if available), a source material extract or a sample of a production batch. Its characterisation must be described. The extent of characterisation of the reference batch depends on the mite source material, knowledge of the allergenic components and availability of suitable reagents. The reference batch is stored under controlled conditions ensuring its stability.

BATCH-TO-BATCH CONSISTENCY

To establish batch-to-batch consistency, one or more of the following tests are performed on each batch. The choice of tests must be justified.

Total protein (*2.5.33*)

Protein profile

Determined by using suitable electrophoresis methods (*2.2.31*, *2.2.54*).

Allergen profile

Relevant allergenic components are identified by means of suitable techniques using allergen-specific antibodies.

Major allergen content

Determined by using suitable immunochemical methods (*2.7.1*) such as enzyme-linked immunosorbent assay (ELISA).

Total allergenic activity

Determined by testing inhibition of the binding capacity of specific immunoglobulin E antibodies or by a suitable equivalent *in vitro* method.

CHARACTERS

Mites for allergen products are supplied as yellow to brown powders, which may contain one or more of the following: mite bodies, parts, eggs, larvae and faecal particles. The mite source material may contain residual amounts of medium components.

IDENTIFICATION

The identity of the mite species is confirmed by their relevant macroscopic (e.g. colour, appearance) and microscopic (e.g. shape of the mites, size of their legs, number and distribution of hairs and if necessary the geometry of dorsal striations) morphological characteristics in comparison to those of a reference batch or reference documents. Identity may also be confirmed using protein analysis methods (e.g. protein profile, individual allergen test) or by genetic identification, if performed by generally accepted methods.

TESTS

Foreign matter

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Foreign matter is defined as any particles that are not part of the mite culture, i.e. any particulate matter not arising from the medium or the mites. Foreign matter is typically detected using a suitable microscopic method; a limit for the amount of foreign matter has to be established based on historical data.

Water (*2.5.12* or *2.5.32*) or **loss on drying** (*2.2.32*)

The water content of dried material is determined; specification limits must be supported by batch analysis and stability data.

Purity

When the source material is a purified fraction of the mite culture (e.g. mite bodies), the purity of the fraction needs to be evaluated and results are within a predefined limit.

STORAGE

The mite source material is stored under controlled conditions justified by stability data.

LABELLING

The label states:

— the species of the mite;

— the fraction of mite culture, where applicable.

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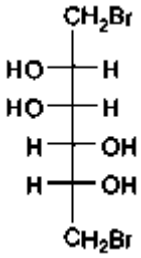
Mitobronitol

General Notices



$C_6H_{12}Br_2O_4$ 308.0 *488-41-5*

Action and use

Cytotoxic.

Preparation

Mitobronitol Tablets

DEFINITION

Mitobronitol is 1,6-dibromo-1,6-dideoxy-D-mannitol. It contains not less than 98.5% and not more than 101.0% of $C_6H_{12}Br_2O_4$ calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white, crystalline solid.

Slightly soluble in *water*, in *acetone* and in *ethanol (96%)*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of mitobronitol *(RS 236)*.

B. Dissolve 0.1 g in 10 mL of 1M *sodium hydroxide*, boil, cool, acidify with 2M *nitric acid* and add 1 mL of *silver nitrate solution*. A pale yellow, curdy precipitate is produced.

C. Dissolve 20 mg in 2 mL of a mixture of 1 volume of *periodic acid solution* and 24 volumes of *water*. Add 1 mL of 0.25M *barium chloride* and shake well. A white, flocculent precipitate is produced.

TESTS

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Acidity

Shake 2 g with 50 mL of *carbon dioxide-free water* for 15 minutes and filter. 40 mL of the filtrate requires not more than 0.3 mL of *0.02M sodium hydroxide VS* for neutralisation using *phenolphthalein solution R1* as indicator.

Clarity and colour of solution

A 4.0% w/v solution in *dimethylformamide* is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method I.

Ionic halide

Shake 0.20 g with 30 mL of *water* for 5 minutes and filter. 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII (500 ppm, calculated as Cl).

Loss on drying

When dried at 105° for 2 hours, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.2%, Appendix IX A.

ASSAY

Dissolve 0.2 g in 20 mL of 1M *sodium hydroxide* by heating gently, cool, add 25 mL of *0.1M silver nitrate VS* and acidify with 5 mL of 5M *nitric acid*. Add 2 mL of *ammonium iron(III) sulfate solution R2* and titrate the excess of silver nitrate with *0.1M ammonium thiocyanate VS*. Each mL of *0.1M silver nitrate VS* is equivalent to 15.40 mg of $C_6H_{12}Br_2O_4$.

STORAGE

Mitobronitol should be protected from light.

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Mitobronitol Tablets

General Notices

Action and use

Cytotoxic.

DEFINITION

Mitobronitol Tablets contain Mitobronitol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mitobronitol, $C_6H_{12}Br_2O_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of Mitobronitol with 10 mL of hot *methanol*, filter and allow the filtrate to cool. The crystalline precipitate, after filtering and drying at 105° for 2 hours, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of mitobronitol *(RS 236)*.

B. Dissolve 0.1 g in 10 mL of 1M *sodium hydroxide*, boil, cool, acidify with 2M *nitric acid* and add 1 mL of *silver nitrate solution*. A pale yellow, curdy precipitate is produced.

TESTS

Ionic halide

Shake a quantity of powdered tablets containing 1 g of Mitobronitol with 50 mL of *water* for 15 minutes, dilute to 100 mL with *water* and filter. To 50 mL of the filtrate add 10 mL of 2M *nitric acid* and 5 mL of *0.01M silver nitrate VS* and mix. Titrate the excess of silver nitrate with *0.01M ammonium thiocyanate VS* using *ammonium iron(III) sulfate solution R2* as indicator. Not more than 3.2 mL of *0.01M silver nitrate VS* is required.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.2 g of Mitobronitol add 40 mL of 0.5M *sodium hydroxide*, heat to boiling, cool, add 25 mL of *0.1M silver nitrate VS*, acidify with 5 mL of 5M *nitric acid* and titrate the excess of silver nitrate with *0.1M ammonium thiocyanate VS* determining the end point potentiometrically. Each mL of *0.1M silver nitrate VS* is equivalent to 15.40 mg of $C_6H_{12}Br_2O_4$.

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STORAGE

Mitobronitol Tablets should be protected from light.

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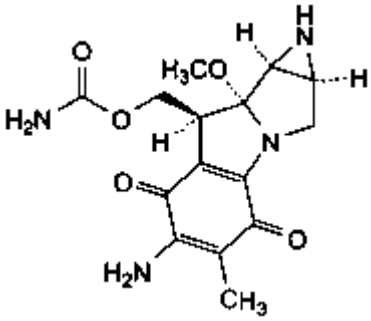
Mitomycin

General Notices

(Ph. Eur. monograph 1655)



$C_{15}H_{18}N_4O_5$ 334.3 *50-07-7*

Action and use

Antibacterial; cytotoxic.

Ph Eur

DEFINITION

[(1a*S*,8*S*,8a*R*,8b*S*)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-8-yl]methyl carbamate (mitomycin C).

Substance produced by a strain of *Streptomyces caespitosus*.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Blue-violet crystals or crystalline powder.

Solubility

Slightly soluble in water, freely soluble in dimethylacetamide, sparingly soluble in methanol, slightly soluble in acetone.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mitomycin CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

pH (2.2.3)

5.5 to 7.5.

Dissolve 10 mg in 10 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 10 mg of *cinnamamide R* (impurity A) in *methanol R* and dilute to 10 mL with the same solvent. Mix 2 mL of this solution and 1 mL of the test solution and dilute to 10 mL with *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, 0.77 g/L solution of *ammonium acetate R* (20:80 *V/V*);

— *mobile phase B*: *methanol R*, 0.77 g/L solution of *ammonium acetate R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 30	100 → 0	0 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
30 - 45	0	100
45 - 50	0 → 100	100 → 0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Relative retention With reference to mitomycin (retention time = about 21 min): impurity D = about 0.6; impurity C = about 1.2; impurity A = about 1.3; impurity B = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 15.0 between the peaks due to mitomycin and impurity A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.35;

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.30 g.

Bacterial endotoxins (*2.6.14, Method B*)

Less than 10 IU/ mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in *dimethylacetamide R* and dilute to 50.0 mL with the same solvent.

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Reference solution (a) Dissolve 25.0 mg of *mitomycin CRS* in *dimethylacetamide R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *cinnamamide R* (impurity A) in *methanol R* and dilute to 20 mL with the same solvent. Mix 2 mL of this solution with 2 mL of reference solution (a).

Column:

— *size*: *l* = 0.30 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped phenylsilyl silica gel for chromatography R* (10 µm) with a specific surface area of 330 m^2/g, a carbon loading of 8 per cent and a pore size of 12.5 nm.

Mobile phase Mix 23 volumes of *methanol R*, 77 volumes of a solution containing 2.05 g/L of *ammonium acetate R* and 2.8 mL/L of *dilute acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 365 nm and 254 nm.

Injection 20 µL.

Run time Twice the retention time of mitomycin.

Relative retention With reference to mitomycin (retention time = about 8 min): impurity A = about 1.2.

System suitability:

— *resolution*: minimum 1.8 between the peaks due to mitomycin and impurity A in the chromatogram obtained with reference solution (b) at 254 nm,

— *symmetry factor*: maximum 1.3 for the principal peak in the chromatogram obtained with reference solution (a) at 365 nm.

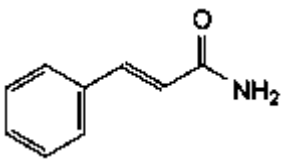
Calculate the percentage content of $C_{15}H_{18}N_4O_5$, using the chromatograms obtained with the test solution and reference solution (a) at 365 nm and taking into account the assigned content of *mitomycin CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D.*



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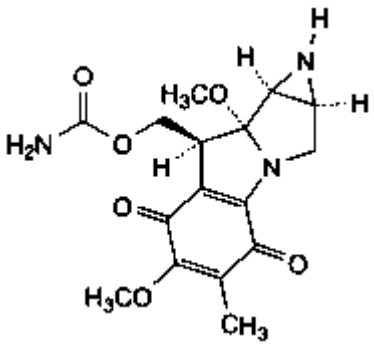
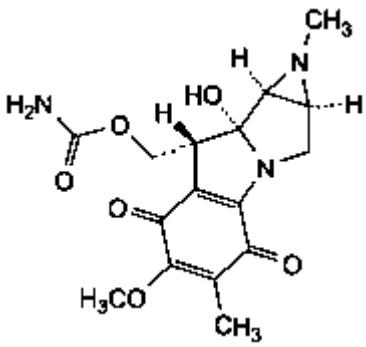
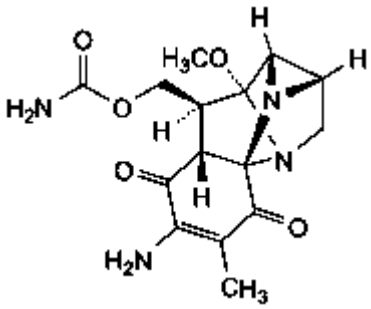
A. (*E*)-3-phenylprop-2-enamide (cinnamamide),



B. [(1a*S*,8*S*,8a*R*,8b*S*)-6,8a-dimethoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-8-yl]methyl carbamate (mitomycin A),



C. [(1a*S*,8*R*,8a*R*,8b*S*)-8a-hydroxy-6-methoxy-1,5-dimethyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indol-8-yl]methyl carbamate (mitomycin B),



D. [(1*S*,2*S*,4*S*,5*R*,6*S*,6a*R*,10a*S*,11*S*)-8-amino-5-methoxy-9-methyl-7,10-dioxo-2,3,6,6a,7,10-hexahydro-1,2,5-metheno-1*H*,5*H*-imidazo[2,1-*i*]indol-6-yl]methyl carbamate (albomitomycin C).

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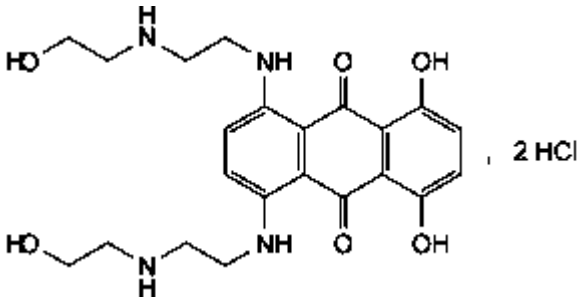
Mitoxantrone Hydrochloride

General Notices

(Ph. Eur. monograph 1243)



$C_{22}H_{30}Cl_2N_4O_6$ 517.4 *70476-82-3*

Action and use

Cytotoxic.

Preparation

Mitoxantrone Infusion

Ph Eur

DEFINITION

1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthracene-9,10-dione dihydrochloride.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Dark blue, electrostatic, hygroscopic powder.

Solubility

Sparingly soluble in water, slightly soluble in methanol, practically insoluble in acetone.

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CAUTION: mitoxantrone hydrochloride and impurity A are electrostatic; the use of an antistatic gun or other suitable method to discharge the solids before weighing or transfer is recommended.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 2-3 mg in 1 mL of methanol R by warming in a water-bath at 40-50 °C. Evaporate to dryness under a stream of dry nitrogen, warming gently if necessary. Examine the residue.

Comparison mitoxantrone hydrochloride CRS.

B. It gives reaction (b) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in about 40 mL of the mobile phase, sonicating if necessary, and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of mitoxantrone hydrochloride CRS in about 40 mL of the mobile phase, sonicating if necessary, and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1 mL of the test solution to 100 mL with the mobile phase.

Reference solution (c) Dissolve 2.0 mg of mitoxantrone impurity A CRS in 1.0 mL of reference solution (a).

Reference solution (d) Dilute 1 mL of reference solution (b) to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.30 m, Ø = 3.0 mm;

— *stationary phase*: phenylsilyl silica gel for chromatography R (10 µm).

Mobile phase Mix 750 volumes of water R, 250 volumes of acetonitrile R and 25 volumes of a solution prepared as follows: dissolve 22.0 g of sodium heptanesulfonate R in about 150 mL of water R and filter through a 0.45 µm filter; wash the filter with water R and combine the filtrate and washings; add 32.0 mL of glacial acetic acid R and dilute to 250 mL with water R.

Flow rate 3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 50 µL of the test solution and reference solutions (b), (c) and (d).

Run time 3 times the retention time of mitoxantrone.

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System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to mitoxantrone and impurity A.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent).

Ethanol

Gas chromatography (2.2.28).

Internal standard solution Dilute 2.0 mL of propanol R to 100 mL with water R. Dilute 5.0 mL of this solution to 100 mL with water R.

Test solution Mix 0.100 g of the substance to be examined with 2.0 mL of the internal standard solution and dilute to 5.0 mL with water R. Place the flask in an ultrasonic bath for 2 min, then shake the flask for 2 min. If necessary, repeat the sonication and shaking until dissolution is complete.

Reference solution Dilute 2.0 mL of anhydrous ethanol R to 100.0 mL with water R. Dilute 5.0 mL of the solution to 100.0 mL with water R. Dilute 10.0 mL of this solution and 10.0 mL of the internal standard solution to 25.0 mL with water R.

Column:

— *size*: *l* = 2 m, Ø = 3 mm;

— *stationary phase*: ethylvinylbenzene-divinylbenzene copolymer R.

Carrier gas helium for chromatography R.

Flow rate 19 mL/min.

Temperature:

— *column*: 120 °C;

— *injection port*: 175 °C;

— *detector*: 210 °C.

Detection Flame ionisation.

Injection 1 µL.

Retention time Ethanol = about 1 min; propanol = about 2 min.

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System suitability Reference solution:

— *resolution*: minimum 6 between the peaks due to ethanol and propanol.

Calculate the content of ethanol, taking its density (2.2.5) to be 0.790 g/mL at 20 °C.

Limit:

— *ethanol*: maximum 1.6 per cent *m/m*.

Water (2.5.12)

Maximum 6.0 per cent, determined on 0.300 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

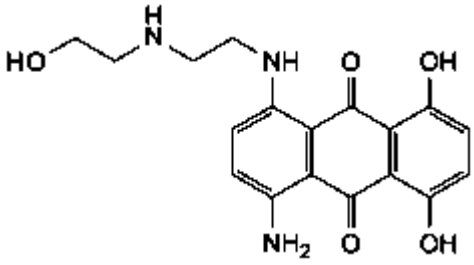
Calculate the percentage content of $C_{22}H_{30}Cl_2N_4O_6$ from the declared content of *mitoxantrone hydrochloride CRS*.

STORAGE

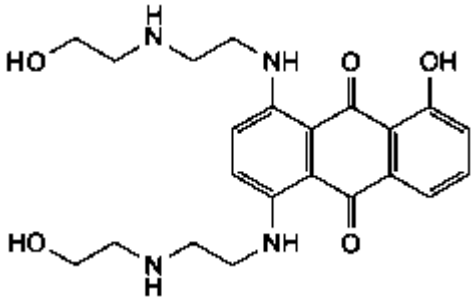
In an airtight container.

IMPURITIES

Specified impurities *A, B, C, D.*



A. 1-amino-5,8-dihydroxy-4-[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthracene-9,10-dione,



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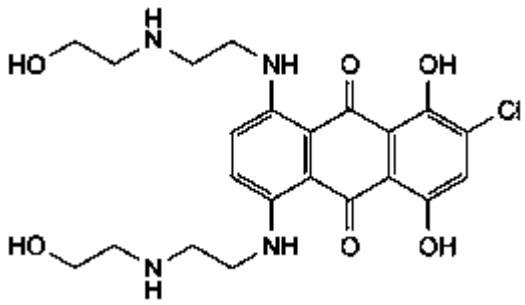
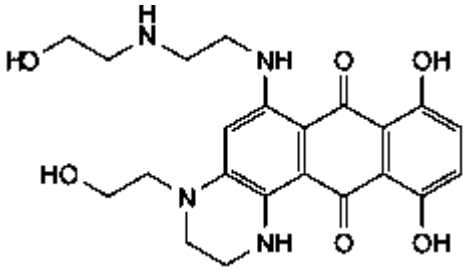
B. 5-hydroxy-1,4-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthracene-9,10-dione,



C. 2-chloro-1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthracene-9,10-dione,



D. 8,11-dihydroxy-4-(2-hydroxyethyl)-6-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-1,2,3,4-tetrahydronaphtho[2,3-*f*]quinoxaline-7,12-dione.

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Mitoxantrone Sterile Concentrate

General Notices

Action and use

Cytotoxic.

DEFINITION

Mitoxantrone Sterile Concentrate is a sterile solution of Mitoxantrone Hydrochloride in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of mitoxantrone, $C_{22}H_{28}N_4O_6$

90.0 to 105.0% of the stated amount.

CHARACTERISTICS

A dark blue solution.

IDENTIFICATION

A. Dilute a volume of the concentrate containing the equivalent of 2 mg of mitoxantrone to about 100 mL with *water* and add 20 mL of 1M *hydrochloric acid* and sufficient *water* to produce 200 mL. The *light absorption* of the solution, Appendix II B, in the range 220 nm to 350 nm shows a maximum at about 240 nm and a shoulder at 274 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a solution diluted, if necessary, with *water* to contain the equivalent of 0.2% w/v of mitoxantrone, 2.5 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dilute a volume of the concentrate containing the equivalent of 20 mg of mitoxantrone to 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.2% w/v of *mitoxantrone impurity A EPCRS* in solution (2).

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(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *phenyl silica gel for chromatography* (10 µm) (µBondapak Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 3 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3 times the retention time of the principal peak.

MOBILE PHASE

Solution A 22 g of *sodium heptanesulfonate* in about 150 mL of *water*, filter through a 0.45-µm filter and wash the filter with *water*. Add 32 mL of *glacial acetic acid* to the combined filtrate and washings, and dilute to 250 mL with *water*.

25 volumes of solution A, 250 volumes of *acetonitrile* and 750 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mitoxantrone are: impurity B, about 0.9; impurity A, about 1.5; impurity D, about 1.7 and impurity C, about 2.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dilute a volume of the concentrate containing the equivalent of 20 mg of mitoxantrone to 50 mL.

(2) 0.047% w/v of *mitoxantrone hydrochloride EPCRS*.

(3) 0.2% w/v of *mitoxantrone impurity A EPCRS* in solution (2).

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}N_4O_6$ in the concentrate using the declared content of $C_{22}H_{28}N_4O_6$,2HCl in *mitoxantrone hydrochloride EPCRS*. Each mg of $C_{22}H_{28}N_4O_6$,2HCl is equivalent to 0.8591 mg of $C_{22}H_{28}N_4O_6$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of mitoxantrone.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mitoxantrone Hydrochloride.

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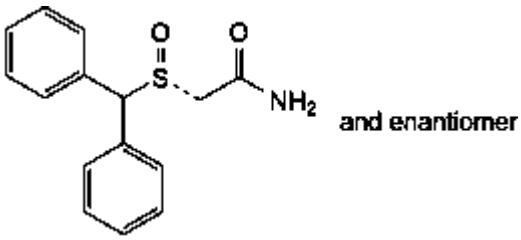
Modafinil

General Notices

(Ph. Eur. monograph 2307)



$C_{15}H_{15}NO_2S$ 273.4 *68693-11-8*

Action and use

Narcolepsy and sleep disorders.

Preparation

Modafinil Tablets

Ph Eur

DEFINITION

2-[(*RS*)-(Diphenylmethyl)sulfinyl]acetamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble or practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison modafinil CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, water R (35:65 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 35 mL of acetonitrile R1 and dilute to 50.0 mL with water R. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of modafinil CRS in 35 mL of acetonitrile R1 and dilute to 50.0 mL with water R. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Add 2.0 mL of the solvent mixture to a vial of modafinil for system suitability CRS (containing impurities A, B and C) and sonicate for 10 min.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 35 volumes of acetonitrile R1 and 65 volumes of a 6.8 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 2.3 with phosphoric acid R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 4 times the retention time of modafinil.

Identification of impurities Use the chromatogram supplied with modafinil for system suitability CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

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Relative retention With reference to modafinil (retention time = about 4 min): impurity A = about 1.3; impurity B = about 1.8; impurity C = about 3.0.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to modafinil.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities B, C*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of modafinil from the declared content of $C_{15}H_{15}NO_2S$ in *modafinil CRS*.

IMPURITIES

Specified impurities *A, B, C.*

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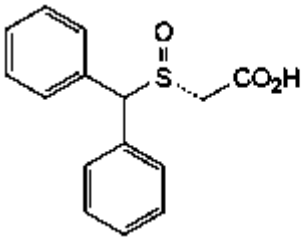
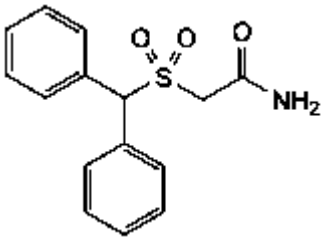
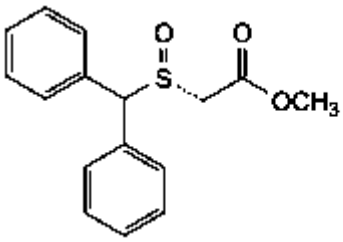


and enantiomer

A. [(*RS*)-(diphenylmethyl)sulfinyl]acetic acid,



B. 2-[(diphenylmethyl)sulfonyl]acetamide,



and enantiomer

C. methyl [(*RS*)-(diphenylmethyl)sulfinyl]acetate.

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Modafinil Tablets

General Notices

Action and use

Narcolepsy and sleep disorders

DEFINITION

Modafinil Tablets contain Modafinil.

The tablets complies with the requirements stated under Tablets and with the following requirements.

Content of modafinil, $C_{15}H_{15}NO_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 0.1 g of Modafinil, add 15 mL of *acetone*, boil and filter the hot solution. Wash the filter paper with two 5-mL quantities of hot *acetone*, combine the filtrates and cool in ice. Evaporate the combined filtrates to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the reference spectrum of modafinil *(RS 505)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter (0.45-µm filter is suitable). Dilute the filtered medium, if necessary, with sufficient dissolution medium to produce a solution expected to contain 0.011% w/v of Modafinil.

(2) 0.011% w/v of *modafinil BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

350 volumes of *acetonitrile* and 650 volumes of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*, previously adjusted to pH 2.3 with *orthophosphoric acid*.

When chromatograms are recorded under the prescribed conditions, the retention time of modafinil is about 4 minutes.

DETERMINATION OF CONTENT

Calculate the total content of modafinil, $C_{15}H_{15}NO_2S$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{15}NO_2S$, in *modafinil BPCRS*.

LIMITS

The amount of modafinil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in a mixture of 1 volume of 5M *acetic acid*, 350 volumes of *acetonitrile* and 650 volumes of *water* (solution A).

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 0.1 g of Modafinil with 80 mL of solution A and dilute to 100 mL. Filter the solution and dilute 1 volume to 10 volumes.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Add 2 mL of solution A to a vial of *modafinil for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used and allow the chromatography to proceed for 4 times the retention time of modafinil.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to modafinil (retention time about 4 minutes) are: impurity A, about 1.3; impurity B, about 1.8 and impurity C, about 3.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 2.5, where *Hp* is the height above the baseline of the peak due to impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to modafinil.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B or C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A described under Related substances.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 0.1 g of Modafinil with 80 mL of solution A and dilute to 100 mL. Dilute 1 volume of the resulting solution to 10 volumes.
(2) 0.01% w/v of *modafinil BPCRS*.
(3) Add 2 mL of solution A to a vial of *modafinil for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 2.5, where *Hp* is the height above the baseline of the peak due to impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to modafinil.

DETERMINATION OF CONTENT

Calculate the content of modafinil, $C_{15}H_{15}NO_2S$, in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{15}NO_2S$, in *modafinil BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Modafinil*.

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You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Molgramostim Concentrated Solution

General Notices

(Ph. Eur. monograph 1641)

APARSPSPST QPWEHVNAIQ EARRLLNLSR
DTAAEMNETV EVISEMFDLQ EPTCLQTRLE
LYKQGLRGSL TKLKGPLTMM ASHYKQHCPP
TPETSCATQI ITFESFKENL KDFLLVIPFD
CWEPVQE

$C_{639}H_{1007}N_{171}O_{196}S_8$ 14 477

Action and use

Recombinant granulocyte macrophage colony-stimulating factor.

Ph Eur

DEFINITION

Solution of a protein having the structure of the granulocyte macrophage colony stimulating factor which is produced and secreted by various human blood cell types. The protein stimulates the differentiation and proliferation of leucocyte stem cells into mature granulocytes and macrophages.

Content

Minimum 2.0 mg of protein per millilitre.

Potency

Minimum 0.7×10^7 IU per milligram of protein.

PRODUCTION

Molgramostim concentrated solution is produced by a method based on recombinant DNA (rDNA) technology, using bacteria as host cells. It is produced under conditions designed to minimise microbial contamination of the product.

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Prior to release, the following tests are carried out on each batch of molgramostim concentrated solution, unless exemption has been granted by the competent authority.

Host-cell derived proteins

The limit is approved by the competent authority.

Host-cell or vector derived DNA

The limit is approved by the competent authority.

CHARACTERS

Appearance

Clear, colourless liquid.

IDENTIFICATION

A. It shows the expected biological activity (see Assay).

B. Isoelectric focusing (*2.2.54*).

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 0.25 mg/mL.

Reference solution (a) Dilute *molgramostim CRS* with *water R* to obtain a concentration of 0.25 mg/mL.

Reference solution (b) Use an isoelectric point (pI) calibration solution, in the pI range of 2.5-6.5, prepared according to the manufacturer's instructions.

Focusing:

— *pH gradient*: 4.0-6.5;

— *catholyte*: 8.91 g/L (0.1 M) solution of *3-aminopropionic acid R*;

— *anolyte*: 14.7 g/L (0.1 M) solution of *glutamic acid R* in a 50 per cent *V/V* solution of *dilute phosphoric acid R* (0.5 M);

— *application*: 20 µL.

Detection Immerse the gel in a suitable volume of a solution containing 115 g/L of *trichloroacetic acid R* and 34.5 g/L of *sulfosalicylic acid R* and shake the container gently for 30 min. Transfer the gel to a mixture of 32 volumes of *glacial acetic acid R*, 100 volumes of *anhydrous ethanol R* and 268 volumes of *water R* (mixture A) and rinse for 5 min. Immerse the gel for 10 min in a staining solution prewarmed to 60 °C and prepared by adding *acid blue 83 R* at a concentration of 1.2 g/L to mixture A. Wash the gel in several containers with mixture A and keep the gel in this mixture until the background is clear (12-24 h). After adequate destaining, soak the gel for 1 h in a 10 per cent *V/V* solution of *glycerol R* in mixture A.

System suitability:

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— in the electropherogram obtained with reference solution (b), the relevant isoelectric point markers are distributed along the entire length of the gel;

— in the electropherogram obtained with reference solution (a), the pI of the principal band is 4.9 to 5.4.

Results The principal band in the electropherogram obtained with the test solution corresponds in position to the principal band in the electropherogram obtained with reference solution (a). Plot the migration distances of the relevant pI markers versus their pI and determine the isoelectric points of the principal component of each of the test solution and reference solution (a). They do not differ by more than 0.2 pI units.

C. Examine the electropherograms obtained under reducing conditions in the test for impurities with molecular masses differing from that of molgramostim. The principal band in the electropherogram obtained with test solution (a) is similar in position to the principal band in the electropherogram obtained with reference solution (a).

D. Peptide mapping (2.2.55).

Test solution Introduce 50 µL of *tris-hydrochloride buffer solution pH 8.0 R* and 50 µL of the preparation to be examined at a concentration of 2 mg/mL into a polypropylene tube of 0.5 mL capacity. Add 4 µL of a 1 mg/mL solution of *trypsin for peptide mapping R* in a 0.01 per cent *V/V* solution of *trifluoroacetic acid R*, cap tightly and mix well. Incubate at about 37 °C for 18 h. Add 125 µL of a 764 g/L (8 M) solution of *guanidine hydrochloride R* and mix well. Add 10 µL of a 154.2 g/L (1 M) solution of *dithiothreitol R* and mix well. Place the capped tube in boiling water for 1 min. Cool to room temperature.

Reference solution Prepare at the same time and in the same manner as for the test solution but use *molgramostim CRS* instead of the preparation to be examined.

Examine the 2 tryptic digests by liquid chromatography (2.2.29).

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* in 1000 mL of *water for chromatography R*;

— *mobile phase B*: dilute 1 mL of *trifluoroacetic acid R* in 100 mL of *water for chromatography R*; add 900 mL of *acetonitrile R1* and mix;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35.0	100 → 65	0 → 35
35.0 - 105.0	65 → 35	35 → 65
105.0 - 107.5	35 → 100	65 → 0

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
107.5 - 120.0	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 12 min.

Injection 200 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the *Ph. Eur. reference chromatogram of molgramostim digest*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

E. *N*-Terminal sequence analysis.
Perform the Edman degradation using an automated solid-phase sequencer, operated in accordance with the manufacturer's instructions.

Load about 1 nmol of the test preparation to a sequencing cartridge using the protocol provided by the manufacturer. Run 16 sequencing cycles, noting, if appropriate, the presence of proline at positions 2, 6, 8 and 12.

Identify the phenylthiohydantoin (PTH)-amino acids released at each sequencing cycle by reverse-phase liquid chromatography. The procedure may be carried out using the column and reagents recommended by the manufacturer of the sequencing equipment for the separation of PTH-amino acids.

The separation procedure is calibrated using:

— the mixture of PTH-amino acids provided by the manufacturer of the sequencer, with the gradient conditions adjusted as indicated to achieve optimum resolution of all amino acids;

— a sample obtained from a blank sequencing cycle obtained as recommended by the equipment manufacturer.

Results The first 16 amino acids are: Ala-Pro-Ala-Arg-Ser-Pro-Ser-Pro-Ser-Thr-Gln-Pro-Trp-Glu-His-Val.

TESTS

Impurities with molecular masses differing from that of molgramostim

Polyacrylamide gel electrophoresis (*2.2.31*) under both reducing and non-reducing conditions.

Gel dimensions 0.75 mm thick.

Resolving gel 14 per cent acrylamide.

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Sample buffer A Mix equal volumes of *water R* and *concentrated SDS-PAGE sample buffer R*.

Sample buffer B (reducing conditions) Mix equal volumes of *water R* and *concentrated SDS-PAGE sample buffer for reducing conditions R*.

Test solution (a) Dilute the preparation to be examined in *water R* to obtain a concentration of 1.0 mg/mL. To 1 volume of this solution add 1 volume of *concentrated SDS-PAGE sample buffer R*.

Test solution (b) (2 per cent control). Dilute 0.020 mL of test solution (a) to 1.0 mL with sample buffer A.

Test solution (c) (1 per cent control). To 0.20 mL of test solution (b) add 0.20 mL of sample buffer A.

Test solution (d) (0.5 per cent control). To 0.20 mL of test solution (c) add 0.20 mL of sample buffer A.

Test solution (e) (0.25 per cent control). To 0.20 mL of test solution (d) add 0.20 mL of sample buffer A.

Test solution (f) (0.1 per cent control). To 0.20 mL of test solution (e) add 0.30 mL of sample buffer A.

Test solution (g) (0.05 per cent control). To 0.20 mL of test solution (f) add 0.20 mL of sample buffer A.

Test solution (h) (0.025 per cent control). To 0.20 mL of test solution (g) add 0.20 mL of sample buffer A.

Test solution (i) Prepare as for test solution (a), but using *concentrated SDS-PAGE sample buffer for reducing conditions R*.

Test solutions (j)-(p) Prepare as for test solutions (b)-(h), but using sample buffer B.

Reference solution (a) Dilute *molgramostim CRS* in *water R* to obtain a concentration of 0.02 mg/mL. Mix 1 volume of this solution with 1 volume of *concentrated SDS-PAGE sample buffer R*.

Reference solution (b) Prepare as for reference solution (a), but using *concentrated SDS-PAGE sample buffer for reducing conditions R*.

Reference solution (c) Use a solution of molecular mass markers suitable for calibrating SDS-PAGE gels in the range of 14 400-94 000. Dissolve in sample buffer or sample buffer (reducing conditions), as appropriate.

Sample treatment Boil for 3 min.

Application 50 µL; apply reduced and non-reduced solutions to separate gels.

Detection Silver staining as described below.

Immerse the gel overnight in a mixture of 10 volumes of *acetic acid R*, 40 volumes of *water R* and 50 volumes of *methanol R*. Transfer the gel to a 100 g/L solution of *glutaraldehyde R* and shake for about 30 min. Replace the glutaraldehyde solution with *water R*, and keep the gel in *water R* for 20 min. Repeat this washing-step twice. Transfer the gel to a mixture containing 0.75 g/L of *sodium hydroxide R*, 14 g/L of *concentrated ammonia R* and 8 g/L of *silver nitrate R*. This solution is prepared immediately before use. Place the gel on a shaker in the dark for 5 min. Wash the gel for 30 s in each of 3 containers with *water R* and shake the gel in a mixture consisting of 0.05 g/L of *citric acid monohydrate R*, 0.05 per cent *V/V* of *formaldehyde R* and 0.005 per cent *V/V* of *methanol R* in *water R*. Protein bands become visible during this step. Keep the gel in the solution until sufficiently stained and then rinse the gel repeatedly with *water R* in a shaking water bath. Soak gels in a solution consisting of 10 per cent *V/V* of *acetic acid R* and 1 per cent *V/V* of *glycerol R*.

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System suitability:

— the validation criteria are met (2.2.31);

— a band is seen in the electropherogram obtained with test solution (h);

— a gradation of intensity of staining is seen in the electropherograms obtained with test solutions (a)-(h) and (i)-(p);

— the molecular mass of the principal band in the electropherogram obtained with reference solution (a) or (b) is within the range of 15 100 to 17 100.

Limits Compare the staining intensity of each non-molgramostim band observed in the electropherogram obtained with test solution (a) to the staining intensity of the principal band in the electropherograms obtained with test solutions (b)-(h). Proceed similarly with the electropherograms obtained with test solutions (i)-(p). The impurity level is estimated as the dilution, in percentage, of the solution giving the electropherogram with the closest intensity of staining.

Reducing conditions:

— *impurity with an apparent molecular mass of 20 000*: maximum 1 per cent;

— *impurity with an apparent molecular mass of 25 000*: maximum 0.1 per cent;

— *impurity with an apparent molecular mass of 30 000*: maximum 0.3 per cent;

— *total*: maximum 2 per cent.

Non-reducing conditions:

— *total of all impurities of molecular masses higher than 30 000*: maximum 1 per cent.

Related proteins

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution (a) Dilute the preparation to be examined with *0.05 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 0.5 mg/mL.

Test solution (b) Mix 1 volume of test solution (a) with 4 volumes of a 0.125 mg/mL solution of *human albumin R* or *bovine albumin R* in *0.05 M phosphate buffer solution pH 7.0 R*.

Reference solution (a) Dilute *molgramostim CRS* with *0.05 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 0.5 mg/mL.

Reference solution (b) Mix 1 volume of reference solution (a) with 4 volumes of a 0.125 mg/mL solution of *human albumin R* or *bovine albumin R* in *0.05 M phosphate buffer solution pH 7.0 R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: to about 800 mL of *water for chromatography R* add 1.0 mL of *trifluoroacetic acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: to 100 mL of *water for chromatography R* add 1.0 mL of *trifluoroacetic acid R* and 900 mL of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	64 → 44	36 → 56
30 - 35	44 → 0	56 → 100
35 - 45	0	100
45 - 50	0 → 64	100 → 36
50 - 60	64	36

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 100 µL of test solution (a), reference solutions (a) and (b).

System suitability Reference solution (b):

— *retention time*: molgramostin = about 22 min,

— *repeatability*: maximum relative standard deviation of 5.0 per cent after 4 injections,

— *resolution*: minimum 2 between the peaks due to albumin and molgramostim.

Limits:

— *any impurity*: for each impurity, maximum 1.5 per cent,

— *total of impurities eluting between 5 min and 30 min*: maximum 4 per cent.

Bacterial endotoxins (*2.6.14*)

Less than 5 IU in the volume that contains 1.0 mg of protein.

ASSAY

Protein

Liquid chromatography (*2.2.29*) as described in the test for related proteins.

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Injection 150 µL of test solution (b) and reference solution (b).

Calculate the content of molgramostim using the declared content of molgramostim in *molgramostim CRS*.

Potency

Determination of the biological activity of molgramostim concentrated solution based on the stimulation of proliferation of TF-1 cells by molgramostim.

The following method uses the conversion of tetrazolium bromide (MTT) as a staining method. Validated alternative stains such as Almar blue have also been found suitable.

TF-1 cells are incubated with varying dilutions of test and reference preparations of molgramostim. They are then incubated with a solution of MTT. This cytochemical stain is converted by cellular dehydrogenases to a purple formazan product. The formazan is then measured spectrophotometrically. The potency of the preparation to be examined is determined by comparison of the dilutions of the test preparation with the dilutions of the appropriate International Standard of molgramostim or with a reference preparation calibrated in International Units, which yield the same response (50 per cent maximal stimulation).

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Add 50 µL of dilution medium to all wells of a 96-well microplate. Add an additional 50 µL of this solution to the wells designed for the blanks. Add 50 µL of each solution to be tested in triplicate (test preparation and reference preparation at a concentration of about 65 IU/mL, plus a series of 10 twofold dilutions to obtain a standard curve). Then add to each well 50 µL of a TF-1 cell suspension containing 3×10^5 cells per millilitre, maintaining the cells in a uniform suspension during addition.

Incubate the plate at 36.0-38.0 °C for a minimum of 24 h in a humidified incubator using 6 ± 1 per cent CO_2. Add 25 µL of a 5.0 g/L sterile solution of *tetrazolium bromide R* to each well. Reincubate for 5 h. Remove the plates from the incubator and add to each well 100 µL of a 240 g/L solution of *sodium dodecyl sulfate R* previously adjusted to pH 2.7 with hydrochloric acid. Reincubate overnight.

Determine the relative quantity of purple formazan product formed in each well by measuring the absorbance (*2.2.25*) using a 96-well microplate reader. Read each plate at 570 nm and at 690 nm. Subtract the reading at 690 nm from the reading at 570 nm. Analyse the data by fitting a sigmoidal dose-response curve to the data obtained and by using a suitable statistical method, for example the 4-parameter model (see *5.3*).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) of the estimated potency are not less than 74 per cent and not more than 136 per cent of the stated potency.

STORAGE

In an airtight container, protected from light, at a temperature below -65 °C.

LABELLING

The label states:

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— the content, in milligrams of protein per millilitre,

— the potency, in International Units per milligram of protein.

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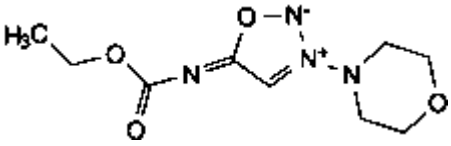
Molsidomine

General Notices

(Ph. Eur. monograph 1701)



$C_9H_{14}N_4O_4$ 242.2 *25717-80-0*

Action and use

Nitric oxide donor; treatment of angina pectoris.

Ph Eur

DEFINITION

N-(Ethoxycarbonyl)-3-(morpholin-4-yl)sydnonimine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in anhydrous ethanol and in methylene chloride.

mp

About 142 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *molsidomine CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Dissolve 1.0 g in *anhydrous ethanol R* by heating at about 50 °C for about 5 min and dilute to 20.0 mL with the same solvent.

pH (*2.2.3*)

5.5 to 7.5.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Impurity B

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of test solution (a) and reference solution (b).

Relative retention With reference to molsidomine (retention time = about 9 min): impurity B = about 0.43.

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 20 for the principal peak.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (3 ppm).

Impurity E

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *morpholine for chromatography R* in 500.0 mL of *water for chromatography R*. Dilute 20.0 mL of the solution to 500.0 mL with *water for chromatography R*. Dilute 5.0 mL of this solution to 100.0 mL with *water for chromatography R*.

Reference solution (b) Mix 10.0 mL of the test solution with 10.0 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *resin for reversed-phase ion chromatography R*;

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— *temperature*: 25 °C.

Mobile phase Mix 3.0 mL of *methanesulfonic acid R* and 75 mL of *acetonitrile R* in *water for chromatography R* and dilute to 5000 mL with *water for chromatography R*.

Suppressor regenerant *water for chromatography R*.

Flow rate 1.0 mL/min.

Expected background conductivity Less than 0.5 µS.

Detection Conductivity detector at 10 µS.

Injection 50 µL.

Run time 20 min.

Relative retention With reference to molsidomine (retention time = about 3 min): impurity E = about 2.4.

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 6 for the peak due to impurity E.

Limit:

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Solvent mixture *methanol R*, mobile phase A (10:90 *V/V*).

Test solution (a) Dissolve 0.200 g of the substance to be examined in 2.5 mL of *methanol R* and dilute to 5.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (b) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.4 mg of *molsidomine impurity B CRS* in 80 mL of *methanol R* and dilute to 100.0 mL with *methanol R*. Dilute 2.0 mL of the solution to 100.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 10 mg of *linsidomine hydrochloride R* (impurity A) and 5 mg of *molsidomine impurity D CRS* in 10 mL of *methanol R* and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 4.0 g of *potassium dihydrogen phosphate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	90	10
3 - 10	90 → 20	10 → 80
10 - 13	20	80

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solution (b) and reference solutions (a) and (c).

Relative retention With reference to molsidomine (retention time = about 9 min): impurity A = about 0.2; impurity D = about 0.3.

System suitability Reference solution (c):

— *resolution*: minimum 3.5 between the peaks due to impurities A and D.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the peak due to molsidomine in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the peak due to molsidomine in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the peak due to molsidomine in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 5 mL of *acetic anhydride R* and 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 24.22 mg of $C_9H_{14}N_4O_4$.

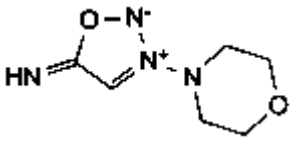
STORAGE

Protected from light.

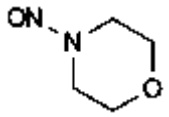
IMPURITIES

Specified impurities B, E.

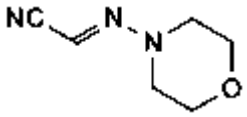
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D.



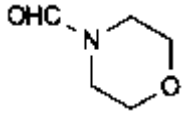
A. 3-(morpholin-4-yl)sydnonimine (linsidomine),



B. 4-nitrosomorpholine,



C. (2*E*)-(morpholin-4-ylimino)acetonitrile,



D. morpholine-4-carbaldehyde,

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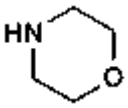

E. morpholine.

Ph Eur

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Mometasone Aqueous Nasal Spray

General Notices

Action and use

Glucocorticoid.

DEFINITION

Mometasone Aqueous Nasal Spray is an aqueous suspension of Mometasone Furoate in a suitable pressurised container fitted with an appropriate nasal delivery system.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of mometasone furoate, $C_{27}H_{30}Cl_2O_6$

80.0 to 120.0% of the amount stated to be delivered by actuation of the valve.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Discharge the container a sufficient number of times to obtain 0.5 mg of Mometasone Furoate and disperse in 4 mL of *methanol (80%)*. Shake vigorously, filter and use the filtrate.

(2) 0.0125% w/v of *mometasone furoate BPCRS* in methanol (80%).

(3) Equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below, allow the tank to saturate for 60 minutes.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *acetonitrile*, 10 volumes of *methanol*, 26 volumes of *ethyl acetate* and 61 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) exhibits a single compact spot the same size and shape as that obtained with solution (2).

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to the peak due to mometasone furoate in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III A, using the following solutions. *Carry out the procedure protected from light and prepare solutions immediately before use.*

Solution A 0.1 volumes of *glacial acetic acid*, 50 volumes of *acetonitrile* and 50 volumes of *water*.

(1) Discharge the container a sufficient number of times to obtain 1 mg of Mometasone Furoate, add 3 mL of *acetonitrile* and 2 mL of solution A. Mix with the aid of ultrasound, add sufficient solution A to produce 10 mL and centrifuge.

(2) Dilute 1 volume of solution (1) to 200 volumes with solution A.

(3) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 25 cm × 4.6 mm packed with *end-capped octydecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 2.5 times the retention time of mometasone furoate.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mometasone furoate (retention time about 24 minutes) are: impurity C, about 0.9; impurity J, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and mometasone furoate is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Carry out the procedure protected from light and prepare solutions immediately before use.*

Solution A 0.1 volumes of *glacial acetic acid,* 50 volumes of *acetonitrile* and 50 volumes of *water*.

Solution B 6 volumes of *acetonitrile* and 94 volumes of solution A.

(1) Discharge the container a sufficient number of times to obtain 1 mg of Mometasone Furoate and disperse in 0.6 mL of *acetonitrile*. Mix with the aid of ultrasound, add sufficient solution A to produce 10 mL and centrifuge.

(2) Dissolve 25 mg of *mometasone furoate BPCRS* in 1.5 mL of *acetonitrile* and dilute to 25 mL with solution A. Dilute 1 volume of this solution to 10 volumes with solution B.

(3) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and mometasone furoate is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the Nasal spray using the declared content of $C_{27}H_{30}Cl_2O_6$ in *mometasone furoate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mometasone Furoate.

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Mometasone Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Mometasone Cream contains Mometasone Furoate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of mometasone furoate, $C_{27}H_{30}Cl_2O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions protected from light.

(1) Disperse a quantity of the cream containing 0.5 mg of Mometasone Furoate in 4 mL of *methanol (80%)* by heating on a water bath until the temperature reaches 68°. Shake for 20 minutes and cool in ice for 30 minutes and filter.

(2) 0.0125% w/v of *mometasone furoate BPCRS* in *methanol (80%)*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below, allow the tank to saturate for 60 minutes.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 105° and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *acetonitrile*, 10 volumes of *methanol*, 26 volumes of *ethyl acetate* and 61 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to mometasone furoate in the chromatogram obtained with solution (2).

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TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Carry out the procedure protected from light and prepare solutions immediately before use.

Solution A 0.1 volumes of *glacial acetic acid*, 50 volumes of *acetonitrile* and 50 volumes of *water*.

(1) To a quantity of the cream containing 10 mg of Mometasone Furoate add 45 mL of *acetonitrile* and place on a water bath, maintained at 60°, for 60 minutes with occasional shaking. Place in a freezer for 30 minutes, shake with 45 mL of solution A, add sufficient solution A to produce 100 mL, centrifuge and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with a solution containing 45 volumes of *acetonitrile* and 55 volumes of solution A.

(3) Dissolve 10 mg of *mometasone impurity D BPCRS* in 45 mL of *acetonitrile* and add sufficient solution A to produce 100 mL. Dilute 1 volume of this solution to 100 volumes with solution A.

(4) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* (containing impurities C and J) in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

(5) Dilute 1 volume of solution (2) to 5 volumes with a solution containing 45 volumes of *acetonitrile* and 55 volumes of solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3.5 times the retention time of mometasone furoate.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to mometasone furoate (retention time about 25 minutes) are: impurity C, about 0.9 and impurity J, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and mometasone furoate is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

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the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of all impurities is not greater than 1.5%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D. Carry out the procedure protected from light and prepare solutions immediately before use.

Solution A 0.1 volumes of *glacial acetic acid*, 50 volumes of *acetonitrile* and 50 volumes of *water*.

(1) To a quantity of the cream containing 1 mg of Mometasone Furoate add 45 mL of *acetonitrile* on a water bath, maintained at 60°, for 60 minutes with occasional shaking. Place in a freezer for 30 minutes, shake with 45 mL of Solution A, add sufficient Solution A to produce 100 mL, centrifuge and filter.

(2) Dissolve 10 mg of *mometasone furoate BPCRS* in 45 mL of *acetonitrile* and add sufficient solution A to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a solution containing 45 volumes of *acetonitrile* and 55 volumes of solution A.

(3) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* (containing impurities C and J) in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and mometasone furoate is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the preparation being examined using the declared content of $C_{27}H_{30}Cl_2O_6$ in *mometasone furoate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity C, impurity D and impurity J listed under Mometasone Furoate.

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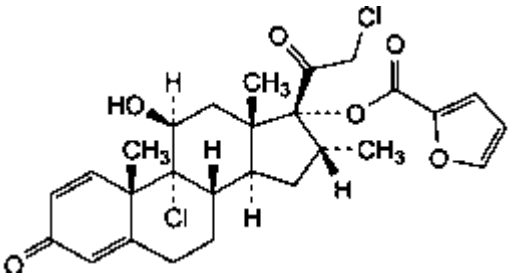
Mometasone Furoate

General Notices

(Ph. Eur. monograph 1449)



$C_{27}H_{30}Cl_2O_6$ 521.4 *83919-23-7*

Action and use

Glucocorticoid.

Preparations

Mometasone Aqueous Nasal Spray

Mometasone Cream

Mometasone Inhalation Powder, Pre-metered

Mometasone Ointment

Mometasone Scalp Application

Ph Eur

DEFINITION

9,21-Dichloro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

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White or almost white powder.

Solubility

Practically insoluble in water, soluble in acetone and in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D, E.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mometasone furoate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *mometasone furoate CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 10 µL; the volume may be adapted based on the type of plate used.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat the plate at 90 °C for 35 min or until the spots appear and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Mix 80 mg with 0.30 g of *anhydrous sodium carbonate R* and ignite in a crucible until an almost white residue is obtained. Allow to cool and dissolve the residue in 5 mL of *dilute nitric acid R*; filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

D. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

E. Loss on drying (see Tests).

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TESTS

Specific optical rotation (2.2.7)

+ 50 to + 55 (dried substance).

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mix 200 mL of *acetonitrile R* and 200 mL of *water R*, then add 0.4 mL of *acetic acid R*.

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *mometasone furoate for system suitability CRS* (containing impurities C and J) in 3 mL of *acetonitrile R* and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of *mometasone furoate monohydrate CRS* in 15 mL of *acetonitrile R* and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *water for chromatography R* (50:50 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 3.5 times the retention time of mometasone furoate.

Identification of impurities Use the chromatogram supplied with *mometasone furoate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and J.

Relative retention With reference to mometasone furoate (retention time = about 24 min): impurity C = about 0.9; impurity J = about 1.5.

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System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity C and mometasone furoate.

Limits:

— *impurity J*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

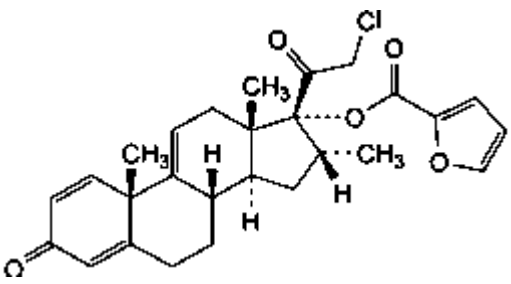
Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{27}H_{30}Cl_2O_6$ taking into account the assigned content of *mometasone furoate monohydrate CRS*.

IMPURITIES

Specified impurities *J*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I, K, L, M, N, O, P, Q, R, S, T, U.*



A. 21-chloro-16α-methyl-3,20-dioxopregna-1,4,9(11)-trien-17-yl furan-2-carboxylate,

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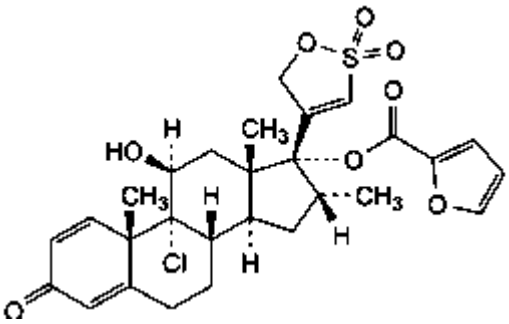
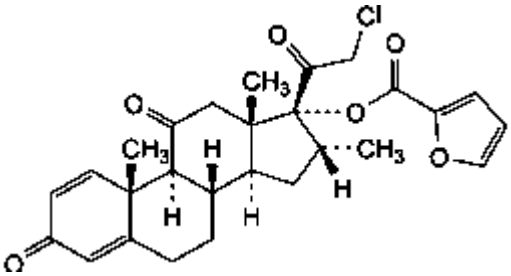
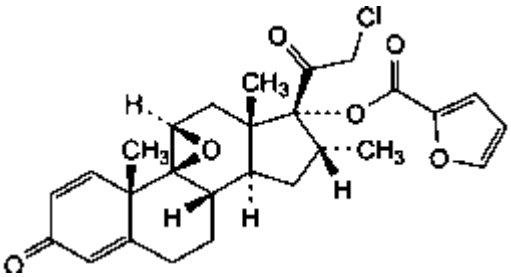


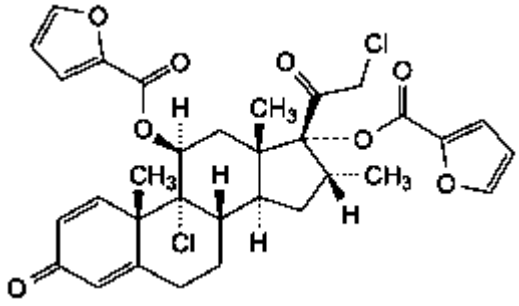
B. 9-chloro-17β-(2,2-dioxo-2,5-dihydro-1,2λ^6-oxathiol-4-yl)-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate,



C. 21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,



D. 21-chloro-9,11β-epoxy-16α-methyl-3,20-dioxo-9β-pregna-1,4-dien-17-yl furan-2-carboxylate,



E. 9,21-dichloro-16α-methyl-3,20-dioxopregna-1,4-diene-11β,17-diyl di(furan-2-carboxylate),

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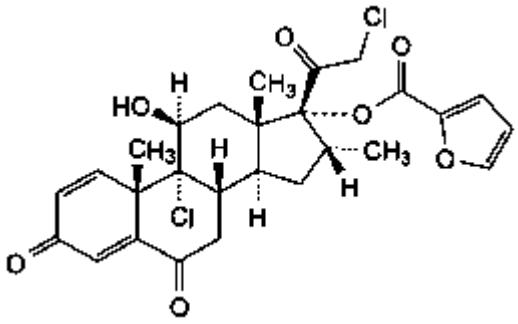
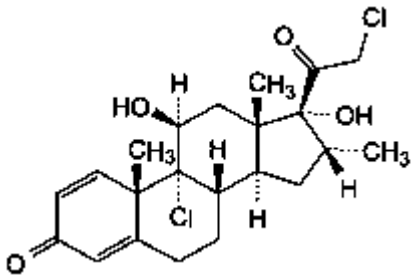
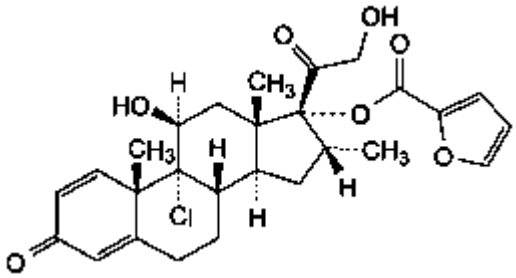


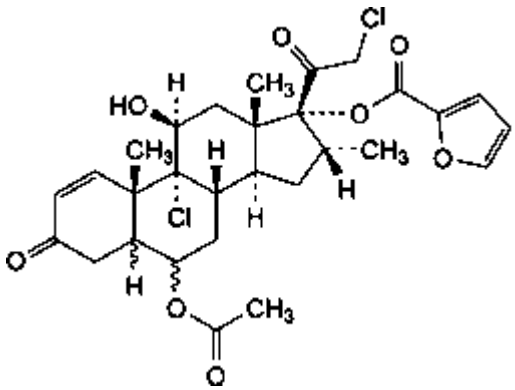
F. 9,21-dichloro-11β-hydroxy-16α-methyl-3,6,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,



G. 9,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione (mometasone),



H. 9-chloro-11β,21-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



I. 6ξ-(acetyloxy)-9,21-dichloro-11β-hydroxy-16α-methyl-3,20-dioxo-5ξ-pregn-1-en-17-yl furan-2-carboxylate,

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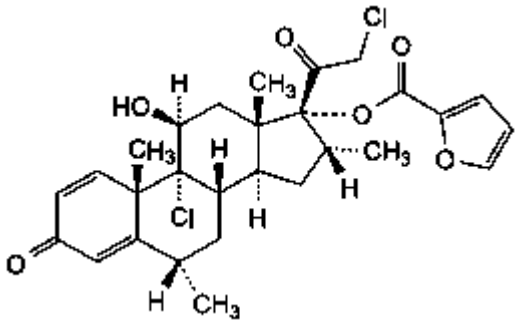
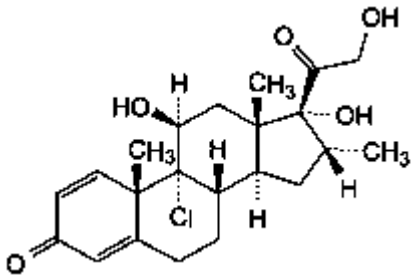
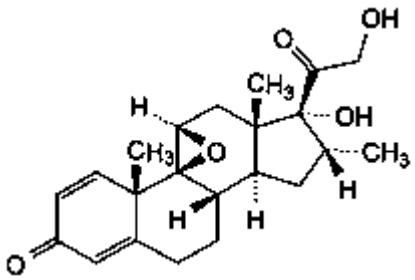


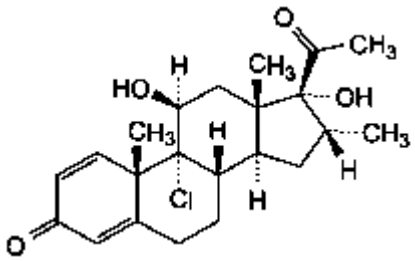
J. 9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



K. 9-chloro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,



L. 9,11β-epoxy-17,21-dihydroxy-16α-methyl-9β-pregna-1,4-diene-3,20-dione,



M. 9-chloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione,

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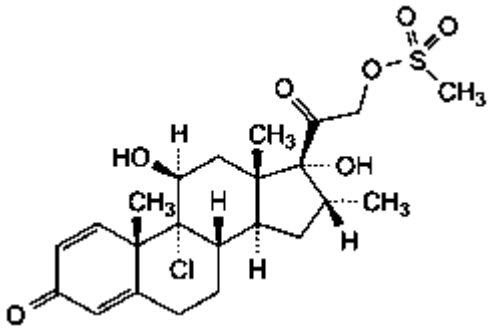
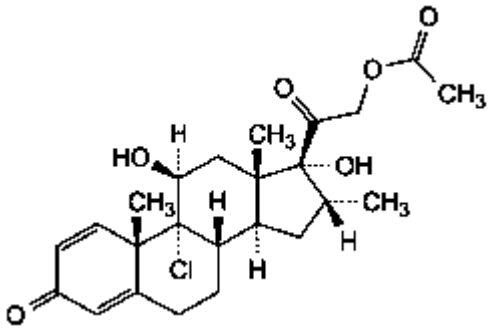
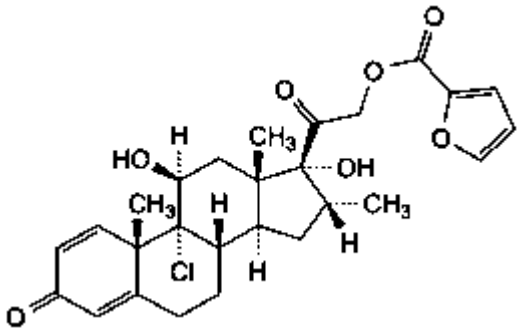


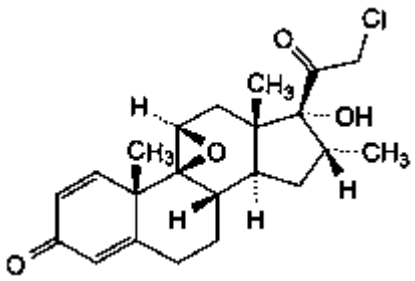
N. 9-chloro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl methanesulfonate,



O. 9-chloro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate,



P. 9-chloro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl furan-2-carboxylate,



Q. 21-chloro-9,11β-epoxy-17-hydroxy-16α-methyl-9β-pregna-1,4-diene-3,20-dione,

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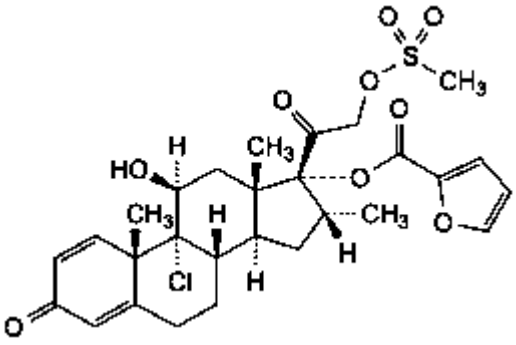
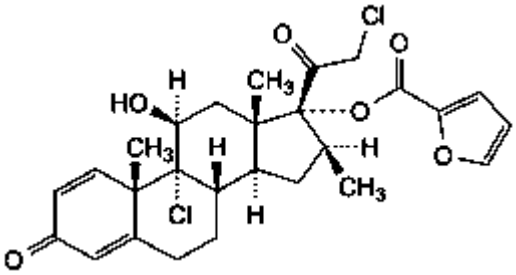
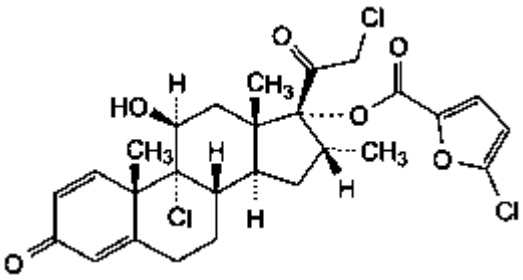


R. 9-chloro-11β-hydroxy-21-[(methanesulfonyl)oxy]-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



S. 9,21-dichloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



T. 9,21-dichloro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl 5-chlorofuran-2-carboxylate,

U. unknown structure.

Ph Eur

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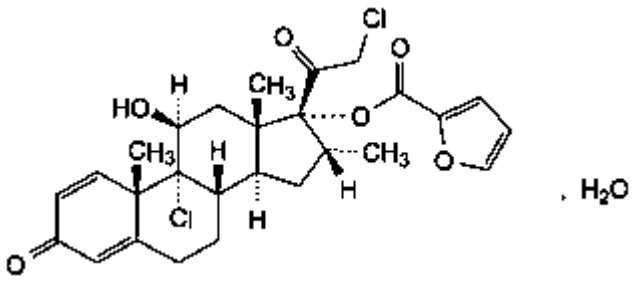
Mometasone Furoate Monohydrate

General Notices

(Ph. Eur. monograph 2858)



$C_{27}H_{30}Cl_2O_6,H_2O$ 539.4 *141646-00-6*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

9,21-Dichloro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in acetone and in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *mometasone furoate monohydrate CRS*.

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B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Water (see Tests).

TESTS

Specific optical rotation (2.2.7)

+ 50 to + 55 (anhydrous substance).

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mix 200 mL of *acetonitrile R* and 200 mL of *water R*, then add 0.4 mL of *acetic acid R*.

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *mometasone furoate for system suitability CRS* (containing impurity C) in 3 mL of *acetonitrile R* and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of *mometasone furoate monohydrate CRS* in 15 mL of *acetonitrile R* and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *water for chromatography R* (50:50 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

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Run time 3.5 times the retention time of mometasone furoate.

Identification of impurities Use the chromatogram supplied with *mometasone furoate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to mometasone furoate (retention time = about 24 min): impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity C and mometasone furoate.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

2.5 per cent to 4.0 per cent, determined on 0.200 g.

ASSAY

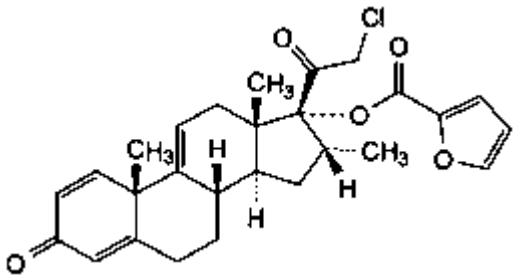
Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{27}H_{30}Cl_2O_6$ taking into account the assigned content of *mometasone furoate monohydrate CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U.*



A. 21-chloro-16α-methyl-3,20-dioxopregna-1,4,9(11)-trien-17-yl furan-2-carboxylate,

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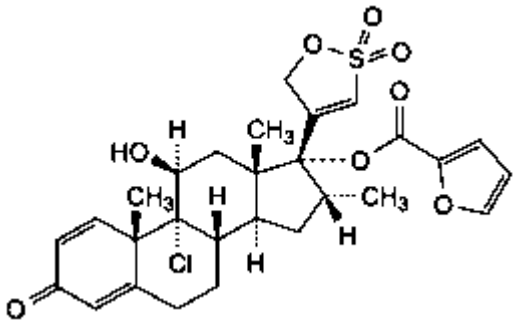
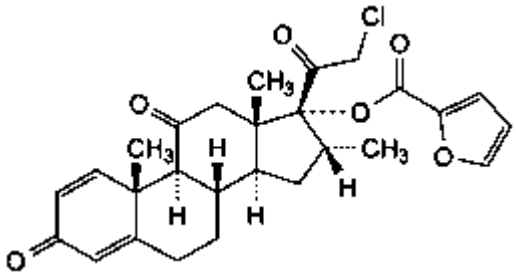
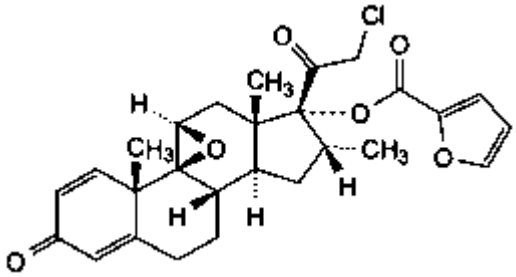


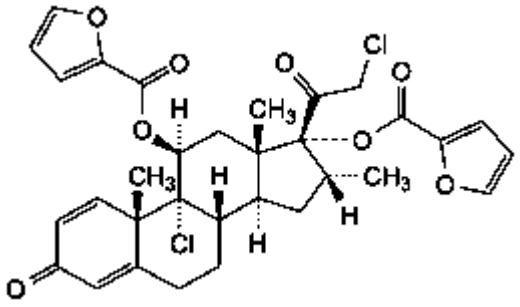
B. 9-chloro-17β-(2,2-dioxo-2,5-dihydro-1,2λ^6-oxathiol-4-yl)-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate,



C. 21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,



D. 21-chloro-9,11β-epoxy-16α-methyl-3,20-dioxo-9β-pregna-1,4-dien-17-yl furan-2-carboxylate,



E. 9,21-dichloro-16α-methyl-3,20-dioxopregna-1,4-diene-11β,17-diyl di(furan-2-carboxylate),

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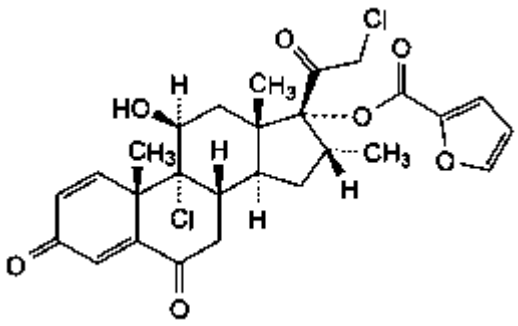
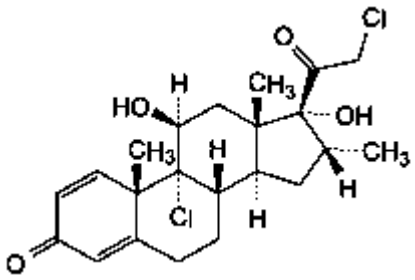
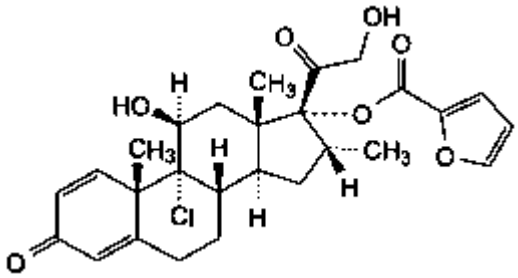


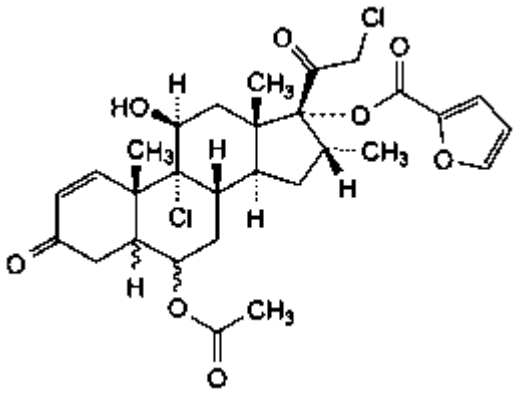
F. 9,21-dichloro-11β-hydroxy-16α-methyl-3,6,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,



G. 9,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione (mometasone),



H. 9-chloro-11β,21-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



I. 6ξ-acetoxy-9,21-dichloro-11β-hydroxy-16α-methyl-3,20-dioxo-5ξ-pregn-1-en-17-yl furan-2-carboxylate,

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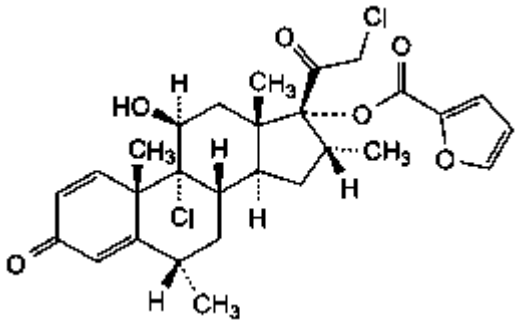
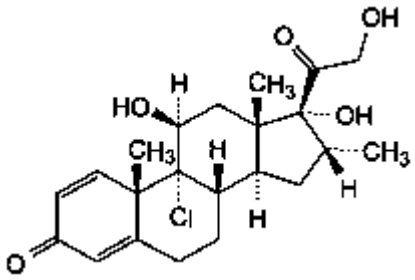
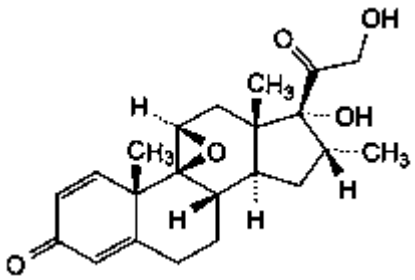


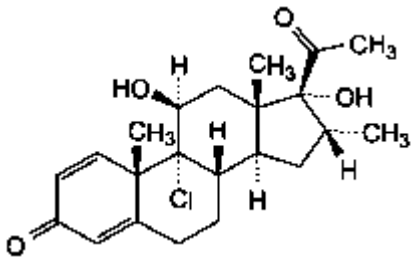
J. 9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



K. 9-chloro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,



L. 9,11β-epoxy-17,21-dihydroxy-16α-methyl-9β-pregna-1,4-diene-3,20-dione,



M. 9-chloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione,

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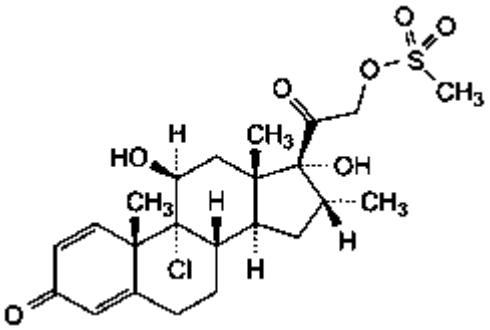
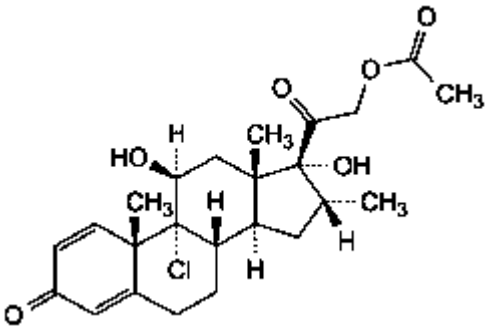
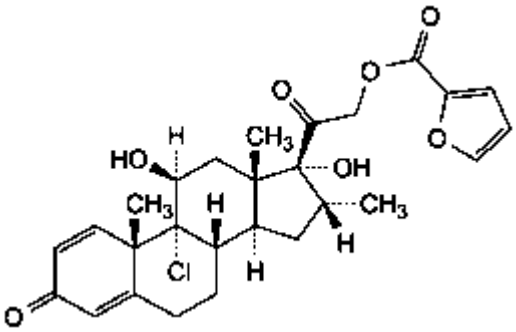


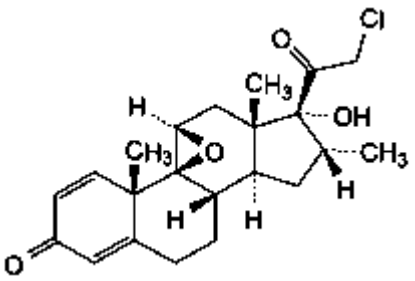
N. 9-chloro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl methanesulfonate,



O. 9-chloro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate,



P. 9-chloro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl furan-2-carboxylate,



Q. 21-chloro-9,11β-epoxy-17-hydroxy-16α-methyl-9β-pregna-1,4-diene-3,20-dione,

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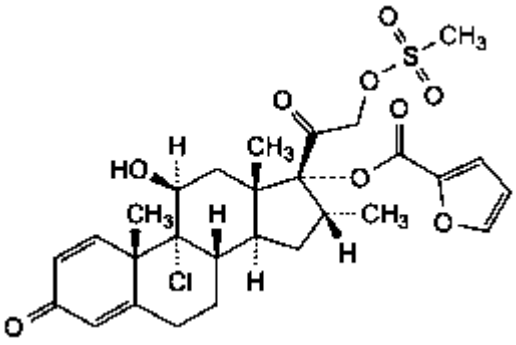
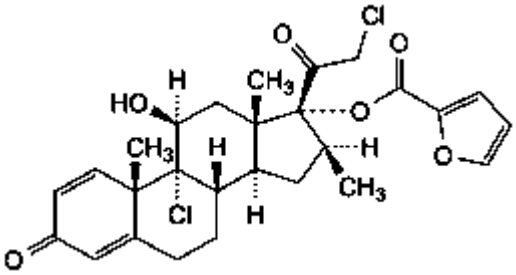
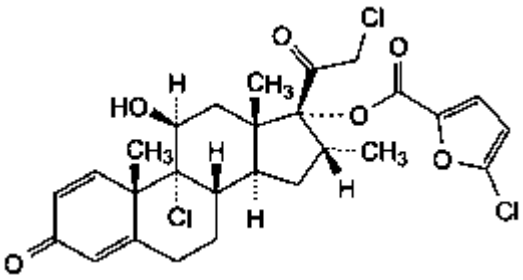


R. 9-chloro-11β-hydroxy-16α-methyl-21-[(methylsulfonyl)oxy]-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



S. 9,21-dichloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate,



T. 9,21-dichloro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl 5-chlorofuran-2-carboxylate,

U. unknown structure.

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Mometasone Inhalation Powder, Pre-metered

General Notices

Mometasone Inhalation Powder, Pre-dispensed

Action and use

Glucocorticoid.

DEFINITION

Mometasone Inhalation Powder, pre-metered consists of Mometasone Furoate in microfine powder or aerodynamically equivalent, either alone or combined with a suitable carrier. It is administered by a dry-powder inhaler.

Content of mometasone furoate, $C_{27}H_{30}Cl_2O_6$

85.0 to 115.0% of the amount stated to be delivered by actuation of the valve.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. *Preparations for inhalation: Aerodynamic Assessment of Fine Particles.* The test and limits should be agreed with the competent authority. The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Discharge the container a sufficient number of times to obtain 1.2 mg of Mometasone Furoate and disperse in 10 mL of *methanol (80%)*. Shake vigorously, filter and use the filtrate.

(2) 0.0125% w/v of *mometasone furoate BPCRS* in methanol (80%).

(3) Equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below, allow the tank to saturate for 60 minutes.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

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3 volumes of *acetonitrile*, 10 volumes of *methanol*, 26 volumes of *ethyl acetate* and 61 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) exhibits a single compact spot the same size and shape as that obtained with solution (2).

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to the peak due to mometasone furoate in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

Complies with the requirements stated under *Inhalation Powders* using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Carry out the procedure protected from light and prepare solutions immediately before use.

Solution A 0.1 volumes of *glacial acetic acid*, 50 volumes of *acetonitrile* and 50 volumes of *water*.

(1) Collect single doses of the preparation being examined using the procedure described under *Inhalation Powders*, *Uniformity of delivered dose* and dissolve the collected dose in a sufficient amount of mixture of 6 volumes of *acetonitrile* and 94 volumes of solution A to produce a solution expected to contain 0.0008% w/v of *mometasone furoate BPCRS* and filter.

(2) Dissolve 25 mg of *mometasone furoate BPCRS* in 6 mL of *acetonitrile* and dilute to 100 mL with solution A. Dilute 1.6 volumes of this solution to 50 volumes with solution a mixture of 6 volumes of *acetonitrile* and 94 volumes of solution A.

(3) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 2.5 times the retention time of mometasone furoate.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

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When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mometasone furoate (retention time about 25 minutes) are: impurity C, about 0.9 and impurity J, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and mometasone furoate is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{30}Cl_2O_6$, per delivered dose from the chromatograms obtained and using the declared content of $C_{27}H_{30}Cl_2O_6$ in *mometasone furoate BPCRS*. Repeat the procedure as described for reservoir systems under Powders for Inhalation, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III A, using the following solutions. *Carry out the procedure protected from light and prepare solutions immediately before use.*

Solution A 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volumes of *acetic acid*.

(1) Discharge the container a sufficient number of times to obtain 1 mg of Mometasone Furoate, add 3 mL of *acetonitrile* and 2 mL of solution A. Mix with the aid of ultrasound, add sufficient solution A to produce 10 mL and centrifuge.

(2) Dilute 1 volume of solution (1) to 200 volumes with solution A.

(3) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of delivered dose may be used.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mometasone furoate (retention time about 24 minutes) are: impurity C, about 0.9; impurity J, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and mometasone furoate is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than four times the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

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ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mometasone Furoate.

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Mometasone Scalp Application

General Notices

Mometasone Cutaneous Suspension

Action and use

Glucocorticoid.

DEFINITION

Mometasone Scalp Application is a cutaneous suspension of Mometasone Furoate in a suitable liquid basis.

The scalp application complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of mometasone furoate, $C_{27}H_{30}Cl_2O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the scalp application containing 0.5 mg of Mometasone Furoate in 4 mL of *methanol (80%)* by heating on a water bath until the temperature reaches 68°. Shake for 20 minutes and cool in ice for 30 minutes and filter.

(2) 0.0125% w/v of *mometasone furoate BPCRS* in *methanol (80%)*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use mobile phase as described as below, allow the tank to saturate for 60 minutes.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 105° and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *acetonitrile*, 10 volumes of *methanol*, 26 volumes of *ethyl acetate* and 61 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to mometasone furoate in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Carry out the procedure protected from light and prepare solutions immediately before use.*

Solution A 0.1 volumes of *glacial acetic acid*, 50 volumes of *acetonitrile* and 50 volumes of *water*.

(1) Completely disperse a quantity of the scalp application containing 10 mg of Mometasone Furoate in 25 mL of *acetonitrile* in a water bath at a temperature of 80° and allow to cool. Add 20 mL of *acetonitrile* and 30 mL of solution A and shake for 30 minutes. Add sufficient solution A to produce 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with a solution containing 45 volumes of *acetonitrile* and 55 volumes of solution A.

(3) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

(4) Dilute 1 volumes of solution (2) to 5 volumes with a solution containing 45 volumes of *acetonitrile* and 55 volumes of solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 2.5 times the retention time of mometasone furoate.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mometasone furoate (retention time about 25 minutes) are: impurity C, about 0.9 and impurity J, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and mometasone furoate is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.1 volumes of glacial acetic acid, 50 volumes of *acetonitrile* and 50 volumes of *water*.

(1) Completely disperse a quantity of the scalp application containing 10 mg of Mometasone Furoate in 25 mL of *acetonitrile* in a water bath at a temperature of 80° and allow to cool. Add 20 mL of *acetonitrile* and 30 mL of solution A and shake for 30 minutes. Add sufficient solution A to produce 100 mL and filter.

(2) Dissolve 10 mg of *mometasone furoate BPCRS* in 45 mL of *acetonitrile* and add sufficient solution A to produce 100 mL.

(3) Dissolve 5 mg of *mometasone furoate for system suitability EPCRS* in 4.5 mL of *acetonitrile* and add sufficient solution A to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and mometasone furoate is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the scalp application using the declared content of $C_{27}H_{30}Cl_2O_6$ in *mometasone furoate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity C and impurity J listed under Mometasone Furoate.

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Montelukast Chewable Tablets

General Notices

Chewable Montelukast Tablets

Action and use

Leukotriene $CysLT_1$ receptor antagonist; treatment of asthma.

DEFINITION

Montelukast Chewable Tablets contain Montelukast Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of montelukast, $C_{35}H_{36}ClNO_3S$

93.0 to 105.0% of the stated amount.

Carry out the following procedures using solutions prepared immediately before use, protected from light and in low-actinic glassware.

IDENTIFICATION

A. Shake a quantity of the powdered tables containing the equivalent of 5 mg of montelukast in 150 mL of a solution of 1 volume of *water* and 3 volumes of *methanol* (solvent A). Mix with the aid of ultrasound for 70 minutes with occasional shaking. Add sufficient solvent A to produce a solution containing the equivalent of 0.0025% w/v of montelukast, mix and centrifuge. The light absorption, Appendix II B, in the range 210 to 400 nm exhibits four maxima, at 284, 328, 345 and 359 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of a 0.5% w/v solution of *sodium dodecyl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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For tablets containing 4 mg of Montelukast

(1) After 20 minutes withdraw a sample of the medium and filter (a Whatman glass fibre 1.0-µm filter is suitable). Use the filtered medium, diluted with dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.00044% w/v of montelukast.
(2) 0.03% w/v solution of *montelukast dicyclohexylamine BPCRS* in *methanol*. Dilute 1 volume of this solution to 50 volumes with a 0.5% w/v solution of *sodium dodecyl sulfate*.

For tablets containing 5 mg of Montelukast

(1) After 20 minutes withdraw a sample of the medium and filter (a Whatman glass fibre 1.0-µm filter is suitable). Use the filtered medium, diluted with dissolution medium if necessary, to produce a solution expected to contain 0.00055% w/v of montelukast.
(2) 0.035% w/v solution of *montelukast dicyclohexylamine BPCRS* in *methanol*. Dilute 1 volume of this solution to 50 volumes with a 0.5% w/v solution of *sodium dodecyl sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 3.0 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Inertsil Phenyl is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.9 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 389 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Equal volumes of a 0.2% v/v solution of *trifluoroacetic acid* in *water* and a 0.2% v/v solution of *trifluoroacetic acid* in *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of montelukast, $C_{35}H_{36}ClNO_3S$, in the medium from the chromatograms obtained and using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

LIMITS

The amount of montelukast released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions. Prepare a mixture of 1 volume of *water* and 3 volumes of *methanol* (solvent A).

For tablets containing 4 mg of Montelukast

(1) To 12 whole tablets add 150 mL of solvent A and mix with the aid of ultrasound. Add sufficient solvent A to produce a solution containing the equivalent of 0.024% w/v of montelukast, mix and filter (a Pall 0.45-µm PTFE filter is suitable).
For solutions (2) and (3) use the solutions described below for 5 mg tablets.

For tablets containing 5 mg of Montelukast

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(1) To 10 whole tablets add 150 mL of solvent A and mix with the aid of ultrasound. Add sufficient solvent A to produce a solution containing the equivalent of 0.025% w/v of montelukast, mix and filter (a Pall 0.45-µm PTFE filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A. Dilute 1 volume of this solution to 5 volumes with solvent A.

(3) To 10 mL of solution (1) add 4 µL of *hydrogen peroxide solution (100 vol)* and mix. Expose the solution to ambient light for 4 hours (generation of impurity G).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *phenylhexylsilyl silica gel for chromatography* (3 µm) (Phenomenex Luna Phenyl-Hexyl is suitable) and a (4 mm x 3.0 mm) guard column (Phenomenex Phenyl is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 255 nm.

(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 0.2% v/v of *trifluoroacetic acid* in *water*.

Mobile phase B 2 volumes of *acetonitrile* and 3 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	48	52	isocratic
5-10	48→45	52→55	linear gradient
10-17	45	55	isocratic
17-27	45→25	55→75	linear gradient
27-28	25	75	isocratic
28-30	25→48	75→52	linear gradient
30-40	48	52	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to montelukast (retention time about 20 minutes) are: impurity C, about 0.45; impurity G, about 0.92; impurity F, about 1.04; impurity D, about 1.16; impurity E, about 1.18 and impurity B, about 1.55.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and montelukast is at least 1.5.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 8.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.7%);

the area of any peak corresponding to impurity G is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peaks corresponding to impurities D and E is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any peak corresponding to impurity F is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 13.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.7%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of Content

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of Montelukast comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For 4 mg tablets

(1) To 1 tablet add 50 mL of *water*. Add 110 mL of *methanol* shake and mix with the aid of ultrasound. Add sufficient *methanol* to produce a solution containing the equivalent of 0.002% w/v of montelukast. Mix and filter (a Pall PDVF filter is suitable).
(2) 0.0026% w/v of *montelukast dicyclohexylamine BPCRS* in a mixture of 1 volume of *water* and 3 volumes of *methanol*.

For 5 mg tablets

(1) To 1 tablet add 50 mL of *water*. Add 110 mL of *methanol*, shake and mix with the aid of ultrasound. Add sufficient *methanol* to produce a solution containing the equivalent of 0.0025% w/v of montelukast. Mix and filter (a Pall PDVF filter is suitable).
(2) 0.0033% w/v of *montelukast dicyclohexylamine BPCRS* in a mixture of 1 volume of *water* and 3 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used. Inject 10 µL of each solution.

DETERMINATION OF CONTENT

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Calculate the content of $C_{35}H_{36}ClNO_3S$ in each tablet using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of montelukast

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of montelukast

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a mixture of 1 volume of *water* and 3 volumes of *methanol* (solvent A).

(1) To 10 whole tablets add 150 mL of solvent A and mix with the aid of ultrasound. Add sufficient solvent A to produce a solution containing the equivalent of 0.025% w/v of montelukast, mix and filter (a Pall 0.45-µm PTFE filter is suitable).
(2) 0.033% w/v of *montelukast dicyclohexylamine BPCRS* in solvent A.
(3) To 10 mL of solution (1) add 4 µL of *hydrogen peroxide solution (100 vol)* and mix. Expose the solution to ambient light for 4 hours (generation of impurity G).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and montelukast is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{35}H_{36}ClNO_3S$ in the tablets using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Montelukast Sodium.

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Montelukast Granules

General Notices

Action and use

Leukotriene $CysLT_1$ receptor antagonist; treatment of asthma.

DEFINITION

Montelukast Granules contain Montelukast Sodium.

The granules comply with the requirements stated under Granules and with the following requirements.

Content of montelukast, $C_{35}H_{36}ClNO_3S$

94.0 to 105.0% of the stated amount.

Carry out the following procedures using solutions prepared immediately before use, protected from light and in low-actinic glassware.

IDENTIFICATION

A. Shake a quantity of the granules containing the equivalent of 5 mg of montelukast in 150 mL of a solution of 1 volume of *water* and 3 volumes of *methanol* (solvent A). Mix with the aid of ultrasound for 70 minutes with occasional shaking. Add sufficient solvent A to produce a solution containing the equivalent of 0.0025% w/v of montelukast, mix and centrifuge. The *light absorption*, Appendix II B, in the range 210 to 400 nm exhibits four maxima, at 284, 328, 345 and 359 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for solid dosage forms* Appendix XII B1. Use one dosage unit of the granules.

TEST CONDITIONS

(a) Use Apparatus 1, and rotate the basket at 50 revolutions per minute.

(b) Use 900 mL of a 0.5% w/v solution of *sodium dodecyl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) After 20 minutes withdraw a sample of the medium and filter (a Pall glass fibre 1.0-µm filter is suitable). Use the filtered medium, diluted with dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.00044% w/v of montelukast.

(2) 0.033% w/v solution of *montelukast dicyclohexylamine BPCRS* in *methanol*. Dilute 1 volume of this solution to 50 volumes with a 0.5% w/v solution of *sodium dodecyl sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 3.0 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Inertsil Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.9 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 389 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

Equal volumes of a 0.2% v/v solution of *trifluoroacetic acid* in *water* and a 0.2% v/v solution of *trifluoroacetic acid* in *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of montelukast, $C_{35}H_{36}ClNO_3S$, in the medium from the chromatograms obtained and using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

LIMITS

The amount of montelukast released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions. Prepare a mixture of 1 volume of *water* and 3 volumes of *methanol* (solvent A).

(1) To a quantity of the granules containing the equivalent of 60 mg of montelukast add 250 mL of solvent A and mix with the aid of ultrasound. Add sufficient solvent A to produce a solution containing the equivalent of 0.024% w/v of montelukast, mix and filter (a Pall 0.45-µm PTFE filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A. Dilute 1 volume of this solution to 5 volumes with solvent A.

(3) To 10 mL of solution (1) add 4 µL of *hydrogen peroxide solution (100 vol)* and mix. Expose the solution to ambient light for 1 hour (generation of impurity G).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *phenylhexylsilyl silica gel for chromatography* (3 µm) (Phenomenex LUNA Phenyl-Hexyl is suitable) and a (4 mm × 3.0 mm) guard column (Phenomenex Phenyl is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 50°.

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(e) Use a detection wavelength of 255 nm.

(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 0.2% v/v of *trifluoroacetic acid* in *water*.

Mobile phase B 2 volumes of *acetonitrile* and 3 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	48	52	isocratic
5-10	48→45	52→55	linear gradient
10-17	45	55	isocratic
17-27	45→25	55→75	linear gradient
27-28	25	75	isocratic
28-30	25→48	75→52	linear gradient
30-40	48	52	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to montelukast (retention time, about 20 minutes) are: impurity C, about 0.45; impurity G, about 0.92; impurity F, about 1.04; impurity D, about 1.16; impurity E, about 1.18 and impurity B, about 1.55.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and montelukast is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 8.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.7%);

the area of any peak corresponding to impurity B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peaks corresponding to impurities D and E is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any peak corresponding to impurity F or G is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

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the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 13.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.7%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Granules containing the equivalent of less than 2 mg and/or less than 2% w/w of Montelukast comply with the requirements stated under Granules using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To the contents of one packet of granules add 130 mL of *methanol* and mix with the aid of ultrasound. Add sufficient *methanol* to produce a solution containing the equivalent of 0.002% w/v of montelukast. Mix and filter (a Pall Acrodisc PTFE 0.45-µm filter is suitable).
(2) 0.00264% w/v of *montelukast dicyclohexylamine BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use stainless steel column (10 cm × 3.0 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Inertsil Phenyl is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.9 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 389 nm.
(f) Inject 5 µL of each solution.

MOBILE PHASE

Equal volumes of a 0.2% v/v solution of *trifluoroacetic acid* in *water* and a 0.2% v/v solution of *trifluoroacetic acid* in *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{35}H_{36}ClNO_3S$ in the granules using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

ASSAY

For granules containing the equivalent of less than 2 mg and/or less than 2% w/w of Montelukast

Use the average of the individual results determined in the test for Uniformity of content.

For granules containing the equivalent 2 mg or more and 2% w/w or more of Montelukast

Carry out the method for *liquid chromatography*, Appendix III D. Prepare a mixture of 1 volume of *water* and 3 volumes of *methanol* (solvent A).

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(1) To a quantity of the granules containing the equivalent of 60 mg of montelukast add sufficient solvent A to produce a solution containing the equivalent of 0.024% w/v of montelukast, mix with the aid of ultrasound and filter (a Pall 0.45-µm PTFE filter is suitable).

(2) 0.033% w/v of *montelukast dicyclohexylamine BPCRS* in solvent A.

(3) To 10 mL of solution (1) add 4 µL of *hydrogen peroxide solution (100 vol)* and mix. Expose the solution to ambient light for 1 hour (generation of impurity G).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and montelukast is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{35}H_{36}ClNO_3S$ in the granules using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Montelukast Sodium.

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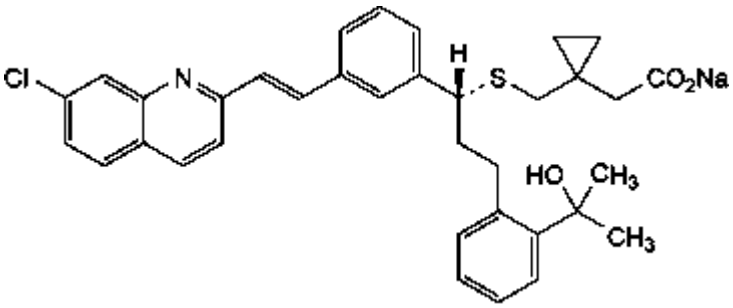
Montelukast Sodium

General Notices

(Ph. Eur. monograph 2583)



$C_{35}H_{35}ClNNaO_3S$ 608 *151767-02-1*

Action and use

Leukotriene $CysLT_1$ receptor antagonist; treatment of asthma.

Preparations

Montelukast Chewable Tablets

Montelukast Granules

Montelukast Tablets

Ph Eur

DEFINITION

Sodium [1-[[[(1*R*)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

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Solubility

Freely soluble in water and in methylene chloride, freely soluble to very soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *montelukast sodium CRS*.

B. Enantiomeric purity (see Tests).

C. Ignite 0.1 g in a crucible until an almost white residue is obtained. Take up the residue in 2 mL of *water R* and filter. The filtrate gives reaction (a) of sodium (2.3.1).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29). *Carry out the test protected from light. Prepare the solutions in amber flasks.*

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *montelukast racemate CRS* in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *silica gel AGP for chiral chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 2.3 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *glacial acetic acid R*;

— *mobile phase B*: *acetonitrile R*, *methanol R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	70 → 60	30 → 40
30 - 35	60	40

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Flow rate 0.9 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Relative retention With reference to montelukast (retention time = about 25 min): impurity A = about 0.7.

System suitability:

— *resolution*: minimum 2.9 between the peaks due to impurity A and montelukast in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (a).

Calculate the percentage content of impurity A using the following expression:

$$100\left(\frac{r_1}{r_2}\right)$$

r_1 = area of the peak due to impurity A in the chromatogram obtained with the test solution;

r_2 = sum of the areas of the peaks due to montelukast and impurity A in the chromatogram obtained with the test solution.

Limit:

— *impurity A*: maximum 0.2 per cent.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Carry out the test protected from light. Prepare the solutions in amber flasks.*

Solvent mixture *water R*, *methanol R* (10:90 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *montelukast for peak identification CRS* (containing impurities B, C, D, E and F) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c) In order to prepare impurity G *in situ*, transfer 1 mL of reference solution (b) to a colourless glass vial and expose to ambient light for about 20 min.

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Reference solution (d) Dissolve 65.0 mg of *montelukast dicyclohexylamine CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (1.8 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 1.5 mL of *trifluoroacetic acid R* and 1000 mL of *water R*;

— *mobile phase B*: mix 1.5 mL of *trifluoroacetic acid R* and 1000 mL of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	60	40
3 - 16	60 → 49	40 → 51

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 238 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (c); 20 µL of reference solution (b).

Identification of impurities Use the chromatogram supplied with *montelukast for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D, E and F; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to montelukast (retention time = about 7 min): impurity C = about 0.4; impurity G = about 0.8; impurities D and E = about 0.9; impurity F = about 1.2; impurity B = about 1.9.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurity G and montelukast; minimum 1.5 between the peaks due to montelukast and impurity F.

Limits:

— *impurity B*: maximum 0.3 per cent;

— *impurity C*: maximum 0.2 per cent;

— *impurities F, G*: for each impurity, maximum 0.15 per cent;

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— *sum of impurities D and E*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.300 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{35}H_{35}ClNNaO_3S$ using the following expression:

$$\frac{A_1 \times m_2 \times 79.24 \times p}{A_2 \times m_1 \times (100 - a)}$$

A_1	=	area of the principal peak in the chromatogram obtained with test solution (b);
A_2	=	area of the principal peak in the chromatogram obtained with reference solution (d);
m_1	=	mass of the substance to be examined used to prepare test solution (a), in milligrams;
m_2	=	mass of *montelukast dicyclohexylamine CRS* used to prepare reference solution (d), in milligrams;
p	=	declared percentage content of *montelukast dicyclohexylamine CRS*;
a	=	percentage content of water in the substance to be examined.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, I.*

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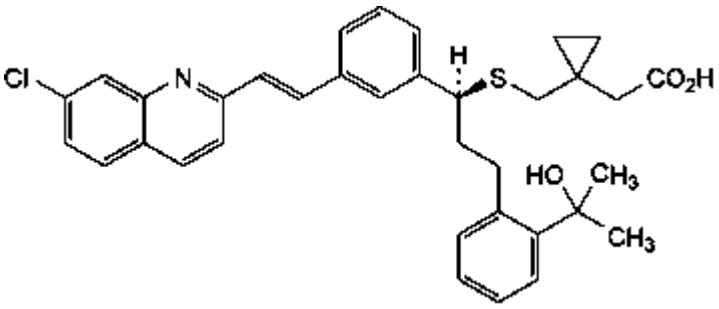
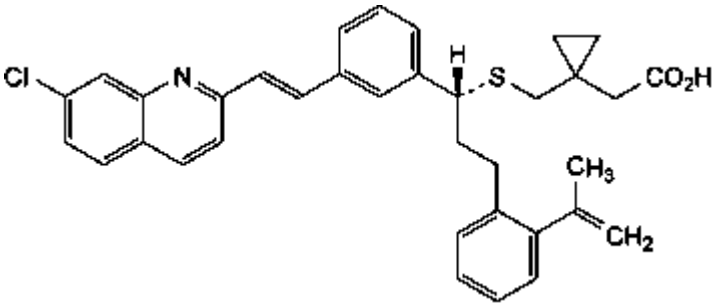
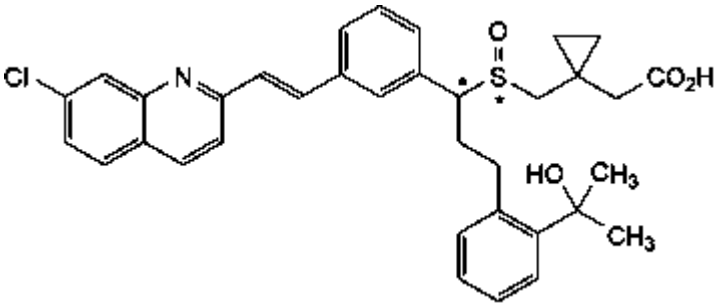


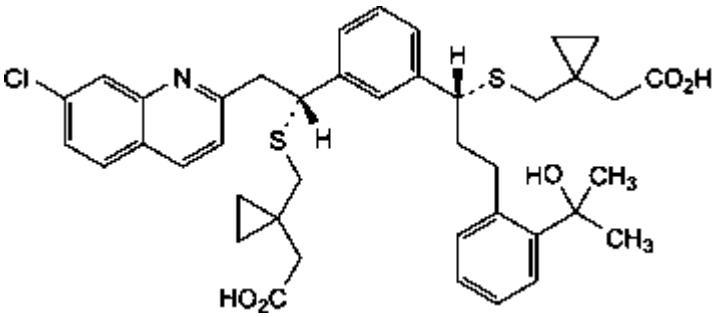
A. [1-[[[(1*S*)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid,



B. [1-[[[(1*R*)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-methylethenyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid,



C. [1-[[[1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfinyl]methyl]cyclopropyl]acetic acid,



D. 1-[[[(1*R*)-1-[3-[(1*R*)-1-[[[1-(carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid,

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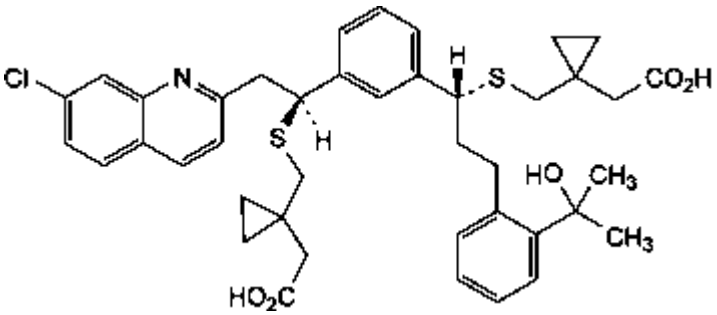
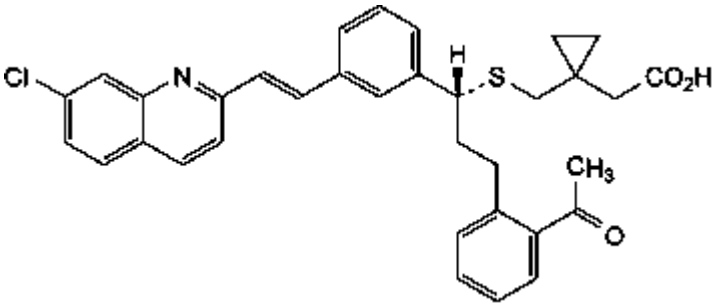
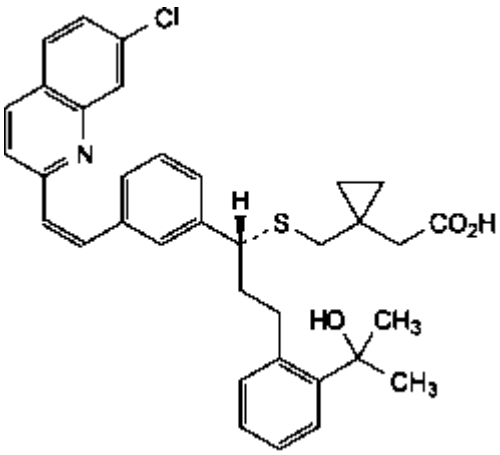


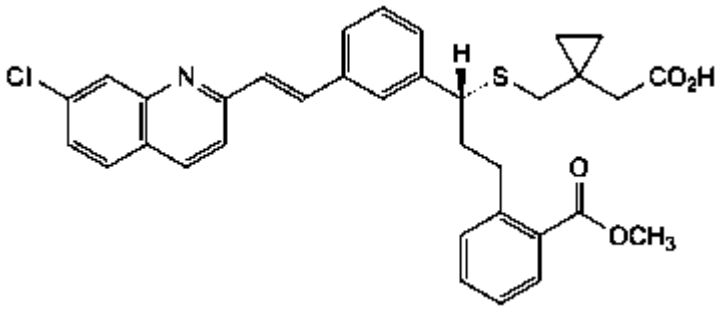
E. 1-[[[(1*R*)-1-[3-[(1*S*)-1-[[[1-(carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid,



F. [1-[[[(1*R*)-3-(2-acetylphenyl)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid,



G. [1-[[[(1*R*)-1-[3-[(*Z*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid,



H. [1-[[[(1*R*)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(methoxycarbonyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid,

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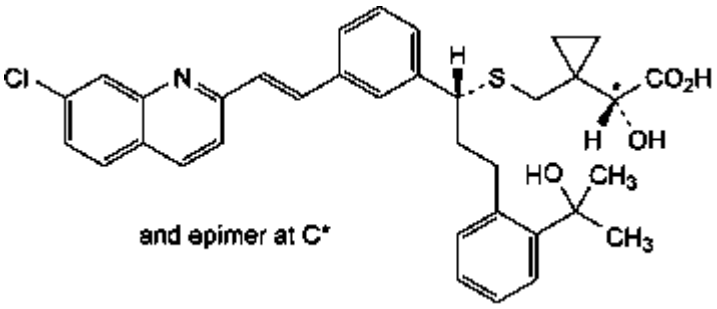

I. (2*RS*)-[1-[[[(1*R*)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl](hydroxy)acetic acid.

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Montelukast Tablets

General Notices

Action and use

Leukotriene $CysLT_1$ receptor antagonist; treatment of asthma.

DEFINITION

Montelukast Tablets contain Montelukast Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of montelukast, $C_{35}H_{36}ClNO_3S$

94.0 to 105.0% of the stated amount.

Carry out the following procedures using solutions prepared immediately before use, protected from light and in low-actinic glassware.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 5 mg of montelukast in 150 mL of a solution of 1 volume of *water* and 3 volumes of *methanol* (solvent A). Mix with the aid of ultrasound for 70 minutes with occasional shaking. Dilute to 200 mL with solvent A to produce a solution containing the equivalent of 0.0025% w/v of montelukast, mix and centrifuge. The *light absorption*, Appendix II B, in the range 210 to 400 nm exhibits four maxima, at 284, 328, 345 and 359 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of a 0.5% w/v solution of *sodium dodecyl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) After 20 minutes withdraw a sample of the medium and filter (a Whatman glass fibre 1.0-µm filter is suitable). Use the filtered medium, diluted with dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.0011% w/v of montelukast.

(2) 0.035% w/v solution of *montelukast dicyclohexylamine BPCRS* in *methanol*. Dilute 1 volume of this solution to 25 volumes with a 0.5% w/v solution of *sodium dodecyl sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 3.0 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Inertsil Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.9 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 389 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Equal volumes of a 0.2% v/v solution of *trifluoroacetic acid* in *water* and a 0.2% v/v solution of *trifluoroacetic acid* in *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of montelukast, $C_{35}H_{36}ClNO_3S$, in the medium from the chromatograms obtained and using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

LIMITS

The amount of montelukast released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions. Prepare a mixture of 1 volume of *water* and 3 volumes of *methanol* (solvent A).

(1) To 10 whole tablets add 180 mL of solvent A and mix with the aid of ultrasound. Shake, add sufficient solvent A to produce a solution containing the equivalent of 0.04% w/v of montelukast, mix and filter (a Pall 0.45-µm PTFE filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A. Dilute 1 volume of this solution to 5 volumes with solvent A.

(3) To 10 mL of solution (1) add 4 µL of *hydrogen peroxide solution (100 vol)* and mix. Expose the solution to ambient light for 4 hours (generation of impurity G).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *phenylhexylsilyl silica gel for chromatography* (3 µm) (Phenomenex Luna Phenyl-Hexyl is suitable) and a (4 mm × 3.0 mm) guard column (Phenomenex Phenyl is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 255 nm.

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(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 0.2% v/v of *trifluoroacetic acid* in *water*.

Mobile phase B 2 volumes of *acetonitrile* and 3 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	48	52	isocratic
5-10	48→45	52→55	linear gradient
10-17	45	55	isocratic
17-27	45→25	55→75	linear gradient
27-28	25	75	isocratic
28-30	25→48	75→52	linear gradient
30-40	48	52	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to montelukast (retention time, about 20 minutes) are: impurity C, about 0.45; impurity G, about 0.92; impurity F, about 1.04; impurity D, about 1.16; impurity E, about 1.18 and impurity B, about 1.55.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and montelukast is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 8.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.7%);

the area of any peak corresponding to impurity G is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peaks corresponding to impurities D and E is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

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the area of any peak corresponding to impurity F is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 13.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.7%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a mixture of 1 volume of *water* and 3 volumes of *methanol* (solvent A).

(1) To 10 whole tablets add 180 mL of solvent A and mix with the aid of ultrasound. Shake, add sufficient solvent A to produce a solution containing the equivalent of 0.04% w/v of montelukast, mix and filter (a Pall 0.45-µm PTFE filter is suitable).
(2) 0.052% w/v of *montelukast dicyclohexylamine BPCRS* in solvent A.
(3) To 10 mL of solution (1) add 4 µL of *hydrogen peroxide solution (100 vol)* and mix. Expose the solution to ambient light for 4 hours (generation of impurity G).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and montelukast is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{35}H_{36}ClNO_3S$ in the tablets using the declared content of $C_{47}H_{59}ClN_2O_3S$ in *montelukast dicyclohexylamine BPCRS*. Each mg of $C_{47}H_{59}ClN_2O_3S$ is equivalent to 0.7637 mg of $C_{35}H_{36}ClNO_3S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Montelukast Sodium.

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Morphine Capsules

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Capsules contain Morphine Sulfate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 5 mg of Morphine Sulfate with 10 mL of *ethanol (48%)* and filter.

(2) 0.05% w/v of *morphine sulfate BPCRS* in *ethanol (48%)*.

(3) 0.05% w/v each of *morphine sulfate BPCRS* and *codeine phosphate BPCRS* in *ethanol (48%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air, spray with *potassium iodobismuthate solution R2* *and* examine in daylight.

MOBILE PHASE

2.5 volumes of 13.5M *ammonia*, 32.5 volumes of *acetone*, 35 volumes of *ethanol (70%)* and 35 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in size, position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. The powdered capsules yield the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 6.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *phosphate buffer pH 6.5* if necessary, to produce a solution expected to contain 0.001% w/v of Morphine Sulfate.

(2) 0.001% w/v of *morphine sulfate BPCRS* in *phosphate buffer pH 6.5*.

(3) 0.03% w/v of *morphine for system suitability EPCRS* in the mobile phase

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex HyperClone BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 281 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile* and 700 volumes of 0.01M *sodium octanesulfonate*.

When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and pseudomorphine are about 2.5 minutes and 3.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to morphine and pseudomorphine is at least 1.5.

DETERMINATION OF CONTENT

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Calculate the total content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in the medium from the chromatograms obtained and using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*

LIMITS

The amount of morphine sulfate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A 1.0% v/v solution of *acetic acid*.

(1) Shake a quantity of powdered capsules containing 62.5 mg of Morphine Sulfate with 30 mL of solvent A, add sufficient solvent A to produce 50 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 5 volumes.
(4) 0.25% w/v of *morphine for system suitability EPCRS* and 0.0625% w/v *codeine phosphate BPCRS*.
(5) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 12.5 minutes) are: impurity A, about 1.43; impurity F, about 0.95; impurity E, about 1.1; impurity C, about 1.6 and impurity B, about 1.9.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and morphine is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to impurity A is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered mixed contents of 20 capsules containing 30 mg of Morphine Sulfate with 50 mL of the mobile phase, dilute to 100 mL with the same solvent and filter.
(2) 0.03% w/v of *morphine sulfate BPCRS* in the mobile phase.
(3) 0.03% w/v of *morphine for system suitability EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to morphine and pseudomorphine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

STORAGE

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Morphine Capsules should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph those listed under Morphine Sulfate.

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Morphine Granules for Oral Suspension

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Granules for Oral Suspension contains Morphine Sulfate.

Morphine Granules for Oral Suspension comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

Content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions in *ethanol* (48%).

(1) Shake a quantity of the granules containing 20 mg of Morphine Sulfate with 10 mL and filter.

(2) 0.05% w/v of *morphine sulfate BPCRS*.

(3) 0.05% w/v each of *morphine sulfate BPCRS* and *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air, spray with *potassium iodobismuthate solution R2* and examine in daylight.

MOBILE PHASE

2.5 volumes of 13.5M *ammonia*, 32.5 volumes of *acetone*, 35 volumes of *ethanol (70%)* and 35 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in size, position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A 0.05 volumes of *orthophosphoric acid*, 20 volumes of *acetonitrile* and 80 volumes of 0.01M *sodium octanesulfonate*.

(1) Shake a quantity of granules containing 30 mg of Morphine Sulfate with 800 mL of solvent A for 6 hours. Dilute to 1000 mL with solvent A and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

(4) 0.025% w/v of *morphine for system suitability EPCRS* and 0.00625% of w/v *codeine phosphate*.

(5) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 200 µL of each solution.

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase A *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 13.4 minutes) are: impurity F, about 0.98; minutes; impurity E, about 1.10; impurity A, about 1.38; impurity C, about 1.52 and impurity B, about 1.76.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity E and morphine is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not more than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity A is not more than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peaks* is not more than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered granules containing 30 mg of Morphine Sulfate with 800 mL for six hours, dilute to 1000 mL and filter.
(2) 0.003% w/v of *morphine sulfate BPCRS*.
(3) 0.003% w/v of *morphine sulfate BPCRS* and 0.00033% w/v of *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex HyperClone BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 281 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volumes of *orthophosphoric acid*, 200 volumes of *acetonitrile* and 800 volumes of 0.01M *sodium octanesulfonate*.

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When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and codeine phosphate are about 7 minutes and 15 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to morphine and codeine is at least 10.0.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in the granules using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

STORAGE

Morphine Granules for Oral Suspension should be protected from light.

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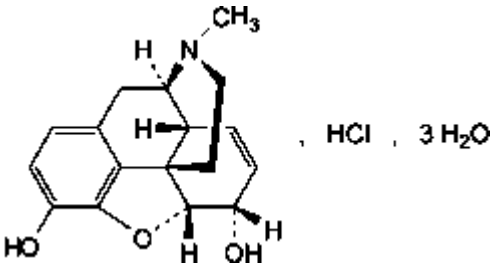
Morphine Hydrochloride

General Notices

(Ph. Eur. monograph 0097)



$C_{17}H_{20}ClNO_3,3H_2O$ 375.8 *6055-06-7*

Action and use

Opioid receptor agonist; analgesic.

Preparation

Morphine Suppositories

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DEFINITION

7,8-Didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol hydrochloride trihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless, silky needles or cubical masses, efflorescent in a dry atmosphere.

Solubility

Soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in toluene.

IDENTIFICATION

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First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *morphine hydrochloride trihydrate CRS*.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Solution A Dissolve 25.0 mg in *water R* and dilute to 25.0 mL with the same solvent.

Test solution (a) Dilute 10.0 mL of solution A to 100.0 mL with *water R*.

Test solution (b) Dilute 10.0 mL of solution A to 100.0 mL with *0.1 M sodium hydroxide*.

Spectral range 250-350 nm for test solutions (a) and (b).

Absorption maximum At 285 nm for test solution (a); at 298 nm for test solution (b).

Specific absorbance at the absorption maximum 37 to 43 for test solution (a); 64 to 72 for test solution (b).

C. To about 1 mg of powdered substance in a porcelain dish add 0.5 mL of *sulfuric acid-formaldehyde reagent R*. A purple colour develops and becomes violet.

D. It gives the reaction of alkaloids (2.3.1).

E. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 or BY_6 (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M sodium hydroxide* or *0.02 M hydrochloric acid* is required to change the colour of the indicator.

Specific optical rotation (2.2.7)

-110 to -115 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

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Test solution Dissolve 0.125 g of the substance to be examined in a 1 per cent *V/V* solution of *acetic acid R* and dilute to 50 mL with the same solution.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with a 1 per cent *V/V* solution of *acetic acid R*. Dilute 2.0 mL of this solution to 10.0 mL with a 1 per cent *V/V* solution of *acetic acid R*.

Reference solution (b) Dissolve 5 mg of *morphine for system suitability CRS* (containing impurities B, C, E and F) in a 1 per cent *V/V* solution of *acetic acid R* and dilute to 2 mL with the same solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 1.01 g/L solution of *sodium heptanesulfonate R* adjusted to pH 2.6 with a 50 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 35	85 → 50	15 → 50
35 - 40	50	50

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *morphine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, E and F.

Relative retention With reference to morphine (retention time = about 12.5 min): impurity F = about 0.95; impurity E = about 1.1; impurity C = about 1.6; impurity B = about 1.9.

System suitability Reference solution (b):

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— *peak-to-valley ratio*: minimum 2, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to morphine.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.25; impurity C = 0.4; impurity E = 0.5;

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurities C, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Water (*2.5.12*)

12.5 per cent to 15.5 per cent, determined on 0.10 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 5 mL of *0.01 M hydrochloric acid* and 30 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.18 mg of $C_{17}H_{20}ClNO_3$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities B, C, E.

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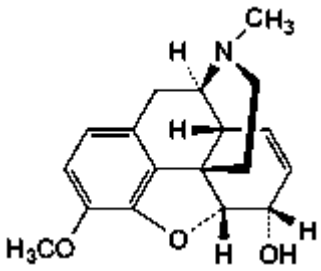
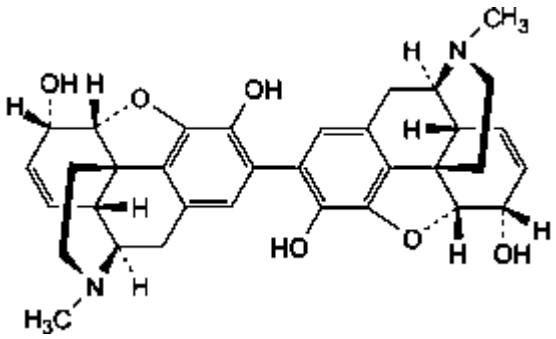
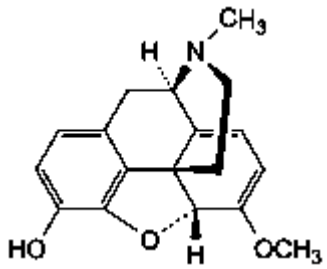
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, D, F.



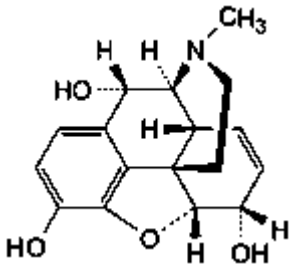
A. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (codeine),



B. 7,7′,8,8′-tetradehydro-4,5α:4′,5′α-diepoxy-17,17′-dimethyl-2,2′-bimorphinanyl-3,3′,6α,6′α-tetrol (2,2′-bimorphine),



C. 6,7,8,14-tetradehydro-4,5α-epoxy-6-methoxy-17-methylmorphinan-3-ol (oripavine),



D. 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α,10α-triol (10*S*-hydroxymorphine),

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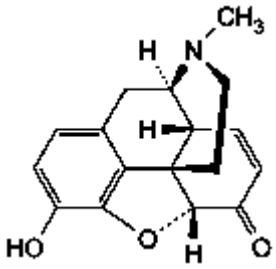
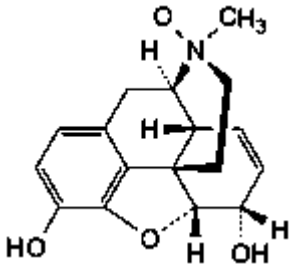


E. 7,8-didehydro-4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one (morphinone),



F. (17*S*)-7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol 17-oxide (morphine *N*-oxide).

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Morphine Oral Solution

General Notices

Morphine Sulfate Oral Solution

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Oral Solution is a solution of Morphine Sulfate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the solution, if necessary, with *ethanol (48%)* to produce a solution containing 0.05% w/v of Morphine Sulfate.

(2) 0.05% w/v of *morphine sulfate BPCRS* in *ethanol (48%)*.

(3) 0.05% w/v each of *morphine sulfate BPCRS* and *codeine phosphate BPCRS* in *ethanol (48%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air, spray with *potassium iodobismuthate solution R2* and examine the plate in daylight.

MOBILE PHASE

2.5 volumes of 13.5M *ammonia*, 32.5 volumes of *acetone*, 35 volumes of *ethanol (70%)* and 35 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in size, position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A a 1.0% v/v solution of *acetic acid*.

(1) Dilute the oral solution to produce a solution containing 0.12% w/v of Morphine Sulfate.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.25% w/v of *morphine for system suitability EPCRS* and 0.0625% w/v *codeine phosphate BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase B *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 12.5 minutes) are: impurity F, about 0.95; impurity A, about 1.15; impurity E, about 1.1; impurity C, about 1.6 and impurity B, about 1.9.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and morphine is at least 1.5.

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LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (3) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity F is not greater than 0.6 times the area of the peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peaks* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (60%)*.

(1) Dilute a weighed quantity of the solution containing 30 mg Morphine Sulfate and dilute with the mobile phase to produce a solution containing 0.03% w/v of Morphine Sulfate.
(2) 0.03% w/v of *morphine sulfate BPCRS*.
(3) 0.03% w/v of *morphine for system suitability EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex HyperClone BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 281 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.05 volumes of *orthophosphoric acid*, 30 volumes of *acetonitrile* and 70 volumes of 0.01M *sodium octanesulfonate*.

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When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and pseudomorphine are about 2.5 minutes and 3.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3) the *resolution* between the peaks due to morphine and pseudomorphine is at least 4.0.

DETERMINATION OF CONTENT

Determine the weight per mL of the oral solution, Appendix V G. Calculate the content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in the oral solution using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

STORAGE

Morphine Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph those listed under Morphine Sulfate.

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Morphine Prolonged-release Capsules

General Notices

Prolonged-release Morphine Capsules

Morphine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Prolonged-release Capsules contain Morphine Sulfate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of morphine sulfate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 5 mg of Morphine Sulfate with 10 mL of *ethanol (48%)* and filter.

(2) 0.05% w/v of *morphine sulfate BPCRS* in a mixture of equal volumes of *ethanol (48%)* and *water*.

(3) 0.05% w/v each of *morphine sulfate BPCRS* and *codeine phosphate BPCRS* in a mixture of equal volumes of *ethanol (48%)* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air, spray with *potassium iodobismuthate solution R2* and examine the plate in daylight.

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MOBILE PHASE

2.5 volumes of 13.5M *ammonia*, 32.5 volumes of *acetone*, 35 volumes of *ethanol (70%)* and 35 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in size, position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A 1.0% v/v solution of *acetic acid*.

(1) Shake a quantity of powdered capsules contents containing 62.5 mg of Morphine Sulfate with 30 mL of solvent A, dilute to 50 mL with solvent A and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 5 volumes.
(4) 0.25% w/v of *morphine for system suitability EPCRS* and 0.0625% w/v of *codeine phosphate BPCRS*.
(5) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 12.5 minutes) are: impurity F, about 0.9; impurity E, about 1.1; impurity A, about 1.4; impurity C, about 1.6 and impurity B, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and morphine is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity A is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%).

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered mixed contents of 20 capsules containing 30 mg of Morphine Sulfate with 50 mL of the mobile phase, dilute to 100 mL with the mobile phase and filter.

(2) 0.03% w/v of *morphine sulfate BPCRS* in the mobile phase.

(3) 0.03% w/v of *morphine for system suitability EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex HyperClone BDS C18).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 281 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.05 volumes of *orthophosphoric acid*, 30 volumes of *acetonitrile* and 70 volumes of 0.01M *sodium octanesulfonate*.

When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and pseudomorphine are about 2.5 minutes and 3.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to morphine and pseudomorphine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Morphine Sulfate.

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Morphine Prolonged-release Tablets

General Notices

Prolonged-release Morphine Tablets

Morphine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Prolonged-release Tablets contain Morphine Sulfate. They are formulated so that the medicament is released over a period of several hours. They are coated.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of morphine sulfate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 5 mg of Morphine Sulfate with 10 mL of *ethanol (48%)* and filter.

(2) 0.05% w/v of *morphine sulfate BPCRS* in *ethanol (48%)*.

(3) 0.05% w/v each of *morphine sulfate BPCRS* and *codeine phosphate BPCRS* in *ethanol (48%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air, spray with *potassium iodobismuthate solution R2* and examine the plate in daylight.

MOBILE PHASE

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2.5 volumes of 13.5M *ammonia*, 32.5 volumes of *acetone*, 35 volumes of *ethanol (70%)* and 35 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in size, position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A 1.0% v/v solution of *acetic acid*.

(1) Shake a quantity of powdered tablets containing 62.5 mg of Morphine Sulfate with 30 mL of solvent A, dilute to 50 mL with solvent A and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 5 volumes.
(4) 0.25% w/v of *morphine for system suitability EPCRS* and 0.0625% w/v of *codeine phosphate BPCRS*.
(5) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase B *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 12.5 minutes) are: impurity F, about 0.9; impurity E, about 1.1; impurity A, about 1.4; impurity C, about 1.6 and impurity B, about 1.9.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and morphine is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity A is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%).

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 30 mg of Morphine Sulfate with 50 mL of the mobile phase, dilute to 100 mL with the mobile phase and filter.

(2) 0.03% w/v of *morphine sulfate BPCRS* in the mobile phase.

(3) 0.03% w/v of *morphine for system suitability EPCRS* in the mobile phase

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex HyperClone BDS C18).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 281 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.05 volumes of *orthophosphoric acid*, 30 volumes of *acetonitrile* and 70 volumes of 0.01M *sodium octanesulfonate*. When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and pseudomorphine are about 2.5 minutes and 3.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to morphine and pseudomorphine is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in the tablets using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Morphine Sulfate.

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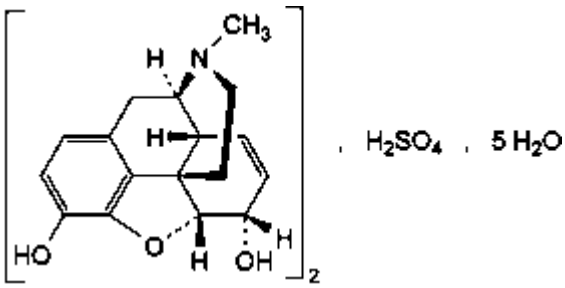
Morphine Sulfate

General Notices

Morphine Sulphate

(Ph. Eur. monograph 1244)



$C_{34}H_{40}N_2O_{10}S,5H_2O$ 759 *6211-15-0*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Morphine Granules for Oral Suspension

Morphine Sulfate Injection

Morphine Sulfate Oral Solution

Morphine Suppositories

Morphine Tablets

Morphine Prolonged-release Capsules

Morphine Prolonged-release Tablets

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DEFINITION

Di(7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol) sulfate pentahydrate.

Content

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98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in toluene.

IDENTIFICATION

First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 20 mg in 1 mL of water R, add 0.05 mL of 1 M sodium hydroxide and shake. A precipitate is formed. Filter, wash with 2 quantities, each of 0.5 mL, of water R and dry the precipitate at 145 °C for 1 h. Prepare discs using the dried precipitate.

Comparison Repeat the operations using 20 mg of morphine sulfate CRS.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Solution A Dissolve 25.0 mg in water R and dilute to 25.0 mL with the same solvent.

Test solution (a) Dilute 10.0 mL of solution A to 100.0 mL with water R.

Test solution (b) Dilute 10.0 mL of solution A to 100.0 mL with 0.1 M sodium hydroxide.

Spectral range 250-350 nm for test solutions (a) and (b).

Absorption maximum At 285 nm for test solution (a); at 298 nm for test solution (b).

Specific absorbance at the absorption maximum 37 to 43 for test solution (a); 64 to 72 for test solution (b).

C. To about 1 mg of powdered substance in a porcelain dish add 0.5 mL of sulfuric acid-formaldehyde reagent R. A purple colour develops and becomes violet.

D. It gives the reaction of alkaloids (2.3.1).

E. It gives the reactions of sulfates (2.3.1).

TESTS

Solution S

Dissolve 0.500 g in carbon dioxide-free water R and dilute to 25.0 mL with the same solvent.

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Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 or BY_6 (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M sodium hydroxide* or *0.02 M hydrochloric acid* is required to change the colour of the indicator.

Specific optical rotation (2.2.7)

-107 to -110 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.125 g of the substance to be examined in a 1 per cent *V/V* solution of *acetic acid R* and dilute to 50 mL with the same solution.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with a 1 per cent *V/V* solution of *acetic acid R*. Dilute 2.0 mL of this solution to 10.0 mL with a 1 per cent *V/V* solution of *acetic acid R*.

Reference solution (b) Dissolve 5 mg of *morphine for system suitability CRS* (containing impurities B, C, E and F) in a 1 per cent *V/V* solution of *acetic acid R* and dilute to 2 mL with the same solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 1.01 g/L solution of *sodium heptanesulfonate R* adjusted to pH 2.6 with a 50 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 35	85 → 50	15 → 50
35 - 40	50	50

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Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *morphine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, E and F.

Relative retention With reference to morphine (retention time = about 12.5 min): impurity F = about 0.95; impurity E = about 1.1; impurity C = about 1.6; impurity B = about 1.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to morphine.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.25; impurity C = 0.4; impurity E = 0.5;

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurities C, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Iron (*2.4.9*)

Maximum 5 ppm.

Dissolve the residue from the test for sulfated ash in *water R* and dilute to 10.0 mL with the same solvent.

Water (*2.5.12*)

10.4 per cent to 13.4 per cent, determined on 0.10 g.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Dissolve 0.500 g in 120 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 66.88 mg of $C_{34}H_{40}N_2O_{10}S$.

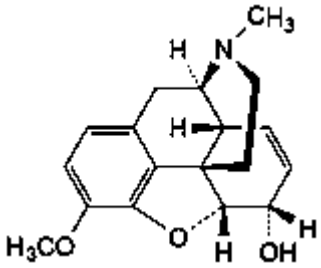
STORAGE

Protected from light.

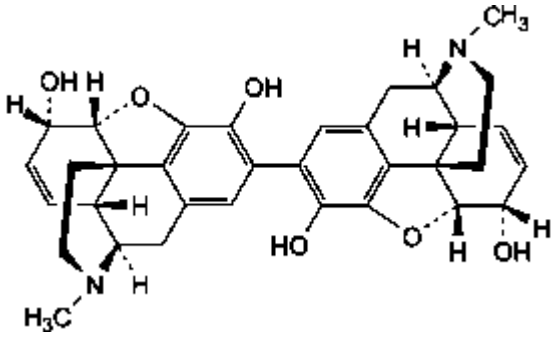
IMPURITIES

Specified impurities B, C, E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, D, F.



A. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (codeine),



B. 7,7′,8,8′-tetradehydro-4,5α:4′,5′α-diepoxy-17,17′-dimethyl-2,2′-bimorphinanyl-3,3′,6α,6′α-tetrol (2,2′-bimorphine),

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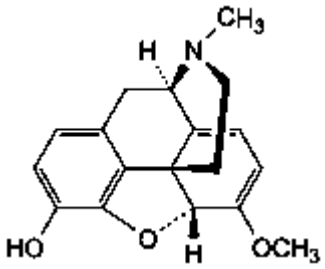
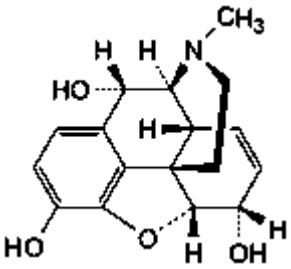
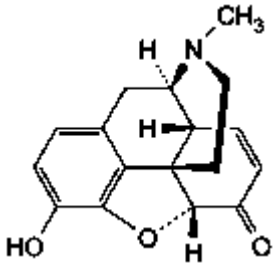


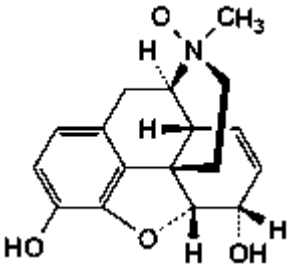
C. 6,7,8,14-tetradehydro-4,5α-epoxy-6-methoxy-17-methylmorphinan-3-ol (oripavine),



D. 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α,10α-triol (10*S*-hydroxymorphine),



E. 7,8-didehydro-4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one (morphinone),



F. (17*S*)-7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol 17-oxide (morphine *N*-oxide).

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Morphine Sulfate Injection

General Notices

Morphine Sulphate Injection

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Sulfate Injection is a sterile solution of Morphine Sulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$

92.5 to 107.5% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the injection, if necessary, with *ethanol (48%)* to produce a solution containing 0.05% w/v of Morphine Sulfate.

(2) 0.05% w/v of *morphine sulfate BPCRS* in *ethanol (48%)*.

(3) 0.05% w/v each of *morphine sulfate BPCRS* and *codeine phosphate BPCRS* in *ethanol (48%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air and spray with *potassium iodobismuthate solution R2* and examine the plate in daylight.

MOBILE PHASE

2.5 volumes of 13.5M *ammonia*, 32.5 volumes of *acetone*, 35 volumes of *ethanol (70%)* and 35 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

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CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in size, position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A a 1.0% v/v solution of *acetic acid*.

(1) Dilute the injection, if necessary, to produce a solution containing 0.125% w/v of Morphine Sulfate.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.25% w/v of *morphine for system suitability EPCRS* and 0.0625% w/v of *codeine phosphate BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase B *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 12.5 minutes) are: impurity F, about 0.95; impurity E, about 1.1; impurity A, about 1.4; impurity C, about 1.6 and impurity B, about 1.9.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and morphine is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (60%)*.

(1) Dilute the injection, if necessary, to produce a solution containing 0.01% w/v of Morphine Sulfate.
(2) 0.01% w/v of *morphine sulfate BPCRS*.
(3) 0.003% w/v of *morphine sulfate BPCRS* and 0.002% w/v of *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 285 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.005M *dioctyl sodium sulfosuccinate* and 0.01M *sodium acetate* in *methanol (60%)* adjusted to pH 5.5 with *glacial acetic acid*.

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When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and codeine phosphate are about 2 minutes and 3 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3) the *resolution* between the peaks due to morphine and codeine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in the injection using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

STORAGE

Morphine Sulfate Injection should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Morphine Sulfate.

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Morphine Suppositories

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Suppositories contain Morphine Hydrochloride or Morphine Sulfate in a suitable suppository basis.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of morphine

As the hydrochloride, $C_{17}H_{19}NO_3,HCl,3H_2O$, or as the sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$, 95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of the suppositories containing 60 mg of Morphine Hydrochloride or Morphine Sulfate in 25 mL of *diethyl ether*, extract with two 50 mL quantities of 0.01M *hydrochloric acid* and wash the aqueous layer with two 20 mL quantities of *diethyl ether*. Make the aqueous layer alkaline with *ammonia buffer pH 10.0* and extract with two 40 mL quantities of a mixture of 3 volumes of *dichloromethane* and 1 volume of *propan-2-ol*. Dry the combined extracts with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of morphine *(RS 237)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A a 1.0% v/v solution of *acetic acid*.

(1) Dissolve a quantity of the suppositories containing 25 mg of Morphine Hydrochloride or Morphine Sulfate in 25 mL of *dichloromethane*, extract with two 20-mL quantities of solvent A, wash the combined aqueous layers with two 20 mL quantities of *dichloromethane*, and dilute to 50 mL with *water*.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.25% w/v of *morphine for system suitability EPCRS* and 0.0625% w/v of *codeine phosphate BPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase B *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 12.5 minutes) are: impurity F, about 0.95; impurity E, about 1.1; impurity A, about 1.43; impurity C, about 1.6 and impurity B, about 1.9.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and morphine is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (3) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peaks* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of mixed suppositories containing 30 mg of Morphine Hydrochloride or Morphine Sulfate in 25 mL of *dichloromethane*. Extract with two quantities of 40 mL and 20 mL of 0.01M *hydrochloric acid*, wash the combined aqueous layers with two 20 mL quantities of *dichloromethane* and add 20 mL of 0.3M *dipotassium hydrogen orthophosphate*. Dilute to 100 mL with *water*

(2) Dissolve 0.03% w/v of *morphine sulfate BPCRS* in *hydrochloric acid* if necessary, and add a mixture of 20 volumes of 0.3M *dipotassium hydrogen orthophosphate*, 20 volumes of *water* and 60 volumes of 0.01M *hydrochloric acid*.

(3) 0.003% w/v of *morphine sulfate BPCRS* and 0.002% w/v of *codeine phosphate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 285 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.005M *dioctyl sodium sulfosuccinate* and 0.01M *sodium acetate* in *methanol (60%)* adjusted to pH 5.5 with *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and pseudomorphine are about 2.5 minutes and 3.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3) the *resolution* between the peaks due to morphine and codeine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}NO_3,HCl,3H_2O$ or $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$, as appropriate, using the declared content of $C_{17}H_{19}NO_3$ in *morphine sulfate BPCRS*. Each g of $C_{17}H_{19}NO_3$ is equivalent to 1.317 g of $C_{17}H_{19}NO_3,HCl,3H_2O$ or 1.330 g of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$.

LABELLING

The label states the quantity of Morphine Hydrochloride or of Morphine Sulfate in each suppository.

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IMPURITIES

The impurities limited by the requirements of this monograph those listed under Morphine Sulfate and Morphine Hydrochloride.

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Morphine Tablets

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Morphine Tablets contain Morphine Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Remove any coating from the tablets and shake a quantity of the powdered tablet cores containing 5 mg of Morphine Sulfate with 10 mL of *ethanol (48%)* and filter.

(2) 0.05% w/v of *morphine sulfate BPCRS* in *ethanol (48%)*.

(3) 0.05% w/v each of *morphine sulfate BPCRS* and *codeine phosphate BPCRS* in *ethanol (48%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air, spray with *potassium iodobismuthate solution R2* and examine in daylight.

MOBILE PHASE

2.5 volumes of 13.5M *ammonia*, 32.5 volumes of *acetone*, 35 volumes of *ethanol (70%)* and 35 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in size, position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer solution pH 6.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *phosphate buffer solution pH 6.5* if necessary, expected to contain 0.001% w/v of Morphine Sulfate.

(2) 0.001% w/v of *morphine sulfate BPCRS* in *phosphate buffer solution pH 6.5*.

(3) 0.03% w/v *morphine for system suitability EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex HyperClone BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 281 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile* and 700 volumes of 0.01M *sodium octanesulfonate*.

When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and pseudomorphine are about 2.5 minutes and 3.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to morphine and pseudomorphine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of morphine sulfate, $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in the medium, using the chromatograms obtained and the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A 1.0% v/v solution of *acetic acid*.

(1) Shake a quantity of powdered tablets containing 62.5 mg of Morphine Sulfate with 30 mL of solvent A, add sufficient solvent A to produce 50 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.00025% w/v *morphine sulfate BPCRS*.
(4) 0.25% w/v of *morphine for system suitability EPCRS* and 0.0625% w/v of *codeine phosphate BPCRS*.
(5) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.101% w/v of *sodium heptanesulfonate*, adjusted to pH 2.6 with a 50% v/v solution of *orthophosphoric acid*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-35	85→50	15→50	linear gradient
35-40	50	50	isocratic
40-42	50→85	50→15	linear gradient
42-50	85	15	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to morphine (retention time about 12.5 minutes) are: impurity F, about 0.95; impurity E, about 1.1; impurity C, impurity A, about 1.4; about 1.6 and impurity B, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and morphine is at least 1.5.

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LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity E, impurity C and impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with *morphine for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E, impurity C and impurity B by the following correction factors respectively: 0.5, 0.4 and 0.25.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity A is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 30 mg of Morphine Sulfate with 50 mL of the mobile phase and dilute to 100 mL with the mobile phase and filter.
(2) 0.03% w/v of *morphine sulfate BPCRS* in the mobile phase.
(3) 0.03% w/v of *morphine for system suitability EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex HyperClone BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 281 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.05 volumes of *orthophosphoric acid*, 30 volumes of *acetonitrile* and 70 volumes of 0.01M *sodium octanesulfonate*.

When the chromatograms are recorded under the prescribed conditions, the retention times of morphine sulfate and pseudomorphine are about 2.5 minutes and 3.5 minutes respectively.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to morphine and pseudomorphine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in the tablets using the declared content of $(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ in *morphine sulfate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Morphine Sulfate.

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Moulds for Allergen Products

General Notices

(Ph. Eur. monograph 2626)

Ph Eur

DEFINITION

Moulds for allergen products primarily consist of inactivated mould cultures, which may contain mycelia and/or spores, and may also contain allergenic constituents released into the culture medium. Moulds are microscopic filamentous fungi belonging mainly to the genera *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium*. This monograph also applies to yeast cells, e.g. *Candida*.

PRODUCTION

The method of cultivation, inactivation, harvesting and post-harvesting is described and must ensure the quality, homogeneity and traceability of the mould or yeast. The type of source material harvested (mycelium and/or spores or yeast cells) is specified. Appropriate measures are taken to avoid contamination by foreign species.

Critical cultivation parameters such as temperature and humidity are controlled and monitored. Unless otherwise justified, the culture medium is selected to avoid the presence of materials with potential allergenicity.

Where major changes to the production of the source material take place (e.g. when a new process or supplier of source materials is introduced), such changes are qualified for each species.

Microbial contamination of the mould or yeast should be monitored on a representative number of batches of source material according to a justified sampling plan and each time a new supplier and/or a new process for the source material production is introduced; if a determination of microbial contamination is not applicable, this must be justified. Microbial contamination values and potential increases in microbial contamination are monitored during stability studies, in order to assess this aspect along with the source material characteristics upon storage.

Control methods and acceptance criteria relating to identity and purity of the mould or yeast are established. The acceptance criteria must ensure the consistency of the source material from a qualitative and quantitative point of view. The source material is stored under controlled conditions justified by stability data. The production, as well as the handling of the source material, are such that consistent composition is ensured from batch to batch.

SOURCE MATERIAL REFERENCE BATCH

An appropriate reference batch is established for each species. The nature of the reference batch depends on the testing approach to verify batch-to-batch consistency and to establish acceptable quality. The reference batch may be, for example, an internal reference preparation (if available), a source material extract or a sample of a production batch. Its characterisation must be described. The extent of

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characterisation of the reference batch depends on the species, knowledge of the allergenic components and availability of suitable reagents. The reference batch is stored under controlled conditions ensuring its stability.

BATCH-TO-BATCH CONSISTENCY

To establish batch-to-batch consistency, one or more of the following tests are performed on each batch. The choice of tests must be justified.

Total protein (*2.5.33*)

Protein profile

Determined by using suitable electrophoresis methods (*2.2.31*, *2.2.54*).

Allergen profile

Relevant allergenic components are identified by means of suitable techniques using allergen-specific antibodies.

Major allergen content

Determined by using suitable immunochemical methods (*2.7.1*) such as enzyme-linked immunosorbent assay (ELISA).

Total allergenic activity

Determined by testing inhibition of the binding capacity of specific immunoglobulin E antibodies or by a suitable equivalent *in vitro* method.

CHARACTERS

Moulds or yeasts for allergen products are supplied as coloured powders or liquid suspensions.

IDENTIFICATION

The identity of the mould or yeast is confirmed by its relevant macroscopic (e.g. colour, appearance) and microscopic (e.g. appearance of the mycelium, spores, specialised cells) morphological characteristics specific to each species, in comparison to those of a reference batch or reference documents. Identity may also be confirmed using protein analysis methods (e.g. protein profile, individual allergen test) or genetic identification, if performed by generally accepted methods.

TESTS

Foreign species

The absence of foreign species is determined by macroscopic and microscopic examination.

Water (*2.5.12* or *2.5.32*) or **loss on drying** (*2.2.32*)

The water content of dried material is determined; specification limits must be supported by batch analysis and stability data.

Mycotoxins

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For moulds, the content of mycotoxin is determined, unless otherwise justified.

STORAGE

Moulds or yeasts for allergen products are stored under controlled conditions justified by stability data.

LABELLING

The label states the species of the mould or yeast.

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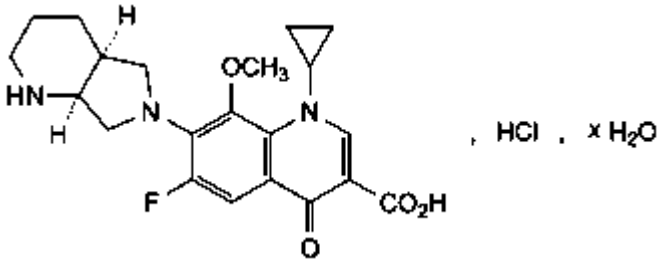
Moxifloxacin Hydrochloride

General Notices

(Ph. Eur. monograph 2254)



$C_{21}H_{25}ClFN_3O_4,xH_2O$ 437.9 (anhydrous substance)

Anhydrous moxifloxacin hydrochloride *186826-86-8*

Action and use

Fluoroquinolone antibacterial.

Preparation

Moxifloxacin Intracameral Injection

Ph Eur

DEFINITION

1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

It may be anhydrous or contain a variable quantity of water.

CHARACTERS

Appearance

Light yellow or yellow powder or crystals.

Solubility

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Sparingly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *moxifloxacin hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

B. Enantiomeric purity (see Tests).

C. Dissolve 50 mg in 5 mL of *water R*, add 1 mL of *dilute nitric acid R*, mix, allow to stand for 5 min and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution GY_2 (2.2.2, *Method II*). If intended for use in the manufacture of parenteral preparations, the solution is clear (2.2.1) and not more intensely coloured than reference solution GY_2 (2.2.2, *Method II*).

Dissolve 1.0 g in 20 mL of *dilute sodium hydroxide solution R*.

pH (2.2.3)

3.9 to 4.6.

Dissolve 0.10 g in 50 mL of *carbon dioxide-free water R*.

Enantiomeric purity

Liquid chromatography (2.2.29).

Buffer solution Dissolve 2.49 g of *anhydrous copper sulfate R* and 2.6 g of *isoleucine R* in 1000 mL of *water for chromatography R*.

Test solution Dissolve 5.0 mg of the substance to be examined in *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 3.0 mL of the test solution to 200.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 5 mg of *moxifloxacin for system suitability CRS* (containing impurity G) in 5 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

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— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, buffer solution (25:75 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 293 nm.

Injection 20 µL.

Run time 1.5 times the retention time of moxifloxacin.

Identification of impurities Use the chromatogram supplied with *moxifloxacin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to moxifloxacin (retention time = about 16 min): impurity G = about 0.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to moxifloxacin.

Calculation of percentage content:

— for impurity G, use the concentration of moxifloxacin hydrochloride in reference solution (a).

Limit:

— *impurity G*: maximum 0.15 per cent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solution A Dissolve 0.50 g of *tetrabutylammonium hydrogen sulfate R* and 1.0 g of *potassium dihydrogen phosphate R* in about 500 mL of *water R*. Add 2 mL of *phosphoric acid R* and 0.050 g of *anhydrous sodium sulfite R* and dilute to 1000 mL with *water R*.

Test solution (a) Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 50.0 mg of *moxifloxacin hydrochloride CRS* in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 10.0 mL with solution A.

Reference solution (c) Dissolve 5 mg of *moxifloxacin for peak identification A CRS* (containing impurities A, B and E) in 5 mL of solution A.

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Reference solution (d) Dissolve 2 mg of *moxifloxacin for peak identification B CRS* (containing impurity F) in 2 mL of solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped phenylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Mix 28 volumes of *methanol R* and 72 volumes of a solution containing 0.5 g/L of *tetrabutylammonium hydrogen sulfate R*, 1.0 g/L of *potassium dihydrogen phosphate R* and 3.4 g/L of *phosphoric acid R*.

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 293 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (c) and (d).

Run time 2.5 times the retention time of moxifloxacin.

Identification of impurities Use the chromatogram supplied with *moxifloxacin for peak identification A CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and E; use the chromatogram supplied with *moxifloxacin for peak identification B CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to moxifloxacin (retention time = about 11 min): impurity F = about 0.9; impurity A = about 1.1; impurity B = about 1.3; impurity E = about 1.7.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to moxifloxacin.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.4; impurity E = 3.5;

— *impurities B, E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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Water (2.5.12)

Maximum 4.5 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (b).

Calculate the percentage content of $C_{21}H_{25}ClFN_3O_4$ taking into account the assigned content of *moxifloxacin hydrochloride CRS*.

STORAGE

In an airtight container, protected from light.

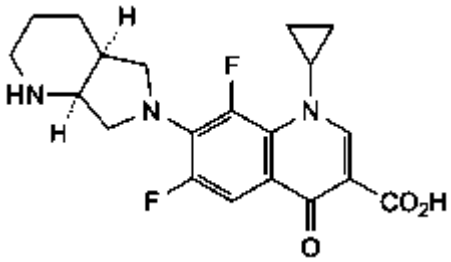
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *B, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, H.*



A. 1-cyclopropyl-6,8-difluoro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

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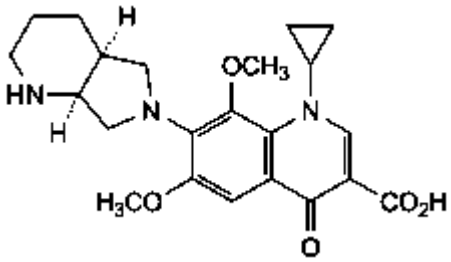
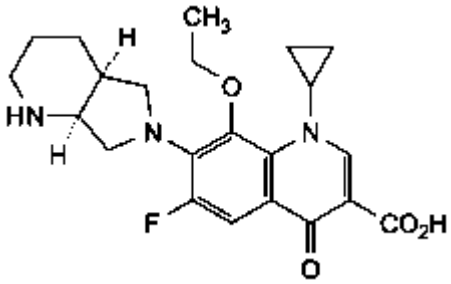
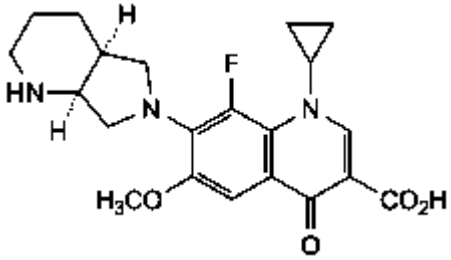


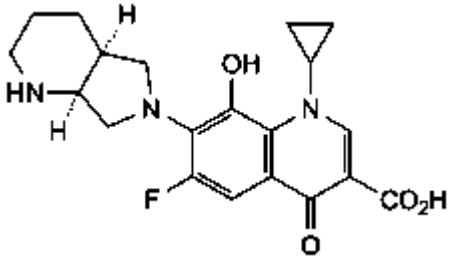
B. 1-cyclopropyl-6,8-dimethoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



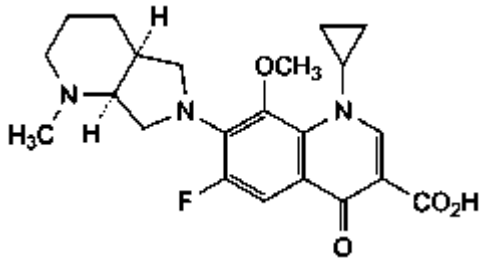
C. 1-cyclopropyl-8-ethoxy-6-fluoro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



D. 1-cyclopropyl-8-fluoro-6-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



E. 1-cyclopropyl-6-fluoro-8-hydroxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



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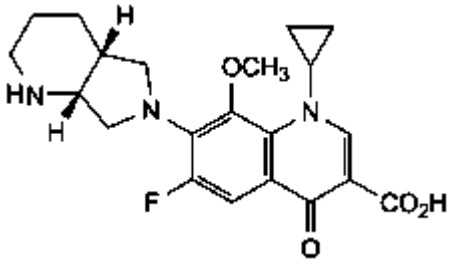
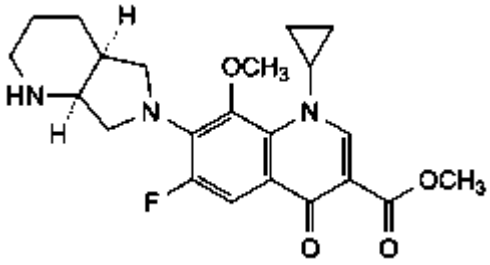
F. 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4a*S*,7a*S*)-1-methyloctahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



G. 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4a*R*,7a*R*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



H. methyl 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylate.

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Moxifloxacin Intracameral Injection

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Fluoroquinolone antibacterial.

DEFINITION

Moxifloxacin Intracameral Injection is a sterile, isotonic solution containing Moxifloxacin Hydrochloride in a suitable diluent. It is supplied as a ready-to-use solution.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of moxifloxacin hydrochloride, $C_{21}H_{24}FN_3O_4,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dilute a quantity of the injection to produce a solution containing 0.004% w/v of Moxifloxacin Hydrochloride.

(2) 0.004% *w/v of moxifloxacin hydrochloride EPCRS*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air for about 5 minutes and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

2 volumes of 6M *ammonia*, 4 volumes of *butanol* and 4 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.9 to 7.5, Appendix V L.

Osmolality

The osmolality of the injection is 300 to 350 mosmol/kg, Appendix V N.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Dilute a quantity of the injection, if necessary, with sufficient of the mobile phase to produce a solution containing 0.1% w/v of Moxifloxacin Hydrochloride.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and then further dilute 1 volume to 10 volumes.
(3) Dissolve 5 mg of *moxifloxacin for peak identification A EPCRS* in 5 mL of a solution prepared by dissolving 0.50 g of *tetrabutylammonium hydrogen sulfate* and 1.0 g of *potassium dihydrogen orthophosphate* in about 500 mL of *water*, then adding 2 mL of *orthophosphoric acid* and 0.050 g of *anhydrous sodium sulfite* and diluting to 1000 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped phenylsilyl silica gel for chromatography* (5 µm) (Luna Phenyl, Metachem Inertsil Phenyl or Zorbax Eclipse XDB Phenyl are suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 293 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for 2.5 times the retention time of moxifloxacin.

MOBILE PHASE

28 volumes of *methanol* and 72 volumes of a buffer solution prepared by dissolving 0.5 g of *tetrabutylammonium hydrogen sulfate*, 1.0 g of *potassium dihydrogen orthophosphate* and 3.4 g of *orthophosphoric acid* in 1000 mL of *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of moxifloxacin is about 14 minutes. The retention times relative to moxifloxacin are: impurity A, about 1.1; impurity B, about 1.3; impurity C, about 1.4; impurity D, about 1.6; impurity E, about 1.7.

SYSTEM SUITABILITY

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The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *moxifloxacin for peak identification A EPCRS* and the *resolution* between the peaks due to moxifloxacin and impurity A is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C, D and E using solution (3). Multiply the areas of the peaks due to impurities B and E by the corresponding correction factors: impurity B, 1.4; impurity E, 3.5.

In the chromatogram obtained with solution (1):

the area of any peaks corresponding to impurities A, B, C, D and E are not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection with sufficient of the mobile phase to produce a solution containing 0.025% w/v of Moxifloxacin Hydrochloride.
(2) 0.025% w/v of *moxifloxacin hydrochloride EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{24}FN_3O_4,HCl$ in the injection using the declared content of $C_{21}H_{24}FN_3O_4,HCl$ in *moxifloxacin hydrochloride EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Moxifloxacin Hydrochloride.

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Moxifloxacin Tablets

General Notices

Action and use

Fluoroquinolone antibacterial.

DEFINITION

Moxifloxacin Tablets contain Moxifloxacin Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of moxifloxacin, $C_{21}H_{24}FN_3O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions, in a mixture of 1 volume of *orthophosphoric acid* and 999 volumes of *water*, protected from light.

(1) Dissolve a quantity of the powdered tablets containing the equivalent of 20 mg of moxifloxacin in 20 mL and filter. Dilute 1 volume of the filtrate to 5 volumes.

(2) 0.022% *w/v of moxifloxacin hydrochloride EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel* F_{254} *plates* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, and examine under ultraviolet light (366 nm).

MOBILE PHASE

2 volumes of 6M *ammonia*, 4 volumes of *n-butanol* and 4 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

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TESTS

Dissolution

Carry out the following procedure protected from light. Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 295 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *moxifloxacin hydrochloride EPCRS* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the content of moxifloxacin, $C_{21}H_{24}FN_3O_4$, using the declared content of $C_{21}H_{24}FN_3O_4$,HCl in *moxifloxacin hydrochloride EPCRS*. Each mg of *moxifloxacin hydrochloride EPCRS* is equivalent to 0.917 mg of moxifloxacin.

LIMITS

The amount of moxifloxacin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, in a solution of 0.05% w/v of *tetrabutylammonium hydrogen sulfate*, 0.1% w/v of *potassium dihydrogen orthophosphate*, 0.2% v/v of *orthophosphoric acid* and 0.005% w/v of *sodium sulfite*, protected from light.

(1) Dissolve a quantity of the powdered tablets containing the equivalent of 100 mg of moxifloxacin, dilute to 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes. Further dilute 1 volume of this solution to 10 volumes.

(3) 0.1% w/v of *moxifloxacin for peak identification A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped* *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 45°C.

(e) Use a detection wavelength of 293 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to run for about 2.5 times the retention time of moxifloxacin.

MOBILE PHASE

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28 volumes of *methanol* and 72 volumes of a solution of 0.05% w/v of *tetrabutylammonium hydrogen sulfate*, 0.1% w/v of *potassium dihydrogen orthophosphate* and 0.34% v/v of *orthophosphoric acid* in *water*.

Under the prescribed conditions, the relative retention times with reference to moxifloxacin (retention time about 14 minutes) are: impurity A, about 1.1; impurity B, about 1.3; impurity C, about 1.4; impurity D, about 1.6; impurity E, about 1.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to moxifloxacin and impurity A is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B and E using solution (3). Multiply the area of any peak corresponding to impurity B by a correction factor of 1.4 and impurity E by a correction factor of 3.5.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than two times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than ten times the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.05% w/v of *tetrabutylammonium hydrogen sulfate*, 0.1% w/v of *potassium dihydrogen orthophosphate*, 0.2% v/v of *orthophosphoric acid* and 0.005% w/v of *sodium sulfite* in *water* (solvent C), protected from light.

(1) Dissolve a quantity of the powdered tablets containing the equivalent of 0.5 g of moxifloxacin, dilute to 500 mL and filter. Dilute 1 volume to 10 volumes.
(2) 0.0109% w/v of *moxifloxacin hydrochloride EPCRS.*
(3) 0.1% w/v of *moxifloxacin for peak identification A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to moxifloxacin and impurity A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of moxifloxacin, $C_{21}H_{24}FN_3O_4$, in the tablets using the declared content of $C_{21}H_{24}FN_3O_4$,HCl in *moxifloxacin hydrochloride EPCRS*. Each mg of *moxifloxacin hydrochloride EPCRS* is equivalent to 0.917 mg of moxifloxacin.

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IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Moxifloxacin Hydrochloride.

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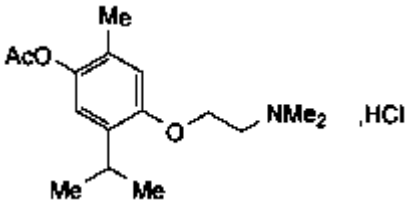
Moxisylyte Hydrochloride

General Notices



$C_{16}H_{25}NO_3$,HCl 315.8 *964-52-3*

Action and use

Alpha-adrenoceptor antagonist.

Preparation

Moxisylyte Tablets

DEFINITION

Moxisylyte Hydrochloride is 4-(2-dimethylaminoethoxy)-5-isopropyl-2-methylphenyl acetate hydrochloride. It contains not less than 99.0% and not more than 101.0% of $C_{16}H_{25}NO_3$,HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white, crystalline powder.

Freely soluble in *water* and in *chloroform*; soluble in *ethanol (96%)*; practically insoluble in *ether* and in petroleum spirit.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of moxisylyte hydrochloride *(RS 238)*.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH of a 5% w/v solution, 4.5 to 5.5, Appendix V L.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using solutions in the mobile phase containing (1) 0.0010% w/v of *2-(6-hydroxythymoxy)ethyldimethylamine hydrochloride BPCRS* and 0.00050% w/v of *2-thymoxyethyldimethylamine hydrochloride BPCRS* and (2) 0.2% w/v of the substance being examined. For solution (3) dilute 1 volume of solution (2) to 100 volumes. For solution (4) dilute 1 volume of solution (3) to 10 volumes.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) 0.005M *sodium hexanesulfonate* in a mixture of 2 volumes of *glacial acetic acid*, 185 volumes of *water* and 315 volumes of *methanol* as the mobile phase with a flow rate of 1.0 mL per minute and (c) a detection wavelength of 276 nm.

The peaks in the chromatogram obtained with solution (1) are due to (a) 2-(6-hydroxythymoxy)ethyldimethylamine hydrochloride and (b) 2-thymoxyethyldimethylamine hydrochloride in order of their elution. In the chromatogram obtained with solution (2) the areas of any peaks corresponding to (a) and (b) are not greater than the areas of the corresponding peaks in the chromatogram obtained with solution (1) (0.5% of 2-(6-hydroxy-thymoxy)ethyldimethylamine hydrochloride and 0.25% of 2-thymoxyethyldimethylamine hydrochloride respectively), the area of any peak with a retention time relative to moxisylyte of 2.3 is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1% of 2-(6-chlorothymoxy)ethyldimethyl-amine hydrochloride) and the area of any peak with a retention time relative to moxisylyte of 0.9 is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.1% of 2-(6-acetylthymoxy)ethyldimethylamine).

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.5 g and *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 31.58 mg of $C_{16}H_{25}NO_3$,HCl.

STORAGE

Moxisylyte Hydrochloride should be protected from light.

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Moxisylyte Tablets

General Notices

Action and use

Alpha-adrenoceptor antagonist.

DEFINITION

Moxisylyte Tablets contain Moxisylyte Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of moxisylyte, $C_{16}H_{25}NO_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 20 mg of moxisylyte with 10 mL of *chloroform*, filter and evaporate the filtrate to dryness. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of moxisylyte hydrochloride *(RS 238)*.

B. Dilute 20 mL of a 0.03% w/v solution to 100 mL with *water* (solution A). Dilute a further 20 mL of the same solution to 100 mL with 0.1M *sodium hydroxide* (solution B). The ratio of the *absorbance* of solution B at 302 nm, measured 30 minutes after preparation, to that of solution A at 275 nm is about 1.7, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.18 g of moxisylyte with 100 mL of the mobile phase for 15 minutes, centrifuge and use the clear supernatant liquid.

(2) 0.0040% w/v of *2-(6-hydroxythymoxy)ethyldimethylamine hydrochloride BPCRS* and 0.00050% w/v of *2-thymoxyethyldimethylamine hydrochloride BPCRS* in the mobile phase.

(3) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(4) Dilute 1 volume of solution (3) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm x 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

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(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.005M *sodium hexanesulfonate* in a mixture of 2 volumes of *glacial acetic acid*, 185 volumes of *water* and 315 volumes of *methanol*.

The peaks in the chromatogram obtained with solution (2) are due to: (a) 2-(6-hydroxythymoxy)ethyldimethylamine hydrochloride and (b) 2-thymoxyethyldimethylamine hydrochloride in order of their elution.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-(6-hydroxythymoxy)ethyldimethylamine hydrochloride is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (2%);

the area of any peak corresponding to 2-thymoxyethyldimethylamine hydrochloride is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (0.25%);

the area of any peak with a retention time relative to moxisylyte of 2.3 (2-(6-chlorothymoxy)ethyldimethylamine hydrochloride) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of any peak with a retention time relative to moxisylyte of 0.9 (2-(6-acetylthymoxy)ethyldimethylamine) is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 13 mg of moxisylyte with 150 mL of 0.1M *hydrochloric acid*, add sufficient 0.1M *hydrochloric acid* to produce 250 mL and filter. Measure the *absorbance* of the filtrate at the maximum at 275 nm, Appendix II B. Calculate the content of $C_{16}H_{25}NO_3$ in the tablets taking 79.7 as the value of A (1%, 1 cm) at the maximum at 275 nm.

STORAGE

Moxisylyte Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of moxisylyte.

40 mg of moxisylyte is equivalent to 45.2 mg of Moxisylyte Hydrochloride.

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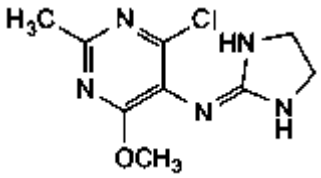
Moxonidine

General Notices

(Ph. Eur. monograph 1758)



$C_9H_{12}ClN_5O$ 241.7 *75438-57-2*

Action and use

Imidazoline I_1 receptor agonist; treatment of hypertension.

Preparation

Moxonidine Tablets

Ph Eur

DEFINITION

4-Chloro-*N*-(imidazolidin-2-ylidene)-6-methoxy-2-methylpyrimidin-5-amine.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride, very slightly soluble in acetonitrile.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison moxonidine CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in a mixture of equal volumes of methanol R and water R and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 10.0 mg of moxonidine CRS in a mixture of equal volumes of methanol R and water R and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with a mixture of equal volumes of methanol R and water R. Dilute 2.0 mL of this solution to 20.0 mL with a mixture of equal volumes of methanol R and water R.

Reference solution (c) Dissolve 5.0 mg of moxonidine impurity A CRS in a mixture of equal volumes of methanol R and water R and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (d) Dilute 6.0 mL of reference solution (c) to 100.0 mL with a mixture of equal volumes of methanol R and water R.

Reference solution (e) Dilute 2.5 mL of reference solution (a) to 50 mL with reference solution (c).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: base-deactivated octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 136 volumes of acetonitrile for chromatography R with 1000 volumes of a 3.48 g/L solution of sodium pentanesulfonate R previously adjusted to pH 3.5 with dilute sulfuric acid R.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of the test solution and reference solutions (b), (d) and (e).

Run time Twice the retention time of moxonidine.

Relative retentions With reference to moxonidine (retention time = about 11.6 min): impurity A = about 0.9; impurity B = about 1.7.

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System suitability Reference solution (e):

— *resolution*: minimum of 2.0 between the peaks due to impurity A and moxonidine.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 3.0 for the peak due to moxonidine.

Calculate the percentage content of $C_9H_{12}ClN_5O$ taking into account the assigned content of *moxonidine CRS*.

IMPURITIES

Specified impurities *A, B*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D*.

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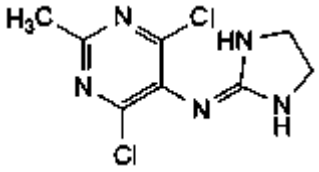
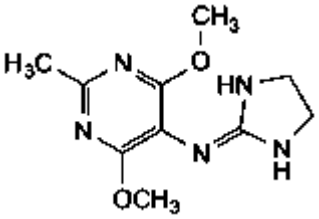
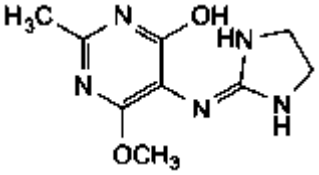


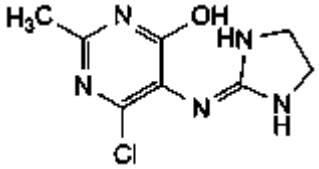
A. 4,6-dichloro-*N*-(imidazolidin-2-ylidene)-2-methylpyrimidin-5-amine (6-chloromoxonidine),



B. *N*-(imidazolidin-2-ylidene)-4,6-dimethoxy-2-methylpyrimidin-5-amine (4-methoxymoxonidine),



C. 5-[(imidazolidin-2-ylidene)amino]-6-methoxy-2-methylpyrimidin-4-ol (4-hydroxymoxonidine),



D. 6-chloro-5-[(imidazolidin-2-ylidene)amino]-2-methylpyrimidin-4-ol (6-demethylmoxonidine).

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Moxonidine Tablets

General Notices

Action and use

Imidazoline I_1 receptor agonist; treatment of hypertension.

DEFINITION

Moxonidine Tablets contain Moxonidine.

The tablets complies with the requirements stated under Tablets and with the following requirements.

Content of moxonidine, $C_9H_{12}ClN_5O$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing 1 mg of Moxonidine with 5 mL of *methanol*. Filter and use the filtrate.

(2) 0.02% w/v of *moxonidine BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

0.1 volume of *triethylamine*, 4 volumes of *methanol* and 6 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III B, using the following solutions.

(1) After 20 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.1M *hydrochloric acid*, if necessary, to produce a solution expected to contain 0.00002% w/v of Moxonidine.

(2) 0.00002% w/v of *moxonidine BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 3.0 mm) packed with *octylsilyl silica gel for chromatography* (3 µm) (Nucleosil C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

200 volumes of *acetonitrile* and 800 volumes of a 0.384% w/v solution of *sodium pentanesulfonate monohydrate R1* in *water* adjusted to pH 3.5 with 0.5M *sulfuric acid*.

DETERMINATION OF CONTENT

Calculate the total content of moxonidine, $C_9H_{12}ClN_5O$, in the medium from the chromatograms obtained and using the declared content of $C_9H_{12}ClN_5O$ in *moxonidine BPCRS*.

LIMITS

The amount of moxonidine released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A.

Equal volumes of *methanol* and 800 volumes of a 0.384% w/v solution of *sodium pentanesulfonate monohydrate R1* in *water* adjusted to pH 3.5 with 0.5M *sulfuric acid* (solution A).

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 6 mg of Moxonidine in 100 mL. Leave to stand for at least 5 minutes and filter using a 0.45-µm filter (Whatman Spartan is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

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(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.006% w/v of *moxonidine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 µm) (Merck Lichrospher 60 RP-select B is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 280 nm for impurities D and C and 230 nm for moxonidine and any other impurities.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A *acetonitrile*.

Mobile phase B 0.384% w/v of *sodium pentanesulfonate monohydrate R1* in *water* adjusted to pH 3.5 with 0.5M *sulfuric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-14	14	86	isocratic
14-15	14→90	86→10	linear gradient
15-20	90	10	isocratic
20-21	90→14	10→86	linear gradient
21-35	14	86	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to moxonidine (retention time about 9 minutes) are: impurity D, about 0.4; impurity C, about 0.5; impurity A, about 0.85 and impurity B, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and moxonidine is at least 2.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C and D using the chromatogram obtained with solution (4) and the chromatogram supplied with *moxonidine impurity standard BPCRS*.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

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the area of any peak corresponding to impurity D is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity B is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity A is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Moxonidine comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake one tablet in 8 mL of *methanol (50%)*, with the aid of ultrasound, for 15 minutes. Add sufficient *methanol (50%)* to produce a solution containing 0.002% w/v of Moxonidine and filter using a 0.45-µm filter (Whatman Spartan is suitable).
(2) 0.002% w/v of *moxonidine BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with an injection volume of 10 µL.

DETERMINATION OF CONTENT

Calculate the content of moxonidine, $C_9H_{12}ClN_5O$, in each tablet using the declared content of $C_9H_{12}ClN_5O$, in *moxonidine BPCRS*.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of content.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Moxonidine.

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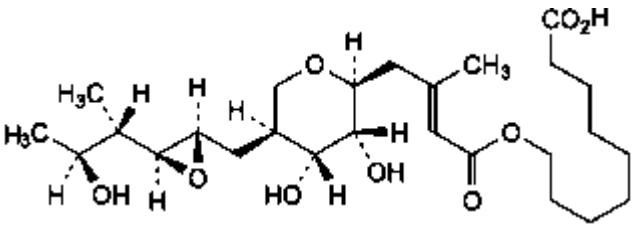
Mupirocin

General Notices

(Ph. Eur. monograph 1450)



$C_{26}H_{44}O_9$ 500.6 *12650-69-0*

Action and use

Antibacterial.

Preparation

Mupirocin Ointment

Ph Eur

DEFINITION

9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-[[(2*S*,3*S*)-3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid.

Substance produced by the growth of certain strains of *Pseudomonas fluorescens* or obtained by any other means.

Content

93.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in acetone, in anhydrous ethanol and in methylene chloride.

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It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of mupirocin*.

TESTS

pH (*2.2.3*)

3.5 to 4.0 for a freshly prepared saturated solution (about 10 g/L) in *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

-21 to -17 (anhydrous substance).

Dissolve 0.50 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mix 50 volumes of *methanol R* and 50 volumes of a 13.6 g/L solution of *sodium acetate R* adjusted to pH 4.0 with *acetic acid R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the solvent mixture.

Reference solution (b) Adjust 10 mL of reference solution (a) to pH 2.0 with *hydrochloric acid R* and allow to stand for 20 h.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 20 volumes of *water for chromatography R*, 30 volumes of *tetrahydrofuran R* and 50 volumes of a 10.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time 3.5 times the retention time of mupirocin.

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Relative retention With reference to mupirocin: impurity C = about 0.75.

System suitability Reference solution (b):

— *resolution*: minimum 7.0 between the 2nd of the 2 peaks due to hydrolysis products and the peak due to mupirocin.

Limits:

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (4 per cent);

— *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (6 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 200.0 mL with a 7.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Reference solution (a) Dissolve 25.0 mg of *mupirocin lithium CRS* in 5 mL of *methanol R* and dilute to 200.0 mL with a 7.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Reference solution (b) Adjust 10 mL of the test solution to pH 2.0 with *hydrochloric acid R* and allow to stand for 20 h.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 19 volumes of *water for chromatography R*, 32 volumes of *tetrahydrofuran R* and 49 volumes of a 10.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

System suitability:

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— *resolution*: minimum 7.0 between the 2nd of the 2 peaks due to hydrolysis products and the peak due to mupirocin in the chromatogram obtained with reference solution (b);

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections of reference solution (a).

Calculate the percentage content of $C_{26}H_{44}O_9$ using the chromatogram obtained with reference solution (a), taking into account the assigned content of *mupirocin lithium CRS* and a conversion factor of 0.988.

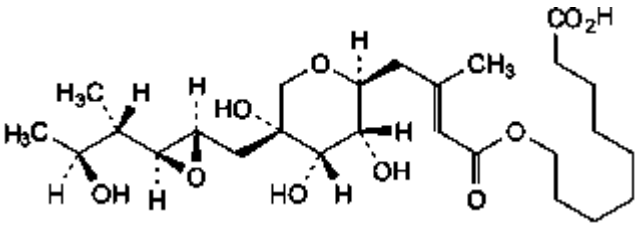
STORAGE

Protected from light.

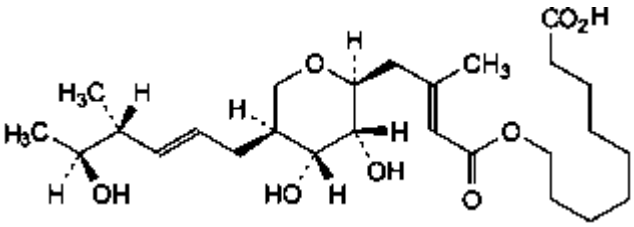
IMPURITIES

Specified impurities C.

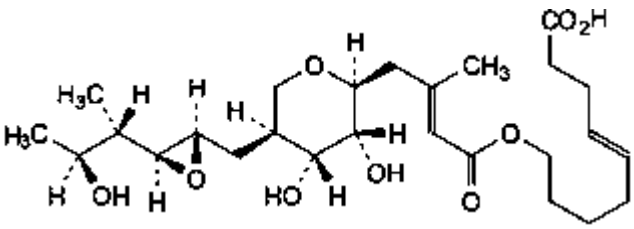
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D, E, F.



A. 9-[[(2*E*)-4-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxy-5-[[(2*S*,3*S*)3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid (pseudomonic acid B),



B. 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(2*E*,4*R*,5*S*)-5-hydroxy-4-methylhex-2-enyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid (pseudomonic acid C),



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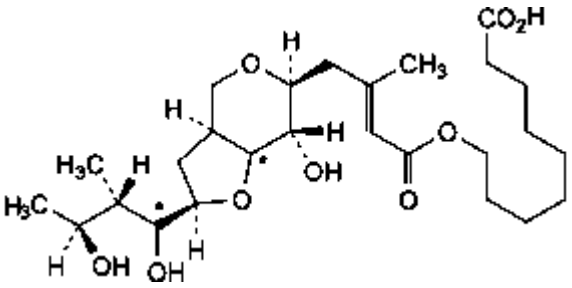
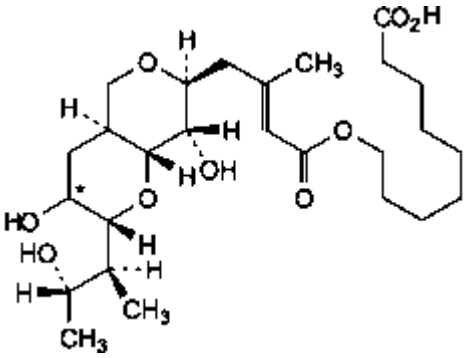
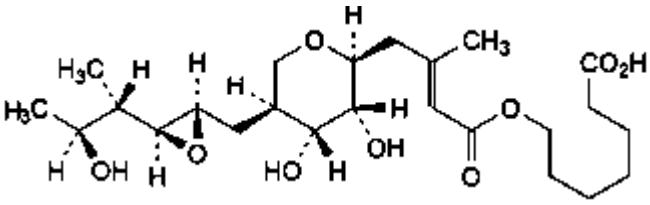
C. (4*E*)-9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[[(2*S*,3*S*)3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]non-4-enoic acid (pseudomonic acid D),



D. 9-[[(2*E*)-4-[(2*R*,3a*S*,6*S*,7*S*)-2-[(2*S*,3*S*)-1,3-dihydroxy-2-methylbutyl]-7-hydroxyhexahydro-4*H*-furo[3,2-*c*]pyran-6-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,



E. 9-[[(2*E*)-4-[(2*R*,3*RS*,4a*S*,7*S*,8*S*,8a*R*)-3,8-dihydroxy-2-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]hexahydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-7-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,



F. 7-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[[(2*S*,3*S*)-3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]heptanoic acid.

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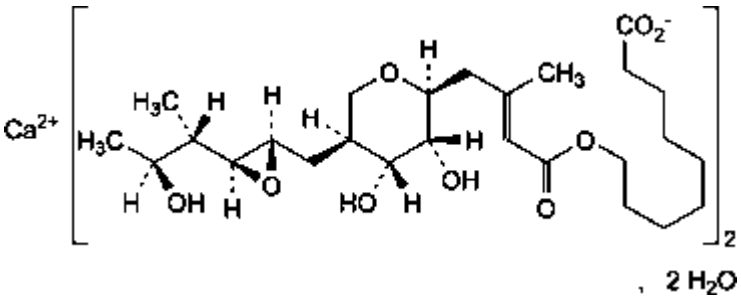
Mupirocin Calcium

General Notices

(Ph. Eur. monograph 1451)



$C_{52}H_{86}CaO_{18},2H_2O$ 1075 *115074-43-6*

Action and use

Antibacterial.

Preparations

Mupirocin Cream

Mupirocin Nasal Ointment

Ph Eur

DEFINITION

Calcium bis[9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5[[(2*S*,3*S*)-3-[(1*S*,2*S*)-2-hydroxy-1methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoate] dihydrate.

Substance produced by the growth of certain strains of *Pseudomonas fluorescens* or obtained by any other means.

Content

93.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

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Solubility

Very slightly soluble in water, sparingly soluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of mupirocin calcium*.

B. It gives reaction (a) of calcium (*2.3.1*).

TESTS

Specific optical rotation (*2.2.7*)

-20 to -16 (anhydrous substance).

Dissolve 0.50 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mix 50 volumes of *methanol R* and 50 volumes of a 13.6 g/L solution of *sodium acetate R* adjusted to pH 4.0 with *acetic acid R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the solvent mixture.

Reference solution (b) Adjust 10 mL of reference solution (a) to pH 2.0 with *hydrochloric acid R* and allow to stand for 20 h.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 20 volumes of *water for chromatography R*, 30 volumes of *tetrahydrofuran R* and 50 volumes of a 10.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time 3.5 times the retention time of mupirocin.

Relative retention With reference to mupirocin: impurity C = about 0.75.

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System suitability Reference solution (b):

— *resolution*: minimum 7.0 between the 2nd of the 2 peaks due to hydrolysis products and the peak due to mupirocin.

Limits:

— *impurity C*: not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent);

— *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

— *total*: not more than 2.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (4.5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Chlorides (2.4.4)

Maximum 0.5 per cent.

Dissolve 10.0 mg in a mixture of 1 mL of *dilute nitric acid R* and 15 mL of *methanol R*.

Water (2.5.12)

3.0 per cent to 4.5 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 200.0 mL with a 7.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Reference solution (a) Dissolve 25.0 mg of *mupirocin lithium CRS* in 5 mL of *methanol R* and dilute to 200.0 mL with a 7.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Reference solution (b) Adjust 10 mL of the test solution to pH 2.0 with *hydrochloric acid R* and allow to stand for 20 h.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 19 volumes of *water for chromatography R*, 32 volumes of *tetrahydrofuran R* and 49 volumes of a 10.5 g/L solution of *ammonium acetate R* adjusted to pH 5.7 with *acetic acid R*.

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 230 nm.

Injection 20 µL.

System suitability:

— *resolution*: minimum 7.0 between the 2nd of the 2 peaks due to hydrolysis products and the peak due to mupirocin in the chromatogram obtained with reference solution (b);

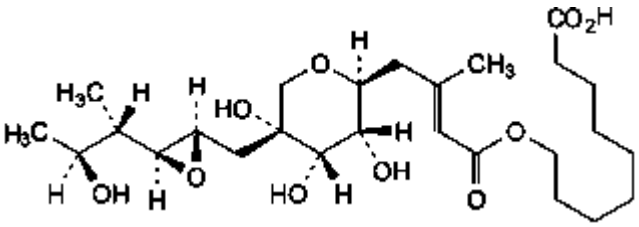
— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections of reference solution (a).

Calculate the percentage content of $C_{52}H_{86}CaO_{18}$ using the chromatogram obtained with reference solution (a), taking into account the assigned content of *mupirocin lithium CRS* and a conversion factor of 1.026.

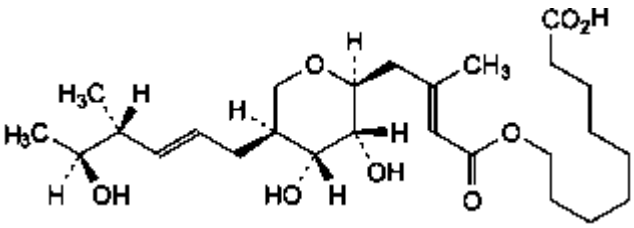
IMPURITIES

Specified impurities *C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D, E, F, G, H, I.*



A. 9-[[(2*E*)-4-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxy-5-[[(2*S*,3*S*)3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid (pseudomonic acid B),



B. 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(2*E*,4*R*,5*S*)-5-hydroxy-4-methylhex-2-enyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid (pseudomonic acid C),

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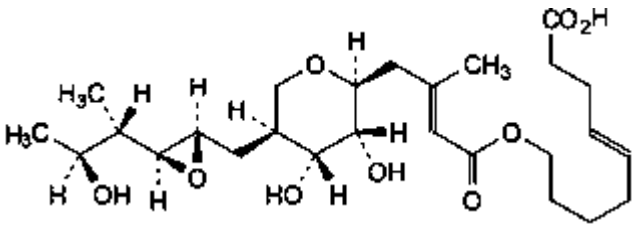
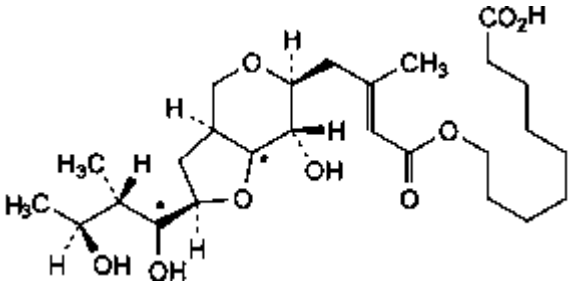
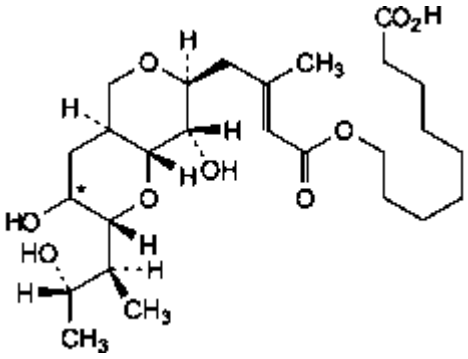


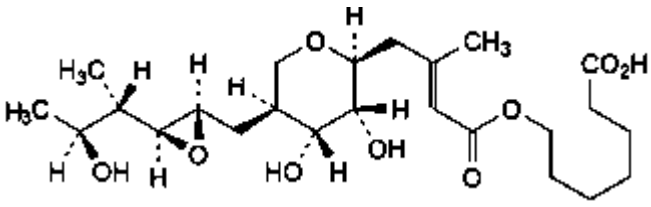
C. (4*E*)-9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[[(2*S*,3*S*)3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]non-4-enoic acid (pseudomonic acid D),



D. 9-[[(2*E*)-4-[(2*R*,3a*S*,6*S*,7*S*)-2-[(2*S*,3*S*)-1,3-dihydroxy-2-methylbutyl]-7-hydroxyhexahydro-4*H*-furo[3,2-*c*]pyran-6-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,



E. 9-[[(2*E*)-4-[(2*R*,3*RS*,4a*S*,7*S*,8*S*,8a*R*)-3,8-dihydroxy-2-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]hexahydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-7-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,



F. 7-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[[(2*S*,3*S*)-3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]heptanoic acid,

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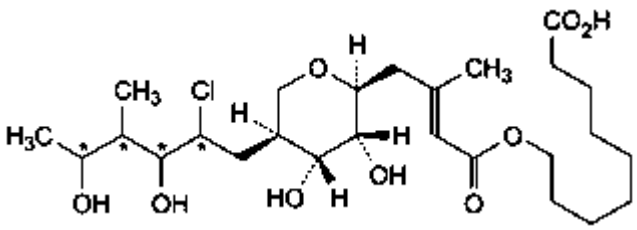
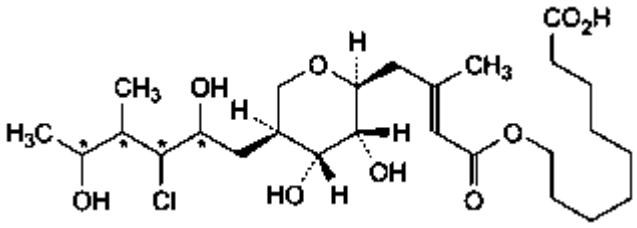
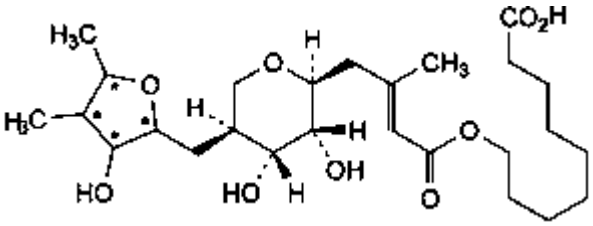


G. 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-5-(2-chloro-3,5-dihydroxy-4-methylhexyl)-3,4-dihydroxytetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,



H. 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-5-(3-chloro-2,5-dihydroxy-4-methylhexyl)-3,4-dihydroxytetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,



I. 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(3-hydroxy-4,5-dimethyltetrahydrofuran-2-yl)methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid.

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Mupirocin Cream

General Notices

Action and use

Antibacterial.

DEFINITION

Mupirocin Cream contains Mupirocin Calcium in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of mupirocin, $C_{26}H_{44}O_9$

90.0 to 120.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the cream containing the equivalent of 100 mg of mupirocin in a mixture of 20 mL of *dichloromethane* and 4 mL of 0.2M *sodium borate buffer pH 8.4,* with shaking, and centrifuge at 3000 revolutions per minute until separate layers are obtained. The upper layer (which may be cloudy) is separated from the lower layer by a band of creamy solid. Remove and retain the upper aqueous layer and re-extract the lower layer with a further 4 mL of 0.2M *sodium borate buffer pH 8.4*. Combine the aqueous extracts, add 10 mL of *dichloromethane* to the combined extracts and centrifuge at 3000 revolutions per minute. Remove the upper layer and adjust the pH to about 4 with 1M *hydrochloric acid* (a slight cloudiness may be observed), add 10 mL of *dichloromethane* and centrifuge. Separate and retain the lower layer; add a further 10 mL of *dichloromethane* to the upper layer and centrifuge. Combine the dichloromethane extracts and evaporate to dryness at room temperature under a current of nitrogen; a jelly-like residue is obtained. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of mupirocin *(RS 425)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the cream containing the equivalent of 50 mg of mupirocin in 5 mL of a mixture of 3 volumes of *tetrahydrofuran* and 1 volume of *water* and shake mechanically for 15 minutes. Add 5 mL of *acetate buffer pH 4.0* and mix thoroughly. Centrifuge for about 15 minutes; remove the lower layer and filter through a 0.5-µm filter. Dilute 1 mL of this solution to 50 mL with a solution containing equal volumes of *acetate buffer pH 4.0* and a mixture of 3 volumes of *tetrahydrofuran* and 1 volume of *water*, mix and filter through a 0.5-µm filter.

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(2) 0.0002% w/v of *mupirocin lithium BPCRS* in 0.1M *phosphate buffer solution pH 6.3*.

(3) A solution containing equal volumes of *acetate buffer pH 4.0* and a mixture of 3 volumes of *tetrahydrofuran* and 1 volume of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (7 µm) (Zorbax C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 5.8 g of *glacial acetic acid* in 900 mL of *water*, adjust the pH to 5.7 with *ammonium hydroxide* and add sufficient *water* to produce 1000 mL (0.1M ammonium acetate solution).Mix 25 volumes of *tetrahydrofuran* and 75 volumes of the 0.1M ammonium acetate solution.

Mobile phase B 30 volumes of *tetrahydrofuran* and 70 volumes of 0.1M ammonium acetate solution.

Use the following gradient. Allow the system to equilibrate for 10 minutes at the start.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-6	100	0	isocratic
6-35	100→0	0→100	linear gradient
35-55	0	100	isocratic
55-55.01	0→100	100→0	re-equilibration
55.01-65	100	0	isocratic

When the chromatograms are recorded under the prescribed conditions the retention time of mupirocin is between 19.4 and 23.7 minutes (about 21.5 minutes).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2):

the *resolution factor* between the peak due to mupirocin and the peak with a retention time relative to mupirocin of about 0.7 (mupirocin impurity C) is at least 3.0;

the *column efficiency*, determined on the peak due to mupirocin, is at least 7000 *theoretical plates* per metre;

the *symmetry factor* of the principal peak is at most 1.75.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to mupirocin impurity C is not greater than 3.2 times the area of the principal peak in the chromatogram obtained with solution (2) (3.2%, with respect to the content of mupirocin);

the area of any peak with a retention time relative to mupirocin of about 0.6 (mupirocin impurity D) is not greater than 8.5 times the area of the principal peak in the chromatogram obtained with solution (2) (8.5%, with respect to the content of mupirocin);

the area of any peak with a retention time relative to mupirocin of about 0.63 (mupirocin impurity E) is not greater than 16 times the area of the principal peak in the chromatogram obtained with solution (2) (16%, with respect to the content of mupirocin);

the area of any other *secondary peak* is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%, with respect to the content of mupirocin);

the sum of the areas of all the *secondary peaks* is not greater than 30 times the area of the principal peak in the chromatogram obtained with solution (2) (30%, with respect to the content of mupirocin).

Disregard any peaks corresponding to the peaks in the chromatogram obtained with solution (3) and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%, with respect to the content of mupirocin).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the cream containing the equivalent of 10 mg of mupirocin in 25 mL of *tetrahydrofuran*, add 50 mL of 0.1M *phosphate buffer solution pH 6.3* and shake vigorously. Add sufficient 0.1M *phosphate buffer solution pH 6.3* to produce 100 mL and mix; filter the solution through a 0.5-µm filter and use the filtrate.
(2) 0.01% w/v of *mupirocin lithium BPCRS* in 0.1M *phosphate buffer solution pH 6.3*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

28 volumes of *acetonitrile* and 72 volumes of 0.1M *phosphate buffer solution pH 6.3*.

When the chromatograms are recorded under the prescribed conditions the retention time of mupirocin is about 5 minutes.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peak due to mupirocin and the peak with a retention time relative to mupirocin of about 0.77 (mupirocin impurity C) is at least 1.5.

DETERMINATION OF CONTENT

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Calculate the content of $C_{26}H_{44}O_9$ in the cream using the declared content of $C_{26}H_{43}O_9Li$ in *mupirocin lithium BPCRS*. Each mg of $C_{26}H_{43}O_9Li$ is equivalent to 0.9882 mg of $C_{26}H_{44}O_9$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of mupirocin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mupirocin Calcium.

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Mupirocin Nasal Ointment

General Notices

Action and use

Antibacterial.

DEFINITION

Mupirocin Nasal Ointment contains Mupirocin Calcium in a suitable basis.

The nasal ointment complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of mupirocin, $C_{26}H_{44}O_9$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the nasal ointment containing the equivalent of 100 mg of mupirocin in a mixture of 20 mL of *dichloromethane* and 4 mL of 0.2M *sodium borate buffer pH 8.4,* with shaking, and centrifuge at 3000 revolutions per minute until separate layers are obtained. Remove and retain the upper aqueous layer and re-extract the lower layer with a further 4 mL of 0.2M *sodium borate buffer pH 8.4*. Combine the aqueous extracts, add 10 mL of *dichloromethane* to the combined extracts and centrifuge at 3000 revolutions per minute. Remove the upper aqueous layer and adjust the pH to about 4 with 1M *hydrochloric acid* (a slight cloudiness may be observed), add 10 mL of *dichloromethane* and centrifuge. Separate and retain the lower layer; add a further 10 mL of *dichloromethane* to the upper layer and centrifuge. Combine the dichloromethane extracts and evaporate to dryness at room temperature under a current of nitrogen; a jelly-like residue is obtained. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of mupirocin *(RS 425)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the nasal ointment containing the equivalent of 50 mg of mupirocin in 5 mL of a solution containing 3 volumes of *tetrahydrofuran* and 1 volume of *water* and shake vigorously on a mechanical shaker for 1 hour. Add 5 mL of a solution prepared by dissolving 13.6 g of *sodium acetate* in 1000 mL of *water*, mixing and adjusting the pH to 4.0 with *glacial acetic acid*, shake for a further 15 minutes. Allow the layers to separate and filter the lower aqueous layer (Whatman GF/F filter paper is suitable).

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(2) Dilute 1 volume of solution (1) to 50 volumes with a solution containing 3 volumes of *tetrahydrofuran* and 1 volume of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (7 µm) (Zorbax C8 is suitable) fitted with a suitable stainless steel guard column packed with the same material.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

25 volumes of *tetrahydrofuran* and 75 volumes of a solution prepared by dissolving 7.7 g of *ammonium acetate* in 900 mL of *water*, adjusting the pH to 5.7 with 0.1M *glacial acetic acid* and diluting to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of mupirocin is about 12 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peak due to mupirocin and the peak with a retention time relative to mupirocin of about 0.75 (mupirocin impurity C) is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 4% by *normalisation*;

the area of any other *secondary peak* is not greater than 1% by *normalisation*;

the sum of the areas of all the *secondary peaks* is not greater than 10% by *normalisation*.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the nasal ointment containing the equivalent of 10 mg of mupirocin in 50 mL of a solution containing 3 volumes of *tetrahydrofuran* and 1 volume of *water* and shake vigorously on a mechanical shaker for 1 hour. Add 50 mL of a solution prepared by dissolving 13.6 g of *sodium acetate* in 1000 mL of *water*, mixing and adjusting the pH to 4.0 with *glacial acetic acid*, shake for a further 15 minutes and filter (Whatman GF/F filter paper is suitable).

(2) 0.01% w/v of *mupirocin lithium BPCRS* in a solution containing 3 volumes of *tetrahydrofuran* and 1 volume of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (7 µm) (Zorbax C8 is suitable) fitted with a suitable stainless steel guard column packed with the same material.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

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(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

25 volumes of *tetrahydrofuran* and 75 volumes of a solution prepared by dissolving 7.7 g of *ammonium acetate* in 900 mL of *water*, adjusting the pH to 5.7 with 0.1M *glacial acetic acid* and diluting to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of mupirocin is about 12 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peak due to mupirocin and the peak with a retention time relative to mupirocin of about 0.75 (mupirocin impurity C) is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{44}O_9$ in the nasal ointment using the declared content of $C_{26}H_{43}O_9Li$ in *mupirocin lithium BPCRS*. Each mg of $C_{26}H_{43}O_9Li$ is equivalent to 0.9882 mg of $C_{26}H_{44}O_9$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of mupirocin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mupirocin Calcium.

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Mupirocin Ointment

General Notices

Action and use

Antibacterial.

DEFINITION

Mupirocin Ointment contains Mupirocin in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of mupirocin, $C_{26}H_{44}O_9$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ointment containing 20 mg of Mupirocin in 20 mL of *methanol*, mix with the aid of ultrasound for 20 minutes and filter through a 0.45-µm nylon filter.

(2) 0.1% w/v of *mupirocin lithium BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 25 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 5 volumes of *methanol* and 93 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing 50 mg of Mupirocin in 50 mL of 0.1M *phosphate buffer solution pH 6.3*, swirl and allow to stand (with occasional swirling) until dissolution is almost complete. Shake vigorously for 10 minutes and add sufficient 0.1M *phosphate buffer solution pH 6.3* to produce 100 mL.

(2) 0.00054% w/v of *mupirocin lithium BPCRS* in 0.1M *phosphate buffer solution pH 6.3*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (7 µm) (Zorbax C8 is suitable) fitted with a stainless steel guard column packed with the same material.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions the retention time of mupirocin is about 13 minutes.

MOBILE PHASE

28 volumes of *tetrahydrofuran* and 72 volumes of a solution prepared by dissolving 7.7 g of *ammonium acetate* in 900 mL of *water*, adjusting the pH to 5.7 with 0.1M *glacial acetic acid* and diluting to 1000 mL with *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peak due to mupirocin and the peak with a retention time relative to mupirocin of about 0.65 (mupirocin impurity C) is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to mupirocin impurity C is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4%, with respect to the content of mupirocin);

the area of any peak with a retention time relative to mupirocin of about 0.5 (mupirocin impurity D) is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%, with respect to the content of mupirocin);

the area of any peak with a retention time relative to mupirocin of about 0.55 (mupirocin impurity E) is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (10%, with respect to the content of mupirocin);

the area of any other *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%, with respect to the content of mupirocin);

the sum of the areas of all the *secondary peaks* is not greater than 20 times the area of the principal peak in the chromatogram obtained with solution (2) (20%, with respect to the content of mupirocin).

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Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%, with respect to the content of mupirocin).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing 50 mg of Mupirocin in 100 mL of 0.1M *phosphate buffer solution pH 6.3*, swirl and allow to stand (with occasional swirling) until dissolution is complete. Add 56 mL of *acetonitrile* and sufficient 0.1M *phosphate buffer solution pH 6.3* to produce 200 mL.

(2) 0.027% w/v of *mupirocin lithium BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions the retention time of mupirocin is about 5 minutes.

MOBILE PHASE

28 volumes of *acetonitrile* and 72 volumes of 0.1M *phosphate buffer solution pH 6.3*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peak due to mupirocin and the peak with a retention time relative to mupirocin of about 0.77 (mupirocin impurity C) is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{44}O_9$ in the ointment using the declared content of $C_{26}H_{43}O_9Li$ in *mupirocin lithium BPCRS*. Each mg of $C_{26}H_{43}O_9Li$ is equivalent to 0.9882 mg of $C_{26}H_{44}O_9$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mupirocin.

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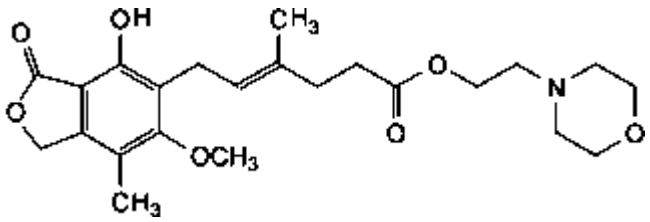
Mycophenolate Mofetil

General Notices

(Ph. Eur. monograph 1700)



$C_{23}H_{31}NO_7$ 433.5 *128794-94-5*

Action and use

Inhibitor of nucleic acid synthesis; immunomodulator.

Preparations

Mycophenolate Mofetil Capsules

Mycophenolate Mofetil for Infusion

Mycophenolate Mofetil Oral Suspension

Mycophenolate Mofetil Tablets

Ph Eur

DEFINITION

2-(Morpholin-4-yl)ethyl (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.

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About 96 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *mycophenolate mofetil CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.10 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light. Prepare the solutions immediately before use, or store them at 4-8 °C. Keep the temperature of the autosampler at 10 °C, allow the temperature of the solutions to equilibrate in the vials for 15 min before injection.*

Test solution Dissolve 20 mg of the substance to be examined in *acetonitrile R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 5 mg of *mycophenolate mofetil for peak identification CRS* (mycophenolate mofetil with impurities A, B, D, E, F, G and H) in *acetonitrile R* and dilute to 2.5 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 45 °C.

Mobile phase Mix 350 mL of *acetonitrile R* with a mixture of 650 mL of *water R* and 2.0 mL of *triethylamine R* previously adjusted to pH 5.3 with *dilute phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 250 nm.

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Injection 10 µL.

Run time 3 times the retention time of mycophenolate mofetil.

Relative retention With reference to mycophenolate mofetil (retention time = about 22 min): impurity F = about 0.3; impurity A = about 0.4; impurity H = about 0.5; impurity G = about 0.6; impurity B = about 0.8; impurity D = about 1.2; impurity E = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and impurity H,

— the chromatogram obtained is similar to the chromatogram supplied with *mycophenolate mofetil for peak identification CRS*.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 2.1,

— *impurity F*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *impurities A, D, E, G, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 43.35 mg of $C_{23}H_{31}NO_7$.

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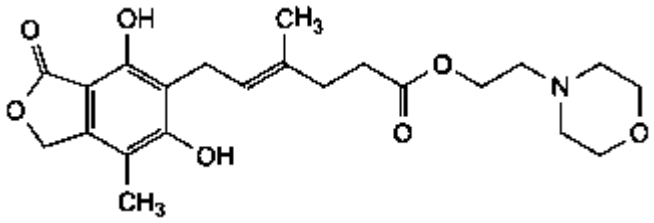
STORAGE

Protected from light.

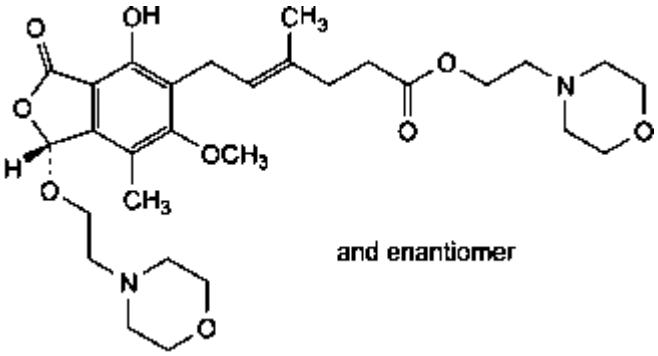
IMPURITIES

Specified impurities *A, B, D, E, F, G, H.*

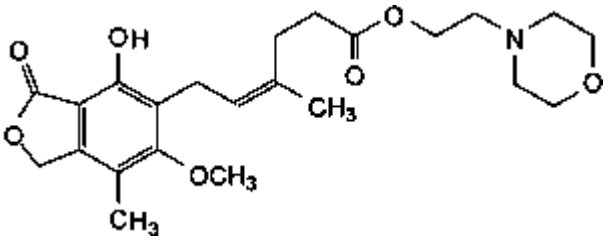
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



A. 2-(morpholin-4-yl)ethyl (4*E*)-6-(4,6-dihydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,



B. 2-(morpholin-4-yl)ethyl (4*E*)-6-[(1*RS*)-4-hydroxy-6-methoxy-7-methyl-1-[2-(morpholin-4-yl)ethoxy]-3-oxo-1,3-dihydroisobenzofuran-5-yl]-4-methylhex-4-enoate,



C. 2-(morpholin-4-yl)ethyl (4*Z*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,

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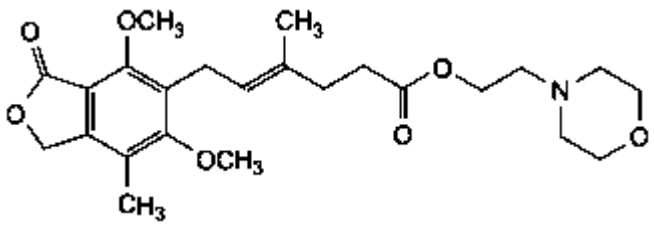
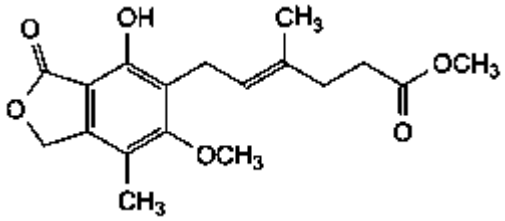
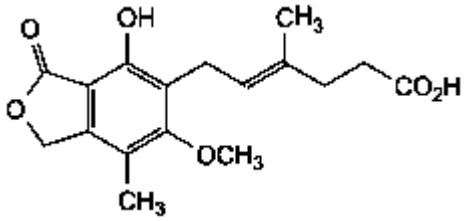


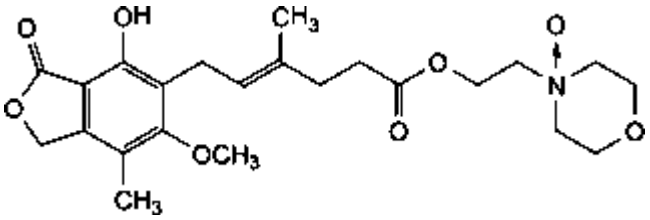
D. 2-(morpholin-4-yl)ethyl (4*E*)-6-(4,6-dimethoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,



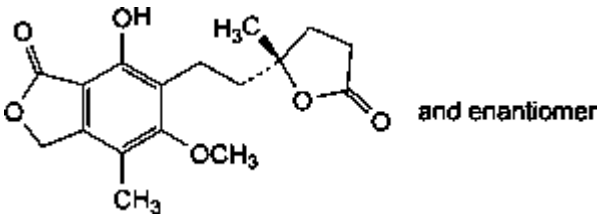
E. methyl (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,



F. (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid (mycophenolic acid),



G. 2-(morpholin-4-yl)ethyl (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate *N*-oxide,



H. 7-hydroxy-5-methoxy-4-methyl-6-[2-[(2*RS*)-2-methyl-5-oxotetrahydrofuran-2-yl]ethyl]isobenzofuran-1(3*H*)-one.

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Mycophenolate Mofetil Capsules

General Notices

Action and use

Inhibitor of nucleic acid synthesis; immunomodulator.

DEFINITION

Mycophenolate Mofetil Capsules contain Mycophenolate Mofetil.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of mycophenolate mofetil, $C_{23}H_{31}NO_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the capsule contents containing 0.1 g of Mycophenolate Mofetil with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of mycophenolate mofetil *(RS 504)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 40 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium, and filter (a 0.45-µm nylon filter is suitable). Dilute the filtered sample with dissolution medium, if necessary, to produce a solution containing 0.0056% w/v of Mycophenolate Mofetil. Immediately measure the *absorbance* of the solution, Appendix II B, at 304 nm using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0056% w/v solution of *mycophenolate mofetil BPCRS* in the dissolution medium.

DETERMINATION OF CONTENT

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Calculate the total content of mycophenolate mofetil, $C_{23}H_{31}NO_7$, in the medium using the declared content of $C_{23}H_{31}NO_7$, in *mycophenolate mofetil BPCRS*.

LIMITS

The amount of mycophenolate mofetil released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

Solution A Add 0.55 volumes of *orthophosphoric acid* to 1300 volumes of a 0.568% w/v solution of *ammonium dihydrogen orthophosphate* in *water*; adjust to pH 3.0 using *orthophosphoric acid* or 1M *potassium hydroxide* and add 700 volumes of *acetonitrile*.

(1) To a quantity of powdered capsule contents containing 1.25 g of Mycophenolate Mofetil, add 125 mL of *acetonitrile* and mix with the aid of ultrasound. Dilute to 250 mL with *acetonitrile* and centrifuge. Dilute 1 volume of the supernatant liquid to 5 volumes with solution A.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) Dilute 1 volume of solution (2) to 10 volumes with solution A.
(4) 0.12% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 249 nm.
(f) Inject 10 µL of each solution.
(g) Use an autosampler temperature of 5°.
(h) Allow the chromatography to proceed for twice the retention time of mycophenolate mofetil.

MOBILE PHASE

200 volumes of solution containing 0.05% v/v of *orthophosphoric acid* and 0.1% v/v of *triethylamine* in water, adjusted to pH 5.4 with *orthophosphoric acid* or 1M *potassium hydroxide*, 350 volumes of *acetonitrile* and 450 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mycophenolate mofetil (retention time about 21 minutes) are: impurity F; about 0.3; impurity A; about 0.4; impurity H, about 0.45; impurity G; about 0.5; impurity B, about 0.9; impurity C; about 1.1; impurity D, about 1.2 and impurity E, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.

LIMITS

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In the chromatogram obtained with solution (1), identify any peaks due to impurities A, B, F and G using the chromatogram obtained with solution (4). Multiply the areas of any peaks corresponding to impurities A, B, F and G by the following correction factors: impurity A, 0.6; impurity B, 2.1; impurity F and impurity G, 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of all *secondary peaks* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for liquid chromatography, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

Solution A Add 0.55 volumes of *orthophosphoric acid* to 1300 volumes of a 0.568% w/v solution of *ammonium dihydrogen orthophosphate* in *water*; adjust to pH 3.0 using *orthophosphoric acid* or 1M *potassium hydroxide* and add 700 volumes of *acetonitrile*.

(1) To a quantity of the capsule contents containing 1.25 g of Mycophenolate Mofetil, add 125 mL of *acetonitrile* and mix with the aid of ultrasound. Dilute to 250 mL with *acetonitrile* and centrifuge. Dilute the supernatant liquid with solution A to produce a solution containing 0.04% w/v of Mycophenolate Mofetil.
(2) 0.04% w/v of *mycophenolate mofetil BPCRS* in solution A.
(3) 0.12% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of mycophenolate mofetil, $C_{23}H_{31}NO_7$, in the capsules from the chromatograms obtained and using the declared content of $C_{23}H_{31}NO_7$ in *mycophenolate mofetil BPCRS*.

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IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mycophenolate Mofetil.

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Mycophenolate Mofetil for Infusion

General Notices

Action and use

Inhibitor of nucleic acid synthesis; immunomodulator.

DEFINITION

Mycophenolate Mofetil for Infusion is a sterile material consisting of Mycophenolate Mofetil with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of mycophenolate mofetil, $C_{23}H_{31}NO_7$

93.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powder for infusion with sufficient 0.1M *hydrochloric acid* to produce a solution containing 0.005% w/v of Mycophenolate Mofetil. The *light absorption*, Appendix II B, in the range 200 to 400 nm of this solution exhibits two maxima at 250 and 304 nm and a minimum at 274 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Acidity

Prepare the infusion as directed on the label.

pH, 2.7 to 4.1, Appendix V L.

Clarity and colour of solution

Prepare the infusion as directed on the label.

The solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution Y4*, Appendix IV B, Method II.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

Solution A 20 volumes of a solution containing 1% v/v of *triethylamine* in *water*, adjusted to pH 3.0 with *orthophosphoric acid* or 1M *potassium hydroxide*, 35 volumes *acetonitrile* and 45 volumes of *water*.

(1) Dissolve a quantity of the contents of the sealed container containing 2 g of Mycophenolate Mofetil in 56 mL of 5% w/v *glucose* in *Water for Injections,* dilute with sufficient *water* to produce 200 mL. Dilute 1 volumes of this solution to 25 volumes with solution A to produce a solution of 0.04% w/v of Mycophenolate Mofetil.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) Dilute 1 volume of solution (2) to 10 volumes with solution A.

(4) 0.04% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated, end-capped phenylsilyl silica gel for chromatography* (5 µm) (Inertsil Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 249 nm.

(f) Inject 10 µL of each solution.

(g) Use an autosampler temperature of 5°.

(h) Allow the chromatography to proceed for twice the retention time of mycophenolate mofetil.

MOBILE PHASE

217 volumes of solution containing 1% v/v of *triethylamine* in *water*, adjusted to pH 7.2 with *orthophosphoric acid* or 1M *potassium hydroxide*, 300 volumes *acetonitrile* and 483 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retentions relative to mycophenolate mofetil (retention time about 27 minutes) are: impurity F, about 0.1; impurity G, about 0.3; impurity A, about 0.4; impurity H, about 0.45; impurity B, about 0.9 and impurity C, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks due to impurities A, B, F and G using the chromatogram obtained with solution (4). Multiply the areas of any peaks corresponding to impurities A, B, F and G by the following correction factors: impurity A, 0.6; impurity B, 2.1; impurity F and impurity G, 0.7.

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity F is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of all *secondary peaks* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use. Prepare the solutions immediately before use and protect from light.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 20 volumes of a solution containing 1% v/v of *triethylamine* in *water*, adjusted to pH 3.0 with *orthophosphoric acid* or 1M *potassium hydroxide*, 35 volumes *acetonitrile* and 45 volumes of *water*.

(1) Shake a quantity of the mixed contents of the 10 containers containing 0.2 g of Mycophenolate Mofetil with 55 mL of a solution containing 5% w/v of *glucose* in *water* until the powder is dissolved, and dilute to 200 mL with *water*. Dilute with solution A to produce a solution containing 0.04% w/v of Mycophenolate Mofetil.
(2) 0.04% w/v of *mycophenolate mofetil BPCRS* in solution A.
(3) 0.04% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of mycophenolate mofetil, $C_{23}H_{31}NO_7$, in a container of average content weight using the chromatograms obtained and the declared content of $C_{23}H_{31}NO_7$ in *mycophenolate mofetil BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mycophenolate Mofetil.

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Mycophenolate Mofetil Oral Suspension

General Notices

Action and use

Inhibitor of nucleic acid synthesis; immunomodulator.

DEFINITION

Mycophenolate Mofetil Oral Suspension is a suspension of Mycophenolate Mofetil in a suitable vehicle. It is prepared by dispersing the dry ingredients in the specified volume of water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Suspensions stated under Oral Liquids.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of mycophenolate mofetil, $C_{23}H_{31}NO_7$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

Solution A 1 volume of a solution of 0.05M *ammonium phosphate* in *water*, adjusted to pH 3.0 with *orthophosphoric acid* or 1M *potassium hydroxide* and 1 volume of *acetonitrile*.

(1) Shake a quantity of the oral suspension containing 0.5 g of Mycophenolate Mofetil with 25 mL of solution A. Dilute to produce 50 mL and further dilute 1 volume to 10 volumes with solution A. Filter and use the filtrate.

(2) 0.1% w/v of *mycophenolate mofetil BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *concentrated ammonia*, 7 volumes of *methanol*, 17 volumes of *toluene* and 75 volumes of *acetonitrile*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity and alkalinity

pH of the suspension, 6.0 to 7.0, Appendix V L.

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 40 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) Shake the oral suspension and place a volume equivalent to one dose into each dissolution vessel. After 20 minutes withdraw a sample of the medium, and filter (a 0.45-µm nylon filter is suitable). Dilute the filtered sample with dissolution medium, if necessary to produce a solution expected to contain 0.0056% w/v of Mycophenolate Mofetil. Immediately measure the *absorbance* of the solution, Appendix II B, at 304 nm using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0056% w/v solution of *mycophenolate mofetil BPCRS* in the dissolution medium.

DETERMINATION OF CONTENT

Calculate the total content of mycophenolate mofetil, $C_{23}H_{31}NO_7$, in the medium using the declared content of $C_{23}H_{31}NO_7$ in *mycophenolate mofetil BPCRS*.

LIMITS

The amount of mycophenolate mofetil released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

Solution B 20 volumes of a solution containing 1% v/v *triethylamine* in *water*, adjusted to pH 3.0 with *orthophosphoric acid* or 1M *potassium hydroxide*, 35 volumes of *acetonitrile* and 45 volumes of *water*.

Solution C 15 volumes of solution containing 1% v/v *triethylamine* in *water*, adjusted to pH 3.0 with *orthophosphoric acid* or 1M *potassium hydroxide*, 35 volumes of *water* and 50 volumes of *acetonitrile*.

(1) Shake a quantity of the oral suspension containing 0.8 g of Mycophenolate Mofetil with 100 mL of solution C and dilute to 200 mL with solution C. Dilute 1 volume of this solution to 10 volumes with solution B and filter through a 0.45-µm PVDF filter to produce a solution

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containing 0.04% w/v of Mycophenolate Mofetil.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution B.

(3) Dilute 1 volume of solution (2) to 10 volumes with solution B.

(4) 0.04% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated, end-capped phenylsilyl silica gel for chromatography* (5 µm) (Inertsil Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 249 nm.

(f) Inject 20 µL of each solution.

(g) Use an autosampler temperature of 5°.

(h) Allow the chromatography to proceed for twice the retention time of mycophenolate mofetil.

MOBILE PHASE

217 volumes of solution containing 1% v/v of *triethylamine* in *water*, adjusted to pH 7.2 with *orthophosphoric acid* or 1M *potassium hydroxide*, 300 volumes *acetonitrile* and 483 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mycophenolate mofetil (retention time about 27 minutes) are: impurity F, about 0.1; impurity 1, about 0.2; impurity G, about 0.3; impurity A, about 0.4; impurity H, about 0.45; impurity B, about 0.9 and impurity C, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0

LIMITS

In the chromatogram obtained with solution (1), identify any peaks due to impurities A, B, F and G using the chromatogram obtained with solution (4). Multiply the areas of any peaks corresponding to impurities A, B, F and G by the following correction factors: impurity A, 0.6; impurity B, 2.1; impurity F and impurity G, 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than 3.3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.3%);

the area of any peaks corresponding to impurity B or impurity 1 is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

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the sum of the areas of all *secondary peaks*, excluding impurity F, is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using solutions B and C as described under Related substances. Prepare the solutions immediately before use and protect from light.

(1) Shake a weighed quantity of the oral suspension containing 0.8 g of Mycophenolate Mofetil with 100 mL of solution C and dilute to 200 mL with solution C. Dilute 1 volume of this solution to 10 volumes with solution B and filter through a 0.45-µm PVDF filter to produce a solution containing 0.04% w/v of Mycophenolate Mofetil.

(2) 0.04% w/v of *mycophenolate mofetil BPCRS*.

(3) 0.04% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

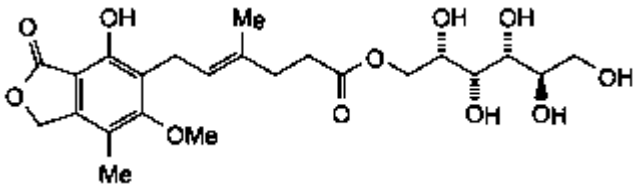
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{23}H_{31}NO_7$, weight in volume, using the declared content of $C_{23}H_{31}NO_7$ in *mycophenolate mofetil BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mycophenolate Mofetil and impurity 1:



1. 2-(morpholin-4-yl)ethyl (4*Z*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoate (sorbitol ester of mycophenolic acid)

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Mycophenolate Mofetil Tablets

General Notices

Action and use

Inhibitor of nucleic acid synthesis; immunomodulator.

DEFINITION

Mycophenolate Mofetil Tablets contain Mycophenolate Mofetil.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mycophenolate mofetil, $C_{23}H_{31}NO_7$

94.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of powdered tablets containing 0.1 g of Mycophenolate Mofetil with 20 mL of *acetone*, filter and evaporate to dryness. The *infrared absorption spectrum*, Appendix II A, is concordant with the reference spectrum of mycophenolate mofetil *(RS 504)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm nylon filter is suitable). Dilute the filtered sample with dissolution medium, if necessary, to produce a solution expected to contain 0.0056% w/v of Mycophenolate Mofetil. Immediately measure the *absorbance* of the solution, Appendix II B, at 304 nm using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0056% w/v solution of *mycophenolate mofetil BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of mycophenolate mofetil, $C_{23}H_{31}NO_7$, in the medium using the declared content of $C_{23}H_{31}NO_7$ in *mycophenolate mofetil BPCRS*.

LIMITS

The amount of mycophenolate mofetil released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

Solution A Add 0.55 volumes of *orthophosphoric acid* to 1300 volumes of a 0.568% w/v solution of *ammonium dihydrogen orthophosphate* in *water*; adjust to pH 3.0 using *orthophosphoric acid* or 1M *potassium hydroxide* and add 700 volumes of *acetonitrile*.

(1) Shake a quantity of powdered tablets containing 1.5 g of Mycophenolate Mofetil with 60 mL of *acetonitrile* and then mix with the aid of ultrasound. Dilute to 250 mL with *acetonitrile* and centrifuge. Dilute 1 volume of the supernatant liquid to 5 volumes with solution A.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) Dilute 1 volume of solution (2) to 10 volumes with solution A.
(4) 0.12% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 249 nm.
(f) Inject 10 µL of each solution.
(g) Use an autosampler temperature of 5°.
(h) Allow the chromatography to proceed for twice the retention time of mycophenolate mofetil.

MOBILE PHASE

200 volumes of a solution containing 0.05% v/v of *orthophosphoric acid* and 0.1% v/v of *triethylamine* in *water*, adjusted to pH 5.4 with *orthophosphoric acid* or 1M *potassium hydroxide*, 350 volumes of *acetonitrile* and 450 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mycophenolate mofetil (retention time about 21 minutes) are: impurity F; about 0.3; impurity A; about 0.4; impurity H, about 0.45; impurity G; about 0.5; impurity B, about 0.9; impurity C; about 1.1; impurity D, about 1.2 and impurity E, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.

LIMITS

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In the chromatogram obtained with solution (1), identify any peaks due to impurities A, B, F and G using the chromatogram obtained with solution (4). Multiply the areas of any peaks corresponding to impurities A, B, F and G by the following correction factors: impurity A, 0.6; impurity B, 2.1; impurity F and impurity G, 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of all *secondary peaks* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

Solution A Add 0.55 volumes of *orthophosphoric acid* to 1300 volumes of a 0.568% w/v solution of *ammonium dihydrogen orthophosphate* in *water*; adjust to pH 3.0 using *orthophosphoric acid* or 1M *potassium hydroxide* and add 700 volumes of *acetonitrile*.

(1) Shake a quantity of powdered tablets containing 1.5 g of Mycophenolate Mofetil with 60 mL of *acetonitrile* and then mix with the aid of ultrasound. Dilute to 250 mL with *acetonitrile* and centrifuge. Dilute the supernatant liquid with sufficient solution A to produce a solution containing 0.036% w/v of Mycophenolate Mofetil.
(2) 0.036% w/v of *mycophenolate mofetil BPCRS* in solution A.
(3) 0.12% w/v of *mycophenolate mofetil impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of mycophenolate mofetil, $C_{23}H_{31}NO_7$, in the tablets from the chromatograms obtained and using the declared content of $C_{23}H_{31}NO_7$ in *mycophenolate mofetil BPCRS*.

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IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mycophenolate Mofetil.

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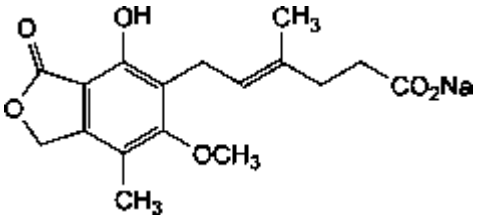
Mycophenolate Sodium

General Notices

(Ph. Eur. monograph 2813)



$C_{17}H_{19}NaO_6$ 342.3 *37415-62-6*

Action and use

Inhibitor of nucleic acid synthesis; immunomodulator.

Ph Eur

DEFINITION

Sodium (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoate, the sodium salt of a fermentation product.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water and in anhydrous ethanol, very slightly soluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *mycophenolate sodium CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Buffer solution Dissolve 0.77 g of *ammonium acetate R* in 600 mL of *water for chromatography R*, adjust to pH 4.86 with a 60 g/L solution of *glacial acetic acid R* and dilute to 1000 mL with *water for chromatography R*.

Solvent mixture *water R*, *acetonitrile R* (40:60 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *mycophenolate sodium CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *mycophenolate for system suitability CRS* (containing impurities A and B) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: buffer solution;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	71	29

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
15 - 34	71 → 21.3	29 → 78.7

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 250 nm.

Autosampler Set at 10 °C.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram supplied with *mycophenolate for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to mycophenolic acid (retention time = about 12 min): impurity B = about 0.93; impurity A = about 1.1.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to mycophenolic acid; minimum 10.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to mycophenolic acid.

Calculation of percentage contents:

— for each impurity, use the concentration of mycophenolate sodium in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.1 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{17}H_{19}NaO_6$ taking into account the assigned content of *mycophenolate sodium CRS*.

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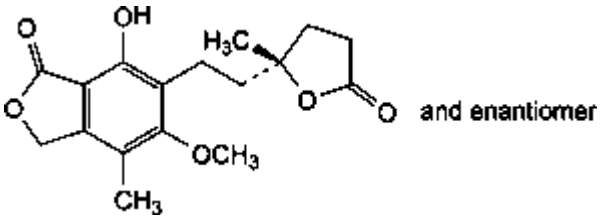
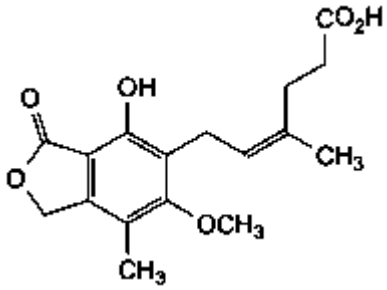
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*

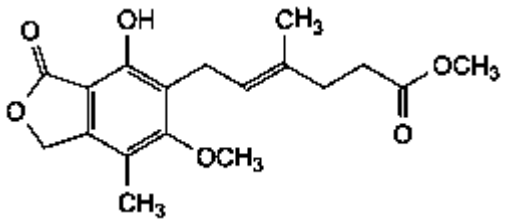


and enantiomer

A. 7-hydroxy-5-methoxy-4-methyl-6-[2-[(2*RS*)-2-methyl-5-oxooxolan-2-yl]ethyl]-2-benzofuran-1(3*H*)-one,



B. (4*Z*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoic acid,



C. methyl (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoate.

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myo-Inositol

General Notices

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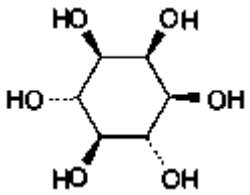

$C_6H_{12}O_6$ 180.2 *87-89-8*

Action and use

Vasodilator.

Ph Eur

DEFINITION

Cyclohexane-1,2,3,5/4,6-hexol.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *myo-inositol CRS*.

B. Examine the chromatograms obtained in the assay.

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Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 10.0 g in *distilled water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Conductivity (*2.2.38*)

Maximum 30 μS·cm^{-1}.

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R*, with gentle warming if necessary, and dilute to 50.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.500 g of *myo-inositol CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (c) Dissolve 0.5 g of *myo-inositol R*, 2 mg of *mannitol R* (impurity A) and 2 mg of *glycerol R* (impurity B) in *water R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 μm);

— *temperature*: 85 ± 2 °C.

Mobile phase *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 μL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of *myo*-inositol.

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Relative retention With reference to *myo*-inositol (retention time = about 16 min): impurity B = about 1.2; impurity A = about 1.3.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity B and impurity A.

Limits:

— *impurities A, B*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

ASSAY

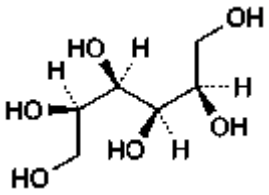
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

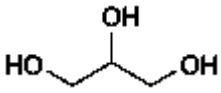
Calculate the percentage content of $C_6H_{12}O_6$ taking into account the assigned content of *myo-inositol CRS*.

IMPURITIES

Specified impurities *A, B.*



A. D-mannitol,



B. propane-1,2,3-triol (glycerol).

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Nabumetone

General Notices

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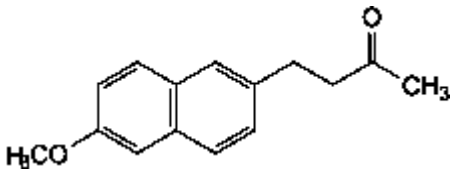

$C_{15}H_{16}O_2$ 228.3 *42924-53-8*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Nabumetone Oral Suspension

Nabumetone Tablets

Ph Eur

DEFINITION

4-(6-Methoxynaphthalen-2-yl)butan-2-one.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, slightly soluble in methanol.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison nabumetone CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in acetonitrile R and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 25.0 mL with acetonitrile R. Dilute 1.0 mL of this solution to 5.0 mL with acetonitrile R.

Reference solution (a) Dissolve 20.0 mg of nabumetone CRS in acetonitrile R and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of this solution to 50.0 mL with acetonitrile R.

Reference solution (b) Dilute 0.5 mL of test solution (a) to 100.0 mL with acetonitrile R.

Reference solution (c) Dissolve 1.5 mg of nabumetone impurity F CRS in acetonitrile R and dilute to 100.0 mL with the same solvent.

Reference solution (d) Dissolve 4 mg of nabumetone impurity D CRS in acetonitrile R and dilute to 100 mL with the same solvent. To 5 mL of this solution, add 5 mL of test solution (b).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated octadecylsilyl silica gel for chromatography R (4 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 12 volumes of tetrahydrofuran R, 28 volumes of acetonitrile for chromatography R and 60 volumes of a 0.1 per cent *V/V* solution of glacial acetic acid R in carbon dioxide-free water R prepared from distilled water R;

— *mobile phase B*: mix 24 volumes of tetrahydrofuran R, 56 volumes of acetonitrile for chromatography R and 20 volumes of a 0.1 per cent *V/V* solution of glacial acetic acid R in carbon dioxide-free water R prepared from distilled water R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	100	0
12 - 28	100 → 0	0 → 100
28 - 33	0	100

Flow rate 1 mL/min.

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Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c) and (d).

Retention time Nabumetone = about 11 min.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to nabumetone and impurity D.

Limits:

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *sum of impurities other than F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

Maximum 0.2 per cent, determined on 1.000 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{15}H_{16}O_2$ from the declared content of *nabumetone CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *F.*

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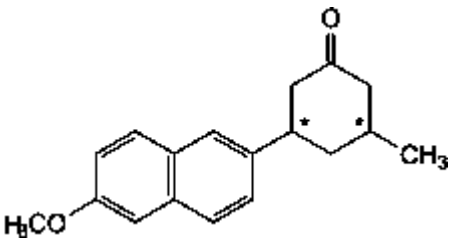
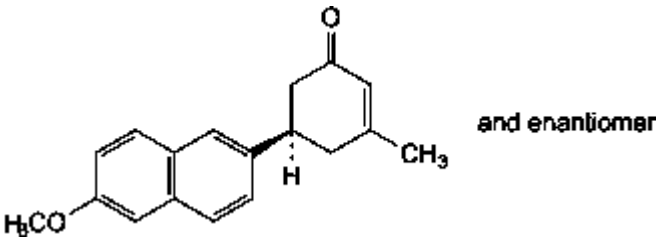
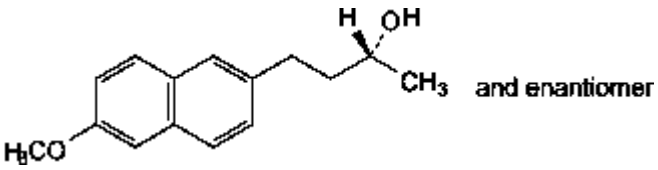
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E.



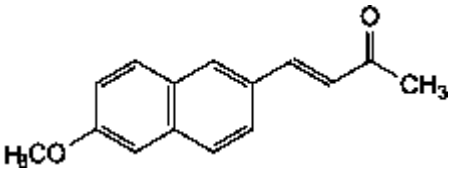
A. 3-(6-methoxynaphthalen-2-yl)-5-methylcyclohexanone,



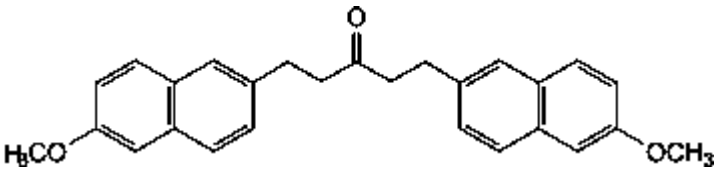
B. (5*RS*)-5-(6-methoxynaphthalen-2-yl)-3-methylcyclohex-2-enone,



C. (2*RS*)-4-(6-methoxynaphthalen-2-yl)butan-2-ol,



D. (*E*)-4-(6-methoxynaphthalen-2-yl)but-3-en-2-one,



E. 1,5-bis(6-methoxynaphthalen-2-yl)pentan-3-one,

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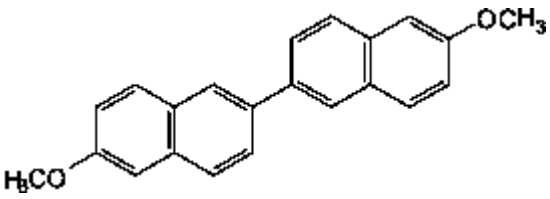

F. 6,6′-dimethoxy-2,2′-binaphthalenyl.

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Nabumetone Oral Suspension

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Nabumetone Oral Suspension contains Nabumetone in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of nabumetone, $C_{15}H_{16}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add a volume of the well-shaken suspension containing 0.1 g of Nabumetone to 10 mL of *dichloromethane*, shake, allow to separate and use the lower layer.

(2) 1.0% w/v of *nabumetone BPCRS* in *dichloromethane*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel GF_{254} precoated plate (Merck 5715 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

dichloromethane

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and colour to the spot in the chromatogram obtained with solution (2) and the chromatogram obtained with solution (3) shows a single, compact spot at the same Rf value as the spot in the chromatogram obtained with solution (2).

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B. In the Assay the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a volume of the suspension containing 0.5 g of Nabumetone with 10 mL of *methanol* until completely dispersed, add sufficient *acetonitrile* to produce 100 mL, shake for a further 5 minutes and filter (Whatman No. 1 paper is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.0015% w/v of *nabumetone impurity F EPCRS* in *acetonitrile*.

(4) 0.002% w/v of each of *nabumetone BPCRS* and *nabumetone impurity D BPCRS* in *acetonitrile*.

(5) Dilute 1 volume of solution (2) to 10 volumes with *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (4 µm) (Genesis C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 12 volumes of *tetrahydrofuran*, 28 volumes of *acetonitrile* and 60 volumes of a 0.1% v/v solution of *glacial acetic acid* in *carbon dioxide-free water*.

Mobile phase B 24 volumes of *tetrahydrofuran*, 56 volumes of *acetonitrile* and 20 volumes of a 0.1% v/v solution of *glacial acetic acid* in *carbon dioxide-free water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-12	100	0	isocratic
12-28	100→0	0→100	linear gradient
28-33	0	100	isocratic
33-34	0→100	100→0	linear gradient
34-35	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nabumetone (retention time about 11 minutes) are: impurity D, about 1.1 and impurity F, about 2.7.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the suspension containing 0.1 g of Nabumetone, add 70 mL of *ethanol (96%)*, mix with the aid of ultrasound for 45 minutes, add sufficient *ethanol (96%)* to produce 100 mL and filter (Whatman GF/C paper is suitable). Dilute 1 volume of the filtrate to 20 volumes with the mobile phase.

(2) Dilute 1 volume of a 0.1% w/v solution of *nabumetone BPCRS* in *acetonitrile* to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (4 µm) (Genesis C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

18 volumes of *tetrahydrofuran*, 40 volumes of a 0.1% v/v solution of *glacial acetic acid* in *carbon dioxide-free water* and 42 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions the retention time of nabumetone is about 4 minutes.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{16}O_2$, weight in volume, from the chromatograms obtained using the declared content of $C_{15}H_{16}O_2$ in *nabumetone BPCRS*.

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IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nabumetone.

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Nabumetone Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Nabumetone Tablets contain Nabumetone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nabumetone, $C_{15}H_{16}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum* of the powdered tablets, Appendix II A, is concordant with the *reference spectrum* of nabumetone *(RS 239)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *acetonitrile*.

(1) Shake a quantity of the powdered tablets containing 0.25 g of Nabumetone with 50 mL of *acetonitrile*, filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.0015% w/v of *nabumetone impurity F EPCRS*.

(4) 0.002% w/v of each of *nabumetone BPCRS* and *nabumetone impurity D BPCRS*.

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (4 µm) (Genesis C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

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(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 12 volumes of *tetrahydrofuran*, 28 volumes of *acetonitrile* and 60 volumes of a 0.1% v/v solution of *glacial acetic acid* in *carbon dioxide-free water*.

Mobile phase B 24 volumes of *tetrahydrofuran*, 56 volumes of *acetonitrile* and 20 volumes of a 0.1% v/v solution of *glacial acetic acid* in *carbon dioxide-free water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-12	100	0	isocratic
12-28	100→0	0→100	linear gradient
28-33	0	100	isocratic
33-34	0→100	100→0	linear gradient
34-35	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nabumetone (retention time about 11 minutes) are: impurity D, about 1.1 and impurity F, about 2.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of powdered tablets containing 0.5 g of Nabumetone, add 400 mL of *acetonitrile*, mix with the aid of ultrasound, allow to cool, add sufficient *acetonitrile* to produce 500 mL, mix and filter through a glass-fibre filter (Whatman GF/C is suitable). Dilute 1 volume of

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the filtrate to 20 volumes with the mobile phase.

(2) Dilute 1 volume of a 0.1% w/v solution of *nabumetone BPCRS* in *acetonitrile* to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (4 µm) (Genesis C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

18 volumes of *tetrahydrofuran*, 40 volumes of a 0.1% v/v solution of *glacial acetic acid* in *carbon dioxide-free water* and 42 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions the retention time of nabumetone is about 4 minutes.

DETERMINATION OF CONTENT

Calculate the content of nabumetone, $C_{15}H_{16}O_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{16}O_2$ in *nabumetone BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nabumetone.

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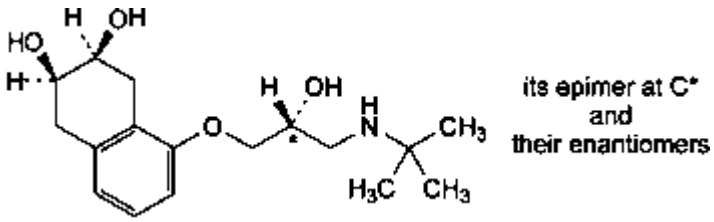
Nadolol

General Notices

(Ph. Eur. monograph 1789)



$C_{17}H_{27}NO_4$ 309.4 *42200-33-9*

Action and use

Beta-adrenoceptor antagonist.

Preparation

Nadolol Oral Suspension

Ph Eur

DEFINITION

cis-5-[(2*RS*)-3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol.

It consists of 2 pairs of enantiomers that are present as 2 racemic compounds: racemate A and racemate B.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *nadolol CRS*.

TESTS

Racemate content

Infrared absorption spectrophotometry (2.2.24).

Prepare a mull in *liquid paraffin R* of the substance to be examined (dried substance), adjusting the thickness of the mull to give an absorbance reading of 0.6 ± 0.1 at 1587 cm^{-1}. Record the spectrum from 1667 to 1111 cm^{-1}, using *liquid paraffin R* as reference. Measure the absorbance A_a, corresponding to racemate A, at the maximum at 1266 cm^{-1} and the absorbance A_b, corresponding to racemate B, at the maximum at 1250 cm^{-1}. The ratio A_a/A_b is 0.72 to 1.08 (corresponding to racemate A content of between 40 per cent and 60 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R1*, *water R* (20:80 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in 4.0 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *nadolol impurity mixture CRS* (impurities A and D) in 1.0 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 5.6 g/L solution of *sodium octanesulfonate R* adjusted to pH 3.5 with a 300 g/L solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	77	23
7 - 30	77 → 65	23 → 35
30 - 35	65 → 55	35 → 45
35 - 55	55	45

Flow rate 1 mL/min.

Detection Spectrophotometer at 206 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *nadolol impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and D.

Relative retention With reference to nadolol (retention time = about 15 min): impurity A = about 0.2; impurity C (doublet) = about 0.47 and 0.53; impurity D = about 1.5.

System suitability Reference solution (b):

— *resolution*: minimum 8.0 between the peaks due to nadolol and impurity D.

Limits:

— *correction factor*: for the calculation of content, multiply the sum of the 2 peak areas of impurity C by 0.7;

— *impurities A, C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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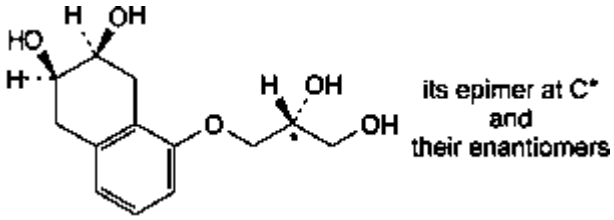
Dissolve 0.250 g in 100 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 30.94 mg of $C_{17}H_{27}NO_4$.

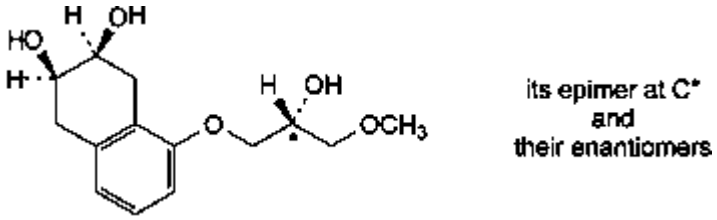
IMPURITIES

Specified impurities A, C, D.

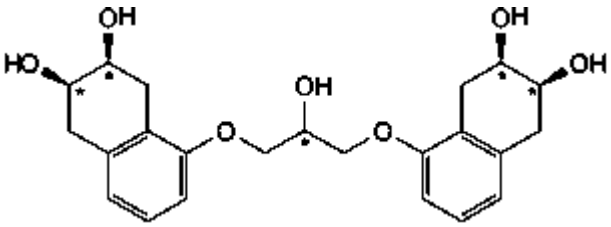
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, E, F, G.



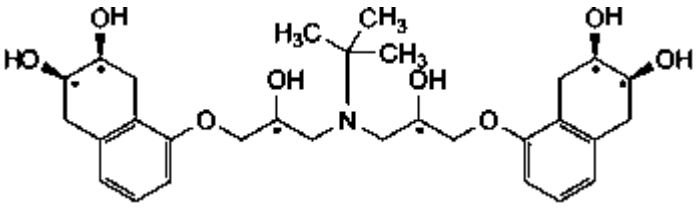
A. *cis*-5-[(2*RS*)-2,3-dihydroxypropoxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol (tetraol),



B. *cis*-5-[(2*RS*)-2-hydroxy-3-methoxypropoxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol,



C. 5,5′-[(2*rs*)-2-hydroxypropane-1,3-diylbis(oxy)]bis(*cis*-1,2,3,4-tetrahydronaphthalene-2,3-diol) (3 diastereoisomers),



D. 5,5′-[[(1,1-dimethylethyl)imino]bis[(2-hydroxypropane-1,3-diyl)oxy]]bis(*cis*-1,2,3,4-tetrahydronaphthalene-2,3-diol) (10 stereoisomers),

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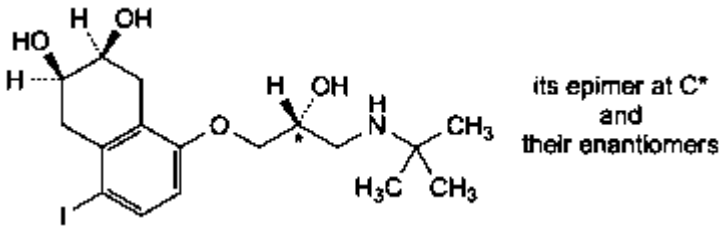
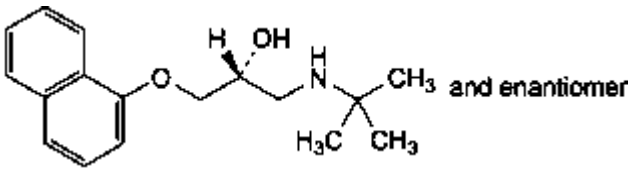
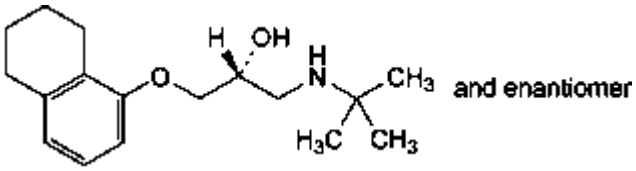


E. *cis*-5-[(2*RS*)-3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-8-iodo-1,2,3,4-tetrahydronaphthalene-2,3-diol,



F. (2*RS*)-1-[(1,1-dimethylethyl)amino]-3-(naphthalen-1-yloxy)propan-2-ol,



G. (2*RS*)-1-[(1,1-dimethylethyl)amino]-3-[(5,6,7,8-tetrahydronaphthalen-1-yl)oxy]propan-2-ol.

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Nadolol Oral Suspension

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Nadolol Oral Suspension is a suspension of Nadolol in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of nadolol, $C_{17}H_{27}NO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in 0.1M *hydrochloric acid*.

(1) Dilute a quantity of the oral suspension containing 10 mg of Nadolol to 10 mL, centrifuge at 3500 rpm for 25 minutes and filter the supernatant liquid through a 0.45-µm nylon filter.

(2) 0.1% w/v of *nadolol BPCRS*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 25 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 2M *ammonium hydroxide*, 1 volume of *dichloromethane* and 8 volumes of *acetone*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) appears as a single compact spot.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in a mixture of 1 volume of *acetonitrile R1* and 3 volumes of *water*.

(1) Disperse a quantity of the oral suspension containing 20 mg of Nadolol in 10 mL and shake for 10 minutes; dilute to contain 0.1% w/v of Nadolol and filter through a 0.45-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume to 20 volumes.

(3) Dissolve the contents of a vial of *nadolol impurity mixture EPCRS* in 1 mL of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher 100 RP 18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 206 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.56% w/v of *sodium octanesulfonate*, adjusted to pH 3.5 with a 30% w/v solution of *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-7	84	16	isocratic
7-30	84→72	16→28	linear gradient
30-35	72→62	28→38	linear gradient
35-55	62	38	isocratic
55-56	62→84	38→16	linear gradient

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
56-60	84	16	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time of nadolol is about 30 minutes and the relative retentions with respect to nadolol are: impurity A, about 0.14; impurity C (doublet), about 0.71 and 0.77; impurity D, about 1.2.

Use the chromatogram supplied with *nadolol impurity mixture EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities A and D.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nadolol and impurity D is at least 8.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity C (doublet) and multiply the sum of the areas of the two peaks by the following correction factor: 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A, C or D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a weighed quantity of the oral suspension containing 20 mg of Nadolol in 75 mL of mobile phase A and shake for 15 minutes. Add sufficient mobile phase A to produce 100 mL and filter through a 0.45-µm nylon filter.
(2) 0.02% w/v of *nadolol BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical particles of silica the surface of which has been modified with chemically bonded dimethylsilyl groups (7 µm) (Nucleosil C2 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 25 volumes of *methanol* and 75 volumes of mobile phase B.

Mobile phase B Dissolve 23.36 g of *sodium chloride* in 5200 mL of water, add 4 mL of 0.1M *hydrochloric acid* and mix.

Mobile phase C *methanol.*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-15	100	0	0	isocratic
15-16	100→0	0→50	0→50	linear gradient
16-25	0	50	50	isocratic wash step
25-26	0→100	0	0	linear gradient
26-35	100	0	0	re-equilibration

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{17}H_{27}NO_4$, weight in volume, using the declared content of $C_{17}H_{27}NO_4$ in *nadolol BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C and D listed under Nadolol.

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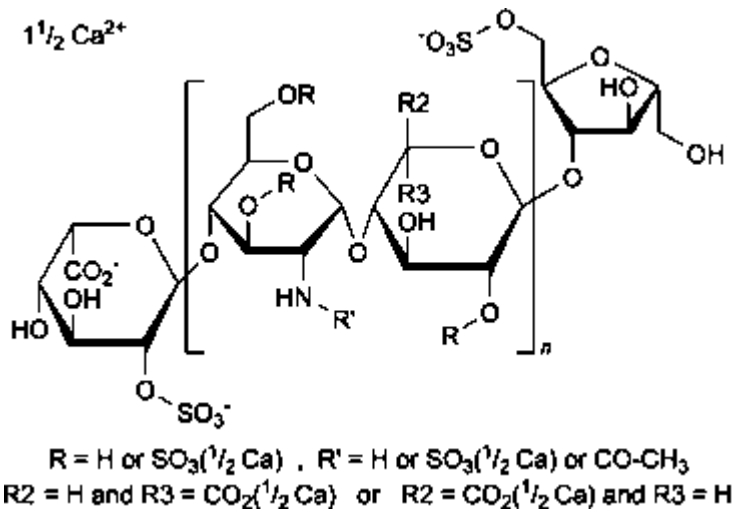
Nadroparin Calcium

General Notices

(Ph. Eur. monograph 1134)



Action and use

Low molecular weight heparin.

Ph Eur

DEFINITION

Calcium salt of low-molecular-mass heparin obtained by nitrous acid depolymerisation of heparin from pork intestinal mucosa, followed by fractionation to eliminate selectively most of the chains with a molecular mass lower than 2000. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain.

Nadroparin calcium complies with the monograph Low-molecular-mass heparins (0828) with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 3600 and 5000 with a characteristic value of about 4300.

The degree of sulfatation is about 2 per disaccharide unit.

The potency is not less than 95 IU and not more than 130 IU of anti-factor Xa activity per milligram, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 2.5 and 4.0.

IDENTIFICATION

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Carry out identification test A as described in the monograph *Low-molecular-mass heparins (0828)* using *nadroparin calcium CRS*.

Carry out identification test C as described in the monograph *Low-molecular-mass heparins (0828)*. The following requirements apply.

The mass-average relative molecular mass ranges between 3600 and 5000. The mass percentage of chains lower than 2000 is not more than 15 per cent. The mass percentage of chains between 2000 and 8000 ranges between 75 per cent and 95 per cent. The mass percentage of chains between 2000 and 4000 ranges between 35 per cent and 55 per cent.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent.

Ethanol

Head-space gas chromatography (*2.2.28*).

Internal standard solution Dilute 1.0 mL of *2-propanol R* to 100.0 mL with *water R*. Dilute 1.0 mL of the solution to 50.0 mL with *water R*.

Blank solution 1.0 mL of *water R*.

Test solution (a) To 10.0 mg of the substance to be examined, add 1.0 mL of *water R*.

Test solution (b) To 10.0 mg of the substance to be examined, add 0.50 mL of *water R* and 0.50 mL of the internal standard solution.

Reference solution (a) Dilute 1.0 mL of *anhydrous ethanol R* to 100.0 mL with *water R*. Dilute 0.5 mL of the solution to 20.0 mL with *water R*.

Reference solution (b) To 0.50 mL of reference solution (a), add 0.50 mL of the internal standard solution.

Column:

— *material*: nickel;

— *size*: *l* = 1.5 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (150-180 µm).

Carrier gas *helium for chromatography R* or *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Static head-space conditions that may be used:

— *equilibration temperature*: 90 °C;

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— *equilibration time*: 15 min;

— *pressurisation time*: 1 min.

Temperature:

— *column*: 150 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Identification of peaks Use the chromatogram obtained with reference solution (b) to identify the peaks due to ethanol and 2-propanol.

Retention time Ethanol = about 2.5 min; 2-propanol = about 4 min.

Calculate the percentage content *m/m* of ethanol taking its density at 20 °C to be 0.792 g/mL.

Limit:

— *ethanol*: maximum 1.0 per cent *m/m*.

N-NO groups

Maximum 0.25 ppm.

The content of N-NO-groups is determined by cleavage of the N-NO bond with hydrobromic acid in ethyl acetate under a reflux condenser and detection of the released NO by chemiluminescence.

Description of the apparatus (Figure 1134.-1). Use a 500 mL borosilicate glass round-bottomed flask, above which is attached a condenser which is equipped with:

— on one side, a torion joint through which a stream of *argon R* can be introduced via a cannula;

— on the other side, a screw joint with a piston equipped with a septum through which the reference solution and test solution will be injected.

The round-bottomed flask is connected in series to 3 bubble traps which are themselves connected to 2 cold traps, which are in turn connected to a chemiluminescence detector. Suitable tubing ensures the junctions are leak-free.

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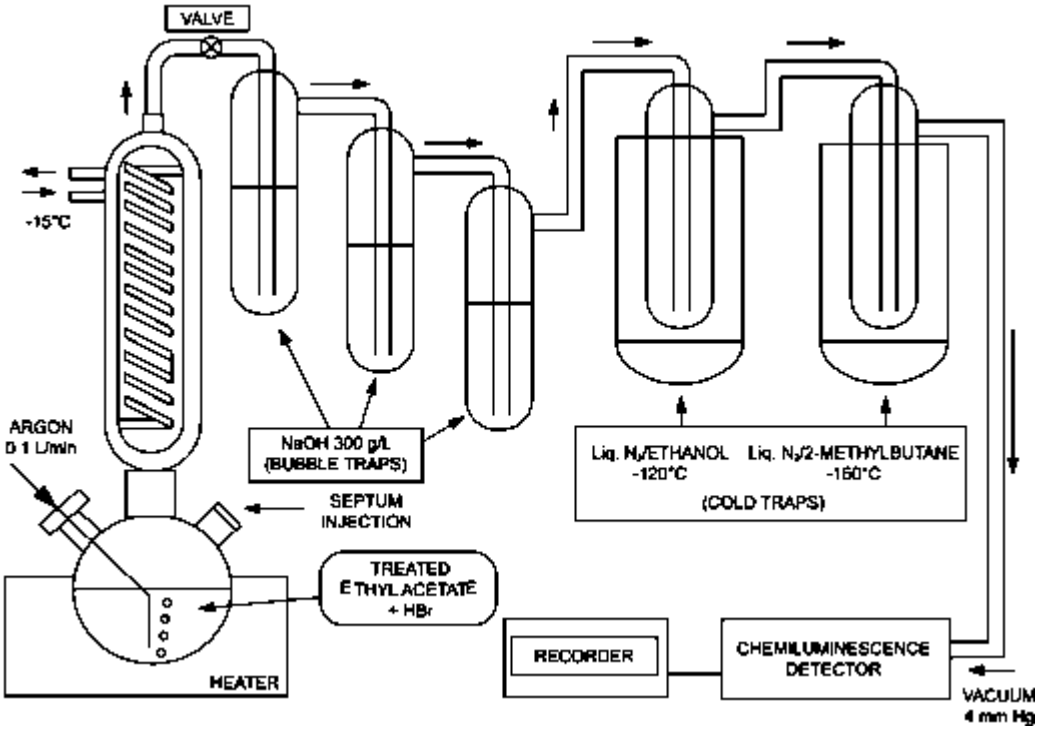

Flask: round-bottom borosilicate glass flask equipped with a central rodavis joint, a torion joint on the left neck and a 15 mm screw joint on the right neck; septum: silicone material, diameter 14 mm and thickness 3.5 mm.

Condenser: height 21 cm and internal diameter 3 cm, with a lower rodavis joint and an upper torion joint.

Bubble traps: height 24 cm and internal diameter 2.5 cm; internal tubing: length 23 cm and internal diameter 0.5 cm. Equipped with a centrally positioned rotulex mounting with torion joints on the inlet and outlet.

Cold traps: height 16.5 cm and internal diameter 4 cm; internal tubing: length 14 cm and internal diameter 1.3 cm. Equipped with torion joints on the inlet and outlet and placed in an isothermic flask: internal depth 22 cm and internal diameter 8 cm.

Tubing: fluorinated ethylene propylene material, internal diameter 3.2 mm and thickness 0.8 mm.

Figure 1134.-1. – *Apparatus used for the assay of N-NO groups*

Preparation of the chemiluminescence detector Switch on the chemiluminescence detector 48 h before use and start the vacuum pump. The vacuum must be less than 0.5 mm Hg. 1 h before use, open the oxygen valve at a pressure of 0.2 MPa and a flow rate of 9.4 mL/min.

Preparation of the bubble trap In each bubble trap, place 30 mL of a 300 g/L solution of *sodium hydroxide R* in *water R*.

Preparation of the cold traps.

— Trap at -120 °C: Slowly add liquid nitrogen to an isothermic flask containing 250 mL of *anhydrous ethanol R* whilst stirring with a wooden spatula until a paste is obtained. Place the cold trap in the isothermic flask prepared as described.

— Trap at -160 °C: Slowly add liquid nitrogen to an isothermic flask containing 250 mL of *2-methylbutane R* whilst stirring with a wooden spatula until a paste is obtained. Place the cold trap in the isothermic flask prepared as described.

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Drying of the 500 mL borosilicate-glass round-bottomed flask and condenser Boil 50 mL of *ethyl acetate R* under reflux for 1 h under *argon R* without connecting the system to the chemiluminescence detector.

Test solution Dry the substance to be examined for 12 h over *diphosphorus pentoxide R* at 60 °C under vacuum. Dissolve 0.10 g of the treated substance to be examined in 1.0 mL of *treated formamide R*. Shake the solution obtained for 30 min.

Reference solution Dilute 0.1 mL of *nitrosodipropylamine solution R* in 6.0 mL of *anhydrous ethanol R*. Dilute 0.1 mL of the solution obtained in 1.0 mL of *treated formamide R*. (This solution is equivalent to 0.05 ppm of N-NO groups).

Place 50 mL of *treated ethyl acetate R* in the dry 500 mL borosilicate glass round-bottomed flask equipped with a septum. Connect the round-bottomed flask to the condenser which has been previously cooled to -15 °C for 2 h.

Connect the *argon R* cannula and adjust the flow rate to 0.1 L/min. Check that the system is leak-free. Only the connector to the chemiluminescence detector remains open in order to avoid excess pressure.

Heat the *treated ethyl acetate R* to boiling.

Evacuate the system by slowly turning the valve of the chemiluminescence detector. At the same time tighten the inlet on the chemiluminescence detector.

When the system is equilibrated, the vacuum reaches 4 mm Hg.

The signal of the zero adjuster on the chemiluminescence detector is set to 10 per cent of the full scale of the recorder.

Through the septum of the 500 mL borosilicate glass round-bottomed flask, sequentially inject 0.5 mL of *water R*, 2.0 mL of *dilute hydrobromic acid R* and then another 2.0 mL of *dilute hydrobromic acid R*, making sure that the recorder pen has returned to the baseline between each injection.

Inject 50.0 µL of the reference solution, then 50.0 µL of the test solution after the recorder pen has returned to the baseline.

Calculate the content of N-NO groups of the substance to be examined.

Free sulfates

Liquid chromatography (*2.2.29*).

Test solution Dissolve 30.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 1.4787 g of *anhydrous sodium sulfate R* in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 1.0 mL of the solution to 200.0 mL with *distilled water R* (5 ppm of sulfate ions).

Column:

— *size*: *l* = 50 mm, Ø = 4.6 mm;

— *stationary phase*: anion-exchange resin.

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Chemical neutralisation system Neutralisation micromembrane in line with the mobile phase for anion detection; continuously pump in counter-flow with a 2.45 g/L solution of *sulfuric acid R*, at a flow rate of 4 mL/min.

Mobile phase:

— *mobile phase A*: 1.91 g/L solution of *disodium tetraborate R*;

— *mobile phase B*: *0.1 M sodium hydroxide*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 15.5	100 → 0	0 → 100
15.5 - 25.5	0	100

Flow rate 1.0 mL/min.

Detection Conductivity detector with a sensitivity of 30 µS.

Injection 50 µL.

Identification of peaks Use the chromatogram obtained with the reference solution to identify the principal peak due to the sulfate ion.

Retention time Sulfate ion = about 7.5 min. Change the composition of the mobile phase, if necessary, to obtain the prescribed retention time.

Limit:

— *free sulfates*: maximum 0.5 per cent.

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Naftidrofuryl Capsules

General Notices

Action and use

Vasodilator.

DEFINITION

Naftidrofuryl Capsules contain Naftidrofuryl Oxalate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of naftidrofuryl oxalate, $C_{26}H_{35}NO_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake, with the aid of ultrasound, a quantity of the powdered contents of the capsules containing 0.1 g of Naftidrofuryl Oxalate with 5 mL of *water* and filter (Whatman GF/C filter paper is suitable). Add 5 mL of 2M *sodium hydroxide* to the filtrate, extract with two 10 mL quantities of *chloroform*, wash the combined chloroform extracts with two 10 mL quantities of *water*, evaporate to dryness using a rotary evaporator and dry the oily residue over *phosphorus pentoxide* at a pressure of 2 kPa for 18 hours. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of naftidrofuryl *(RS 240)*.

B. Mix a quantity of the powdered contents of the capsules containing 0.25 g of Naftidrofuryl Oxalate with 5 mL of *water*, shake for 10 minutes and filter. Add *calcium chloride solution* to the filtrate; a white precipitate is produced. The residue dissolves in mineral acids but is practically insoluble in 2M *acetic acid* and in 6M *ammonia*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using 20 µL of the following solutions. For solution (1) mix with the aid of ultrasound a quantity of the powdered contents of the capsules with sufficient of the mobile phase to produce a solution containing 0.1% w/v of Naftidrofuryl Oxalate and filter (Whatman GF/C filter paper is suitable). Solution (2) contains 0.001% w/v of *3-(1-naphthyl)-2-tetrahydrofurfurylpropionic acid BPCRS* in the mobile phase. Solution (3) contains 0.0002% w/v of *2-diethylaminoethyl-3-(1-naphthyl)-2-(1-naphthylmethyl)propionate oxalate BPCRS* in the mobile phase. Solution (4) contains 0.01% w/v of *naftidrofuryl oxalate BPCRS* and 0.005% w/v of *2-diethylaminoethyl-3-(1-naphthyl)-2-(1-naphthylmethyl)-propionate oxalate BPCRS* in the mobile phase.

The chromatographic conditions described under Assay may be used.

The test is not valid unless in the chromatogram obtained with solution (4) the *resolution factor* between the two principal peaks is at least 4.

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Inject solution (1) and record the chromatography for twice the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to 3-(1-naphthyl)-2-tetrahydrofurfurylpropionic acid is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%), the area of any peak corresponding to 2-diethylaminoethyl-3-(1-naphthyl)-2-(1-naphthylmethyl)-propionate oxalate is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.2%), the area of any other *secondary peak* is not greater than half the area of the peak in the chromatogram obtained with solution (3) (0.1%) and the sum of the areas of all the *secondary peaks* other than those corresponding to the named impurities is not greater than 1.5 times the area of the peak in the chromatogram obtained with solution (3) (0.3%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using 20 µL of the following solutions. For solution (1) finely powder the contents of 10 capsules, mix with the aid of a spatula, dissolve with the aid of ultrasound in sufficient of the mobile phase to produce a solution containing 1% w/v of Naftidrofuryl Oxalate, filter (Whatman GF/C filter paper is suitable) and dilute 1 volume of the filtrate to 10 volumes with the mobile phase. Solution (2) contains 0.1% w/v of *naftidrofuryl oxalate BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with particles of silica the surface of which has been modified by chemicallybonded phenyl groups (5 µm) (Spherisorb Phenyl is suitable), (b) a mixture of 40 volumes of 0.05M *sodium acetate*, adjusted to pH 4.0 with an 85% v/v solution of *orthophosphoric acid*, and 60 volumes of *acetonitrile* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 283 nm.

Calculate the content of $C_{26}H_{35}NO_7$ in the capsules using the declared content of $C_{26}H_{35}NO_7$ in *naftidrofuryl oxalate BPCRS*.

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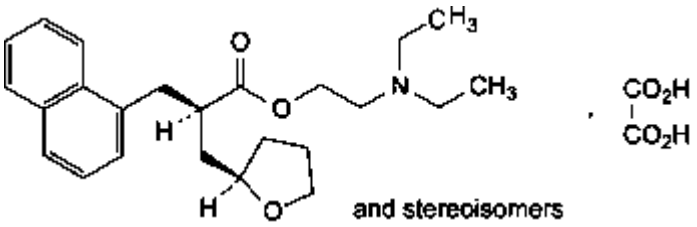
Naftidrofuryl Oxalate

General Notices

(Naftidrofuryl Hydrogen Oxalate, Ph. Eur. monograph 1594)



$C_{26}H_{35}NO_7$ 473.6 *3200-06-4*

Action and use

Vasodilator.

Preparation

Naftidrofuryl Capsules

Ph Eur

DEFINITION

Mixture of 4 stereoisomers of 2-(diethylamino)ethyl 2-[(naphthalen-1-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoate hydrogen oxalate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, freely soluble or soluble in ethanol (96 per cent), slightly or sparingly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Preparation Dissolve 1.0 g in *water R* and dilute to 50 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 10 mL, of *methylene chloride R*. To the combined lower layers, add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate by suitable means at a temperature not exceeding 30 °C. Use the residue obtained.

Comparison *Ph. Eur. reference spectrum of naftidrofuryl*.

B. Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent. Add 2.0 mL of *calcium chloride solution R*. A white precipitate is formed. The precipitate dissolves after the addition of 3.0 mL of *hydrochloric acid R*.

TESTS

Absorbance (*2.2.25*)

Maximum 0.1 at 430 nm.

Dissolve 1.5 g in *water R* and dilute to 10 mL with the same solvent. If necessary use an ultrasonic bath.

Related substances

A. Liquid chromatography (*2.2.29*).

Test solution Dissolve 80.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase. Sonicate for 10 s. A precipitate is formed. Filter through a membrane filter (nominal pore size 0.45 µm), discarding the first 5 mL. *Use a freshly prepared solution.*

Reference solution (a) Dissolve 5.0 mg of *naftidrofuryl impurity A CRS* in *acetonitrile R* and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *naftidrofuryl impurity B CRS* and 5 mg of the substance to be examined in *acetonitrile R* and dilute to 50 mL with the same solvent. Dilute 1 mL of the solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 60 mL of *methanol R* with 150 mL of *tetrabutylammonium buffer solution pH 7.0 R* and dilute to 1000 mL with *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 283 nm.

Injection 20 µL.

Run time 2.3 times the retention time of naftidrofuryl.

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Relative retention With reference to naftidrofuryl (retention time = about 7 min): impurity A = about 0.5; impurity B = about 0.8; impurity C = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity B and naftidrofuryl.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

B. Gas chromatography (2.2.28).

Test solution (a) Dissolve 1.0 g of the substance to be examined in water R and dilute to 50 mL with the same solvent. Add 2 mL of concentrated ammonia R and shake with 3 quantities, each of 10 mL, of methylene chloride R. To the combined lower layers, add anhydrous sodium sulfate R, shake, filter and evaporate the filtrate by suitable means at a temperature not exceeding 30 °C. Take up the residue with methylene chloride R and dilute to 20.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with methylene chloride R.

Reference solution Dissolve 5 mg of naftidrofuryl impurity F CRS in methylene chloride R and dilute to 50 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: phenyl(5)methyl(95)polysiloxane R (film thickness 0.45 µm).

Carrier gas helium for chromatography R.

Splitter flow rate 25 mL/min.

Flow rate 2.9 mL/min.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 4	210
	4 - 8	210 → 230
	8 - 18	230 → 260
	18 - 30	260
Injection port		290
Detector		290

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to the second eluting peak of naftidrofuryl: impurity D = about 0.14; impurity B = about 0.55 (for the second eluting peak); impurity E = about 0.86; impurity F = about 1.04 (for the second eluting peak).

System suitability Test solution (b):

— *resolution*: minimum 1.0 between the 2 peaks due to the diastereoisomers of naftidrofuryl.

Limits Test solution (a):

— *impurity F*: for the sum of the areas of the 2 peaks, maximum 0.20 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.20 per cent);

— *impurity E*: maximum 0.20 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.20 per cent);

— *impurity D*: maximum 0.10 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.10 per cent);

— *any other impurity*: for each impurity, maximum 0.10 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.10 per cent);

— *total*: maximum 0.50 per cent of the sum of the areas of the 2 peaks due to naftidroduryl (0.50 per cent);

— *disregard limit*: 0.02 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl (0.02 per cent); disregard any peaks due to impurity B.

Diastereoisomer ratio

Gas chromatography (*2.2.28*) as described in test B for related substances.

Limits Test solution (b):

— *first eluting naftidrofuryl diastereoisomer*: minimum 30 per cent of the sum of the areas of the 2 peaks due to naftidrofuryl.

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Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

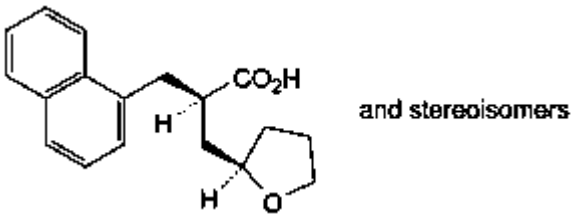
ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

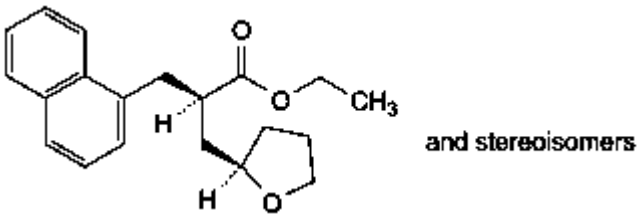
1 mL of *0.1 M perchloric acid* is equivalent to 47.36 mg of $C_{26}H_{35}NO_7$.

IMPURITIES

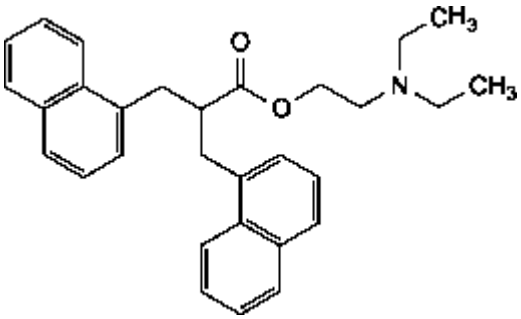
Specified impurities *A, B, C, D, E, F.*



A. 2-[(naphthalen-1-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoic acid,



B. ethyl 2-[(naphthalen-1-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoate,



C. 2-(diethylamino)ethyl 3-(naphthalen-1-yl)-2-[(naphthalen-1-yl)methyl]propanoate,

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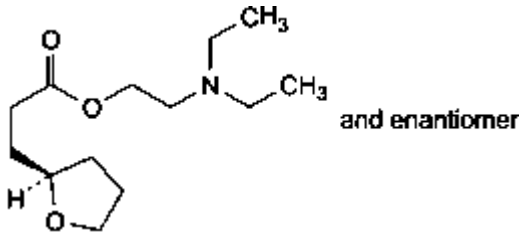
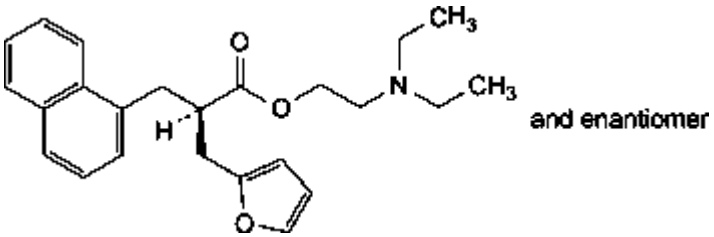
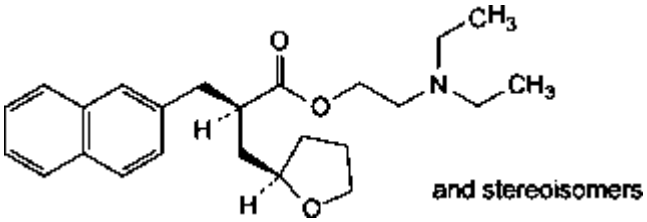


D. 2-(diethylamino)ethyl 3-[(2*RS*)-tetrahydrofuran-2-yl]propanoate,



E. 2-(diethylamino)ethyl (2*RS*)-2-[(furan-2-yl)methyl]-3-(naphthalen-1-yl)propanoate,



F. 2-(diethylamino)ethyl 2-[(naphthalen-2-yl)methyl]-3-(tetrahydrofuran-2-yl)propanoate.

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Nalidixic Acid Oral Suspension

General Notices

Action and use

Quinolone antibacterial.

DEFINITION

Nalidixic Acid Oral Suspension is a suspension of Nalidixic Acid in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of nalidixic acid, $C_{12}H_{12}N_2O_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

To 5 mL add 30 mL of *water* and 20 mL of *dilute sodium carbonate solution*, mix and shake with two 30 mL quantities of *chloroform*; discard the chloroform layers. Acidify the aqueous solution with 5M *hydrochloric acid*, shake with 40 mL of *chloroform*, wash the chloroform layer with 10 mL of *water* to which has been added 0.5 mL of 5M *hydrochloric acid*, filter the chloroform layer through absorbent cotton and evaporate the filtrate to dryness. Dissolve the residue in sufficient 0.1M *sodium hydroxide* to produce a solution containing 0.0008% w/v of Nalidixic Acid. The *light absorption* of the solution, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 258 nm and 334 nm.

ASSAY

Dilute a weighed quantity containing 0.12 g of Nalidixic Acid to 100 mL with 0.01M *sodium hydroxide*, dilute 2 mL to 250 mL with 0.01M *sodium hydroxide* and measure the *absorbance* of the resulting solution at the maximum at 334 nm, Appendix II B. Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{12}H_{12}N_2O_3$, weight in volume, taking 494 as the value of A(1%, 1 cm) at the maximum at 334 nm.

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Nalidixic Acid Tablets

General Notices

Action and use

Quinolone antibacterial.

DEFINITION

Nalidixic Acid Tablets contain Nalidixic Acid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nalidixic acid, $C_{12}H_{12}N_2O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 1 g of Nalidixic Acid add 50 mL of *chloroform*, shake for 15 minutes, filter and evaporate the filtrate to dryness. The residue, after drying at 105°, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of nalidixic acid *(RS 241)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.0008% w/v solution in 0.1M *sodium hydroxide* exhibits maxima at 258 nm and 334 nm.

C. *Melting point*, about 228°, Appendix V A.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Rotate the paddle at 60 revolutions per minute and use as the medium 900 mL of a methanolic phosphate buffer prepared in the following manner: mix 2.3 volumes of 0.2M *sodium hydroxide* with 2.5 volumes of 0.2M *potassium dihydrogen orthophosphate* and 2.0 volumes of *methanol*, dilute to 10 volumes with *water* and, if necessary, adjust the pH to 8.6 using 1M *sodium hydroxide*. Withdraw a sample of 10 mL of the medium, filter and measure the *absorbance* of the solution, suitably diluted if necessary, at the maximum at 334 nm, Appendix II B. Calculate the total content of nalidixic acid, $C_{12}H_{12}N_2O_3$, in the medium taking 494 as the value of A(1%, 1 cm) at the maximum at 334 nm.

Related substances

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Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of 5M *ammonia*, 20 volumes of *dichloromethane* and 70 volumes of *ethanol (96%)* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.10 g of Nalidixic Acid with 50 mL of *dichloromethane* for 15 minutes, filter, evaporate to dryness and dissolve the residue in 5 mL of *dichloromethane*. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *dichloromethane* and further dilute 1 volume of the resulting solution to 2 volumes with *dichloromethane*. For solution (3) dilute 1 volume of solution (2) to 2.5 volumes with *dichloromethane*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powdered tablets containing 0.1 g of Nalidixic Acid add 150 mL of 1M *sodium hydroxide*, shake for 3 minutes, dilute to 200 mL with 1M *sodium hydroxide*, mix and allow to stand for 15 minutes. Dilute 2 mL to 200 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 334 nm, Appendix II B, using 0.01M *sodium hydroxide* in the reference cell. Calculate the content of $C_{12}H_{12}N_2O_3$ taking 494 as the value of A(1%, 1 cm) at the maximum at 334 nm.

STORAGE

Nalidixic Acid Tablets should be protected from light.

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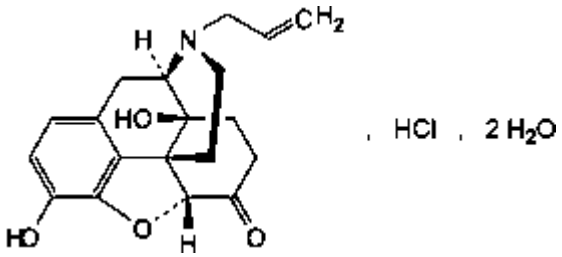
Naloxone Hydrochloride

General Notices

(Naloxone Hydrochloride Dihydrate, Ph. Eur. monograph 0729)



, HCl , $2\,H_2O$

$C_{19}H_{22}ClNO_4,2H_2O$ 399.9 *51481-60-8*

Action and use

Opioid receptor antagonist.

Preparation

Naloxone Injection

Ph Eur

DEFINITION

4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in toluene.

IDENTIFICATION

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First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *naloxone hydrochloride dihydrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 8 mg of the substance to be examined in 0.5 mL of *water R* and dilute to 1 mL with *methanol R*.

Reference solution Dissolve 8 mg of *naloxone hydrochloride dihydrate CRS* in 0.5 mL of *water R* and dilute to 1 mL with *methanol R*.

Plate *TLC silica gel G plate R*.

Mobile phase Mix 5 volumes of *methanol R* and 95 volumes of the upper layer from a mixture of 60 mL of *dilute ammonia R2* and 100 mL of *butanol R*.

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a freshly prepared 5 g/L solution of *potassium ferricyanide R* in *ferric chloride solution R1*; examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 10.0 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M sodium hydroxide* or *0.02 M hydrochloric acid* is required to change the colour of the indicator.

Specific optical rotation (2.2.7)

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-181 to -170 (anhydrous substance), determined on solution S.

Impurity D

Liquid chromatography (2.2.29).

Solution A Dissolve 1.58 g of *ammonium hydrogen carbonate R* in 950 mL of *water for chromatography R*, adjust to pH 9.0 with *concentrated ammonia R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.500 g of the substance to be examined in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 20.0 mL with the same solution.

Reference solution (a) Dissolve 10.0 mg of *naloxone impurity D CRS* in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 20.0 mL with the same solution. Dilute 5.0 mL of this solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Reference solution (c) To 4.0 mL of the test solution add 2.0 mL of reference solution (a) and dilute to 20.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, solution A (20:80 *V/V*);

— *mobile phase B*: *acetonitrile R1*, solution A (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100	0
50 - 51	100 → 0	0 → 100
51 - 60	0	100

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

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Relative retention With reference to naloxone (retention time = about 50 min): impurity D = about 0.8.

System suitability Reference solution (c):

— *symmetry factor*: maximum 1.8 for the peak due to impurity D.

Limit:

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (75 ppm).

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 1.10 g of *sodium octanesulfonate R* in 950 mL of *water for chromatography R*, adjust to pH 2.0 with a 50 per cent *V/V* solution of *phosphoric acid R*, filter and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.125 g of the substance to be examined in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

Reference solution (a) Dissolve the contents of a vial of *naloxone for peak identification CRS* (containing impurities A, B, C, D, E and F) in 1 mL of a 10.3 g/L solution of *hydrochloric acid R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with a 10.3 g/L solution of *hydrochloric acid R*. Dilute 1.0 mL of this solution to 25.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *tetrahydrofuran R*, solution A (2:4:94 *V/V/V*);

— *mobile phase B*: *tetrahydrofuran R*, *acetonitrile R*, solution A (4:17:79 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	100 → 0	0 → 100
40 - 50	0	100

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to naloxone (retention time = about 11 min): impurity C = about 0.6; impurity A = about 0.8; impurity F = about 0.9; impurity D = about 1.1; impurity E = about 3.0; impurity B = about 3.2.

Identification of impurities Use the chomatogram supplied with *naloxone for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E and F.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to naloxone.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.5;

— *impurities A, B, C, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

7.5 per cent to 11.0 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 0.50 g.

ASSAY

Dissolve 0.300 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 36.38 mg of $C_{19}H_{22}ClNO_4$.

STORAGE

In an airtight container, protected from light.

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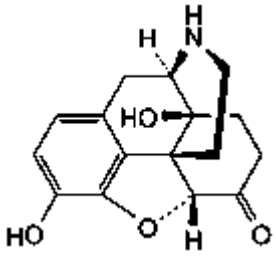
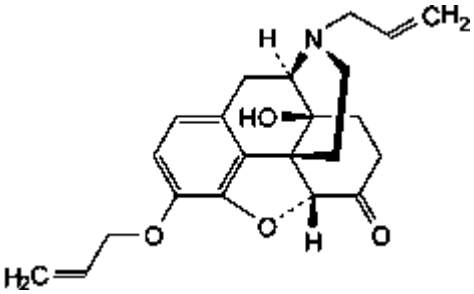
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

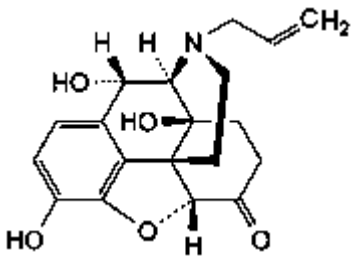
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*



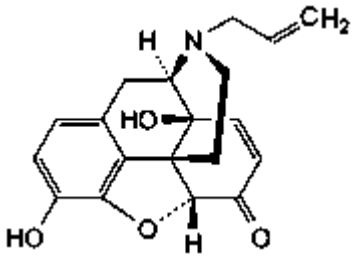
A. 4,5α-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone),



B. 4,5α-epoxy-14-hydroxy-17-(prop-2-enyl)-3-(prop-2-enyloxy)morphinan-6-one (3-*O*-allylnaloxone),



C. 4,5α-epoxy-3,10α,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one (10α-hydroxynaloxone),



D. 7,8-didehydro-4,5α-epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one (7,8-didehydronaloxone),

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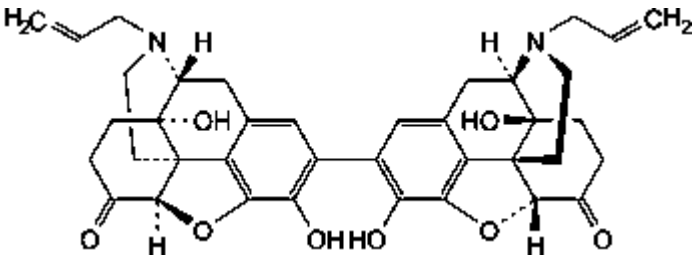
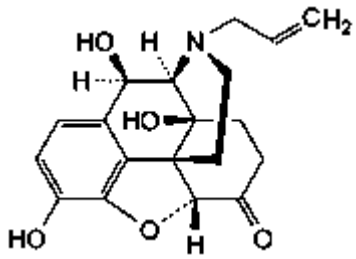
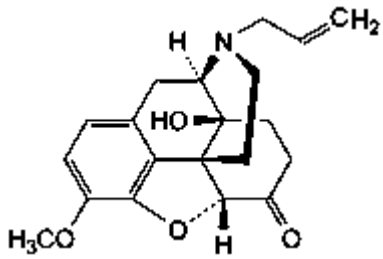


E. 4,5α:4′,5′α-diepoxy-3,3′,14,14′-tetrahydroxy-17,17′-bis(prop-2-enyl)-2,2′-bimorphinanyl-6,6′-dione (2,2′-binaloxone),



F. 4,5α-epoxy-3,10β,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one (10β-hydroxynaloxone),



G. 4,5α-epoxy-14-hydroxy-3-methoxy-17-(prop-2-enyl)morphinan-6-one (3-*O*-methylnaloxone).

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Naloxone Injection

General Notices

Action and use

Opioid receptor antagonist.

DEFINITION

Naloxone Injection is a sterile solution of Naloxone Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of anhydrous naloxone hydrochloride, $C_{19}H_{21}NO_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the injection with *water*, if necessary, to produce a solution containing the equivalent of 0.002% w/v of anhydrous naloxone hydrochloride. Add 1 mL of *ammonia buffer pH 10.0* to a volume of the solution containing the equivalent of 0.1 mg of anhydrous naloxone hydrochloride, extract with three 20-mL quantities of a mixture of 1 volume of *propan-2-ol* and 3 volumes of *chloroform*, dry the combined extracts over *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness and dissolve the residue in 1 mL of *methanol*.

(2) 0.01% w/v of *naloxone hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* and heat the plate at 105° for 15 minutes immediately before use.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Protect the plate from light during development and develop to 10 cm.

(e) After removal of the plate, dry in a current of air, spray with a freshly prepared 0.5% w/v solution of *potassium hexacyanoferrate(III)* in *iron(III) chloride solution R1* and examine in daylight.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of the upper layer from a mixture of 60 mL of 2M *ammonia* and 100 mL of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.0 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.0025M *hydrochloric acid R*.

(1) Dilute a quantity of injection, if necessary, to produce a solution containing the equivalent of 0.002% w/v of anhydrous naloxone hydrochloride.

(2) Dilute 1 volume of solution (1) to 20 volumes. Further dilute 1 volume of this solution to 25 volumes.

(3) 0.005% w/v *naloxone for peak identification EPCRS*.

CHROMATOGRAPHIC CONDITIONS

Use a stainless steel column (12.5 cm × 4.0 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Hypersil C8, 5 µm is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 94 volumes of 0.11% w/v *sodium octanesulfonate R* in *water R* adjusted to pH 2.0 with 50% v/v solution of *phosphoric acid R* (solution A), 4 volumes *tetrahydrofuran*, 2 volumes *acetonitrile R*.

Mobile phase B 79 volumes solution A, 17 volumes *acetonitrile R*, 4 volumes *tetrahydrofuran*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-40	100	0	isocratic
40-50	100→0	0→100	linear gradient
50-60	0→100	100→0	linear gradient
60-70	100	0	re-equilibration

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When the chromatograms are recorded under the prescribed conditions, the retention times relative to naloxone hydrochloride (retention time about 11 minutes) are: impurity C, about 0.6; impurity A, about 0.8; impurity F, about 0.9; impurity D, about 1.1; impurity E, about 3.0; impurity B, about 3.2.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3):

The peak-to-valley ratio at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity D and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to naloxone.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C, D, E and F using solution (3) and multiply the area of the peak corresponding to impurity E using a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A, B, C, E and F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any secondary peaks is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8 %).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *orthophosphoric acid*, 450 volumes of *methanol* and 550 volumes of *water*.

(1) Dilute a weighed quantity of injection containing 0.1 mg of anhydrous naloxone hydrochloride to 10 mL.
(2) 0.001% w/v of *naloxone hydrochloride BPCRS*.
(3) 0.001% w/v of *naloxone hydrochloride BPCRS* and 0.0005% w/v of *noroxymorphone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 to 10 µm) (Zorbax C18, 7 to 8 µm is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 229 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

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0.068% w/v of *sodium octanesulfonate* and 0.1% w/v of *sodium chloride* in a mixture of 1 volume of *orthophosphoric acid*, 450 volumes of *methanol* and 550 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times of noroxymorphone and naloxone are about 3.1 minutes and 3.8 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to naloxone and noroxymorphone is at least 1.3.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{21}NO_4$,HCl in the injection using the declared content of $C_{19}H_{21}NO_4$,HCl in *naloxone hydrochloride BPCRS*.

STORAGE

Naloxone Injection should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous naloxone hydrochloride.

When Neonatal Naloxone Injection is prescribed or demanded, an injection containing 20 mg/mL of naloxone hydrochloride shall be dispensed or supplied.

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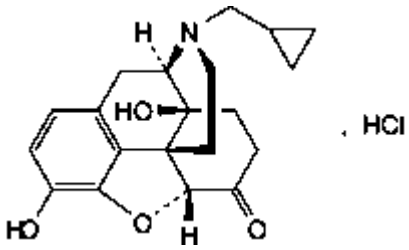
Naltrexone Hydrochloride

General Notices

(Ph. Eur. monograph 1790)



$C_{20}H_{24}ClNO_4$ 377.9

Action and use

Opioid receptor antagonist.

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DEFINITION

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. It may be anhydrous, a monohydrate or a dihydrate, a mixture or a solvate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, very hygroscopic.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Dissolve 20 mg in *water R* and dilute to 5 mL with the same solvent. Make alkaline with *dilute ammonia R1*. Shake with 10 mL of *methylene chloride R*, separate the organic layer and evaporate the solvent. Dry the residue obtained *in vacuo*.

Comparison *naltrexone hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.40 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 or B_6 (*2.2.2, Method II*).

Acidity and alkalinity

To 10 mL of solution S, add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M sodium hydroxide* or *0.02 M hydrochloric acid* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*)

-187 to -195 (anhydrous substance).

Dissolve 0.40 g in *water R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in *0.1 M hydrochloric acid* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *naltrexone impurity C CRS* in *0.1 M hydrochloric acid* and dilute to 2.5 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution and 1.0 mL of reference solution (a) to 100.0 mL with *0.1 M hydrochloric acid*. Dilute 1.0 mL of this solution to 10.0 mL with *0.1 M hydrochloric acid*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

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— *mobile phase A*: 1.1 g/L solution of *sodium octanesulfonate R* adjusted to pH 2.3 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 45	90 → 55	10 → 45
45 - 47	55 → 90	45 → 10
47 - 55	90	10

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 230 nm.

Equilibration 8 min.

Injection 10 µL.

Relative retention With reference to naltrexone (retention time = about 16 min): impurity A = about 0.4; impurity B = about 0.7; impurity F = about 0.8; impurity G = about 0.9; impurity C = about 1.05; impurity H = about 1.1; impurity I = about 1.2; impurity J = about 1.3; impurity D = about 1.4; impurity E = 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to naltrexone and impurity C.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 0.4;

— *impurities C, D, E, F, G*: for each impurity, not more than twice the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities A, B, H, I, J*: for each impurity, not more than the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *total*: not more than 10 times the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the peak due to naltrexone in the chromatogram obtained with reference solution (b) (0.05 per cent).

Ethanol (*2.4.24, System A*)

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Maximum 3.0 per cent.

Test solution Dissolve 0.25 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dilute 0.750 g of *anhydrous ethanol R* to 1000.0 mL with *water R*.

Water (*2.5.12*)

Maximum 10.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 60 mL of *ethanol (96 per cent) R*, add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. The curve shows 3 points of inflexion. Read the volume added between the first 2 points of inflexion.

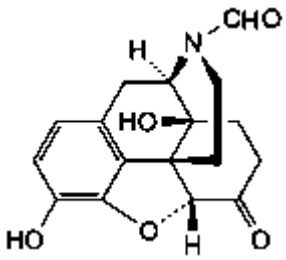
1 mL of *0.1 M sodium hydroxide* is equivalent to 37.79 mg of $C_{20}H_{24}ClNO_4$.

STORAGE

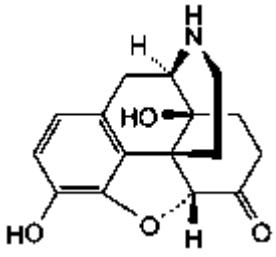
In an airtight container. Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J.*



A. 17-formyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,



B. 4,5α-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone),

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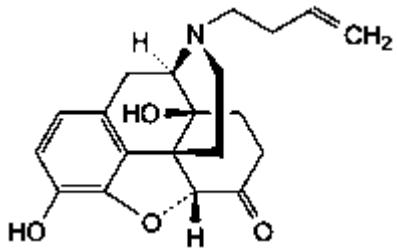
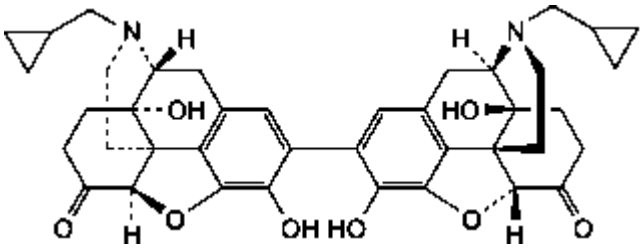
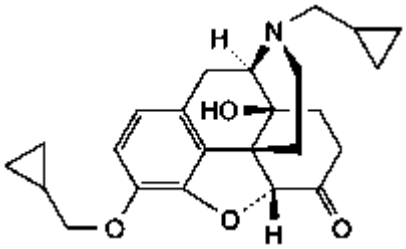


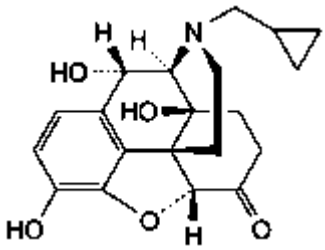
C. 17-but-3-enyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,



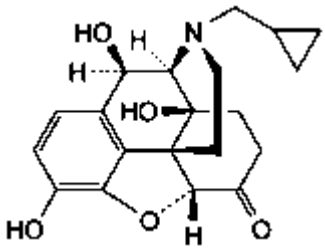
D. 17,17′-bis(cyclopropylmethyl)-4,5α:4′,5′α-diepoxy3,3′,14,14′-tetrahydroxy-2,2′-bimorphinanyl-6,6′-dione (pseudonaltrexone),



E. 3-(cyclopropylmethoxy)-17-(cyclopropylmethyl)-4,5α-epoxy-14-hydroxymorphinan-6-one,



F. 17-(cyclopropylmethyl)-4,5α-epoxy-3,10α,14-trihydroxymorphinan-6-one,



G. 17-(cyclopropylmethyl)-4,5α-epoxy-3,10β,14-trihydroxymorphinan-6-one,

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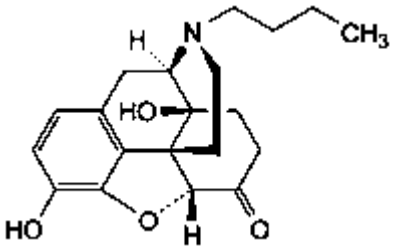
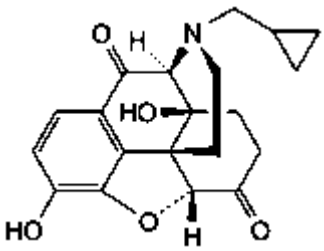
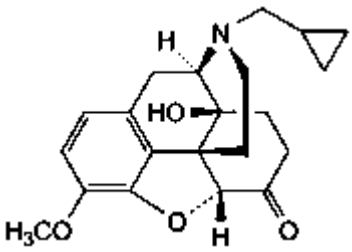


H. 17-butyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,



I. 17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6,10-dione,



J. 17-(cyclopropylmethyl)-4,5α-epoxy-14-hydroxy-3-methoxymorphinan-6-one.

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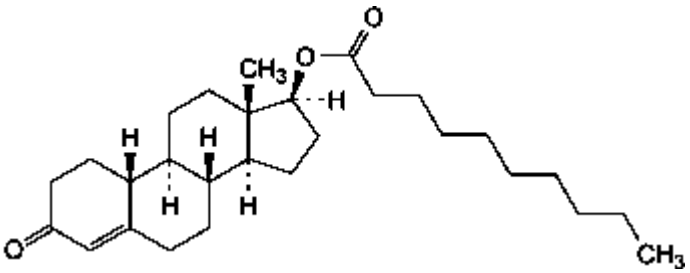
Nandrolone Decanoate

General Notices

(Ph. Eur. monograph 1992)



$C_{28}H_{44}O_3$ 428.7 *360-70-3*

Action and use

Anabolic steroid; androgen.

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DEFINITION

3-Oxoestr-4-en-17β-yl decanoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Melting point (*2.2.14*): 34 °C to 38 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *nandrolone decanoate CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 0.20 g in 10 mL of *methanol R*.

Specific optical rotation (*2.2.7*)

+ 35.0 to + 40.0 (dried substance).

Dissolve 0.200 g in *anhydrous ethanol R* and dilute to 20.0 mL with the same solvent.

Impurities A, B, C

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 50 mg of the substance to be examined in *methylene chloride R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *methylene chloride R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *methylene chloride R*.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 20.0 mL with *methylene chloride R*.

Reference solution (d) Dissolve 5 mg of *nandrolone decanoate for system suitability CRS* (containing impurities A, B, C) in 0.5 mL of *methylene chloride R*.

Plate *TLC silica gel plate R*.

Mobile phase *acetone R*, *heptane R* (30:70 *V/V*).

Application 10 µL of the test solution and reference solutions (b), (c) and (d).

Development Over 2/3 of the plate.

Drying In air.

Detection Treat with *alcoholic solution of sulfuric acid R* and heat at 130 °C until the spots appear. Examine in ultraviolet light at 366 nm.

Retardation factors Nandrolone decanoate = about 0.37; impurity A = about 0.45; impurity B = about 0.55; impurity C = about 0.58.

System suitability Reference solution (d):

— the chromatogram shows 4 clearly separated spots.

Limits:

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— *impurity A*: any spot due to impurity A is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurities B, C*: any spot due to impurity B or C is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.5 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *nandrolone decanoate for peak identification CRS* (containing impurities D, F, G, H, I, K, L) in *methanol R* and dilute to 2.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	35	65
5 - 40	35 → 0	65 → 100
40 - 75	0	100
75 - 80	0 → 35	100 → 65

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Relative retention With reference to nandrolone decanoate (retention time = about 30 min): impurity D = about 0.05; impurity F = about 0.6; impurity K = about 0.7; impurity L = about 0.9; impurity G = about 0.97; impurity H = about 1.1;

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impurity I = about 1.2.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to nandrolone decanoate.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.5; impurity F = 0.6; impurity H = 1.1; impurity I = 1.3; impurity K = 0.8;

— *impurities D, F, G, H, I, K, L*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at a pressure not exceeding 0.7 kPa for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 10.0 mg in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 50.0 mL with *anhydrous ethanol R*. Measure the absorbance (2.2.25) at the absorption maximum at 240 nm. Calculate the content of $C_{28}H_{44}O_3$ taking the specific absorbance to be 407.

STORAGE

Under nitrogen, protected from light and at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A, B, C, D, F, G, H, I, K, L.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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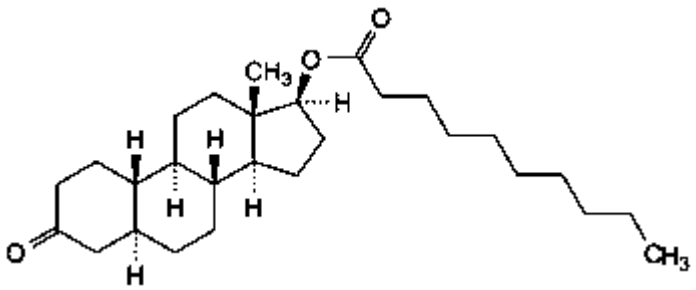
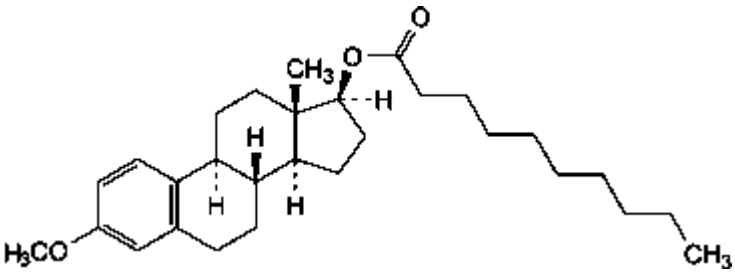
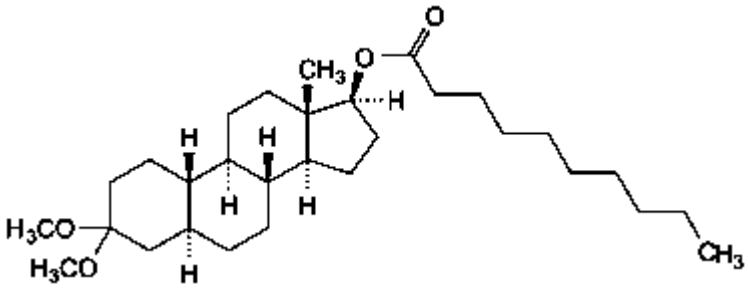
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E, J.



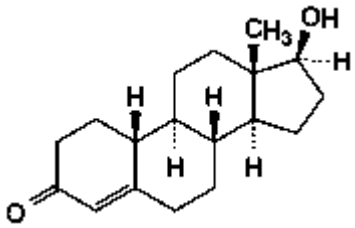
A. 3-oxo-5α-estran-17β-yl decanoate,



B. 3-methoxyestra-1,3,5(10)-trien-17β-yl decanoate,



C. 3,3-dimethoxy-5α-estran-17β-yl decanoate,



D. 17β-hydroxyestr-4-en-3-one,

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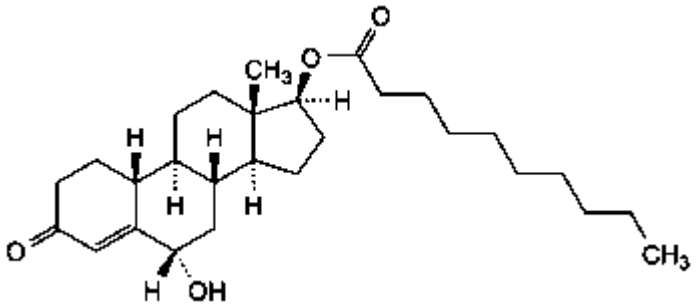
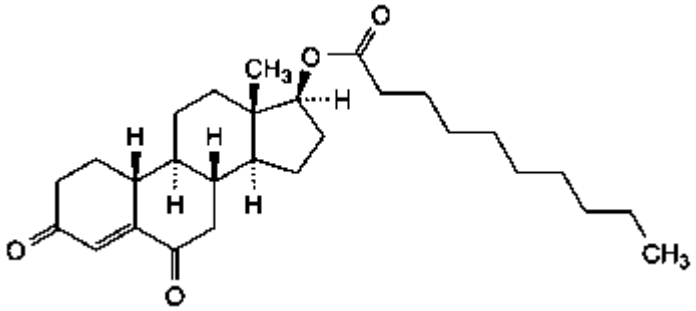
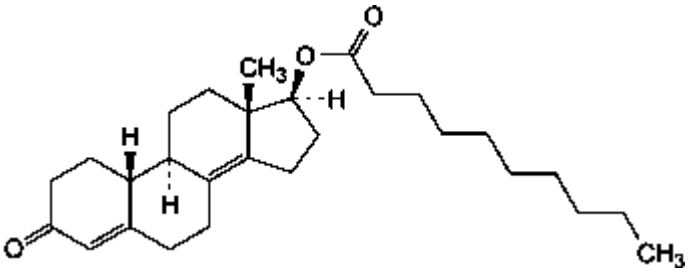


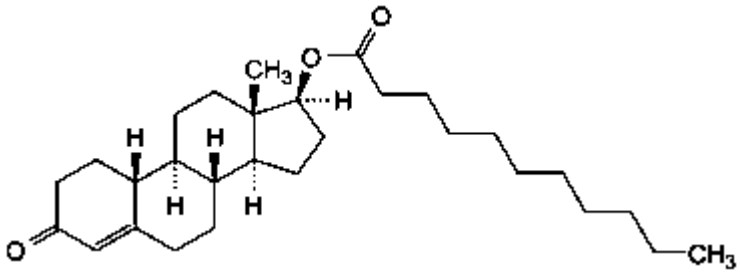
E. 6α-hydroxy-3-oxoestr-4-en-17β-yl decanoate,



F. 3,6-dioxoestr-4-en-17β-yl decanoate,



G. 3-oxoestra-4,8(14)-dien-17β-yl decanoate,



H. 3-oxoestr-4-en-17β-yl undecanoate,

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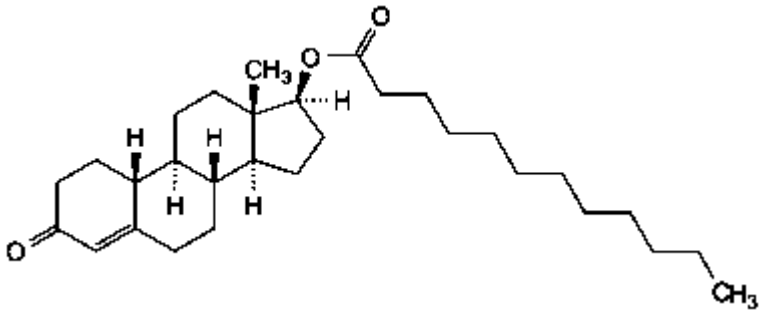
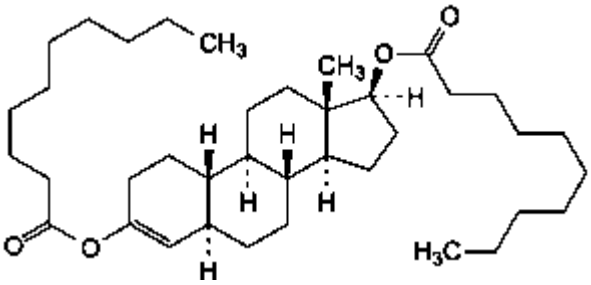
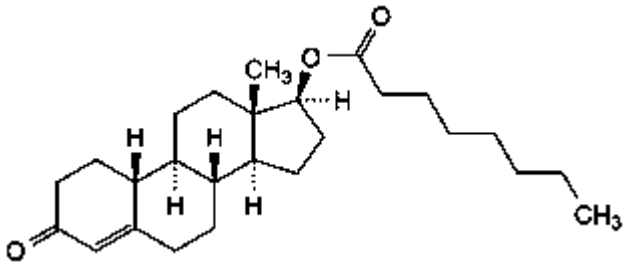


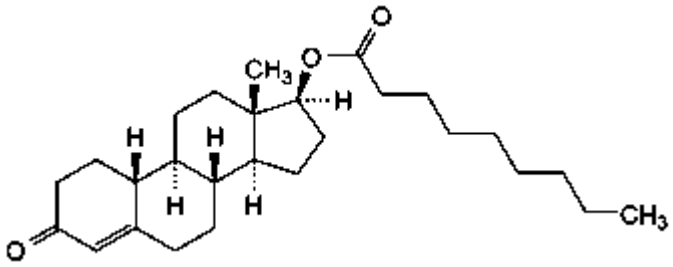
I. 3-oxoestr-4-en-17β-yl dodecanoate,



J. 5α-estr-3-ene-3,17β-diyl didecanoate,



K. 3-oxoestr-4-en-17β-yl octanoate,



L. 3-oxoestr-4-en-17β-yl nonanoate.

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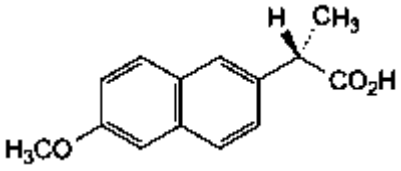
Naproxen

General Notices

(Ph. Eur. Monograph 0731)



$C_{14}H_{14}O_3$ 230.3 *22204-53-1*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Naproxen Oral Suspension

Naproxen Tablets

Naproxen Gastro-resistant Tablets

Ph Eur

DEFINITION

(2*S*)-2-(6-Methoxynaphthalen-2-yl)propanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent) and in methanol.

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IDENTIFICATION

First identification: A, D.

Second identification: A, B, C.

A. Specific optical rotation (2.2.7): + 59 to + 62 (dried substance).

Dissolve 0.50 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

B. Melting point (2.2.14): 154 °C to 158 °C.

C. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 40.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *methanol R*.

Spectral range 230-350 nm.

Absorption maxima At 262 nm, 271 nm, 316 nm and 331 nm.

Specific absorbances at the absorption maxima:

— at 262 nm: 216 to 238;

— at 271 nm: 219 to 241;

— at 316 nm: 61 to 69;

— at 331 nm: 79 to 87.

D. Infrared absorption spectrophotometry (2.2.24).

Comparison *naproxen CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Dissolve 1.25 g in *methanol R* and dilute to 25 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (2.2.29). *Protect the solutions from light.*

Test solution Dissolve 25.0 mg of the substance to be examined in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 2.5 mL of the test solution to 100.0 mL with the mobile phase.

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Reference solution (b) Dissolve 5 mg of racemic naproxen CRS in 10.0 mL of tetrahydrofuran R and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: silica gel π-acceptor/π-donor for chiral separations R (5 µm) (*S*,*S*);

— *temperature*: 25 °C.

Mobile phase glacial acetic acid R, acetonitrile R, 2-propanol R, hexane R (0.5:5:10:84.5 *V/V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 263 nm.

Injection 20 µL.

Run time 1.5 times the retention time of naproxen (retention time = about 5 min).

System suitability Reference solution (b):

— *resolution*: minimum 3 between the peaks due to impurity G and naproxen.

Limit:

— *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent).

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light.*

Test solution Dissolve 12 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 6 mg of bromomethoxynaphthalene R (impurity N), 6.0 mg of naproxen impurity L CRS, 6 mg of 6-methoxy-2-naphthoic acid R (impurity O) and 6 mg of (1RS)-1-(6-methoxynaphthalen-2-yl)ethanol R (impurity K) in acetonitrile R and dilute to 10.0 mL with the same solvent. To 1.0 mL of the solution add 1.0 mL of the test solution and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 50 °C.

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Mobile phase Mix 42 volumes of *acetonitrile R* and 58 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 1.5 times the retention time of impurity N.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities K, L, N and O.

Relative retention With reference to naproxen (retention time = about 2.5 min): impurity O = about 0.8; impurity K = about 0.9; impurity L = about 1.4; impurity N = about 5.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.2 between the peaks due to impurity K and naproxen.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity O by 2.0;

— *impurity O*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *impurity L*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.200 g in a mixture of 25 mL of *water R* and 75 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, using 1 mL of *phenolphthalein solution R* as indicator.

1 mL of *0.1 M sodium hydroxide* is equivalent to 23.03 mg of $C_{14}H_{14}O_3$.

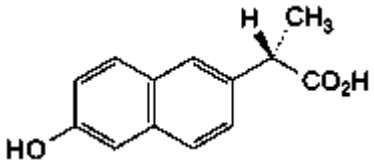
STORAGE

Protected from light.

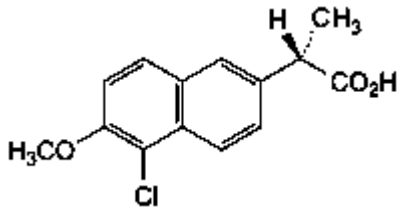
IMPURITIES

Specified impurities G, L, O.

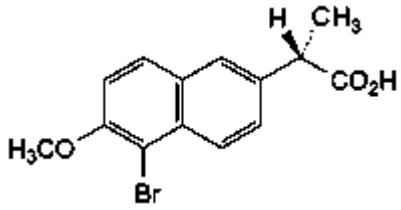
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, H, I, J, K, M, N.



A. (2*S*)-2-(6-hydroxynaphthalen-2-yl)propanoic acid,



B. (2*S*)-2-(5-chloro-6-methoxynaphthalen-2-yl)propanoic acid,



C. (2*S*)-2-(5-bromo-6-methoxynaphthalen-2-yl)propanoic acid,

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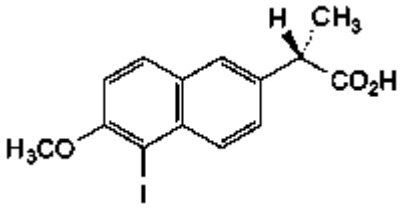
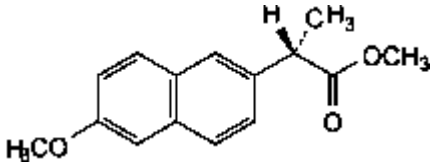
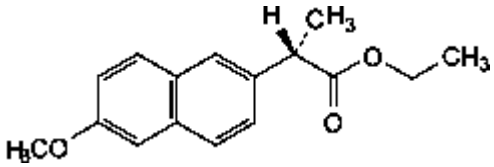


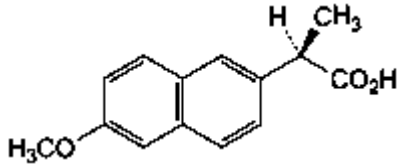
D. (2*S*)-2-(5-iodo-6-methoxynaphthalen-2-yl)propanoic acid,



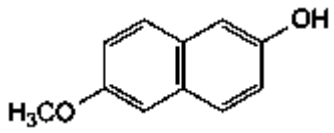
E. methyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate,



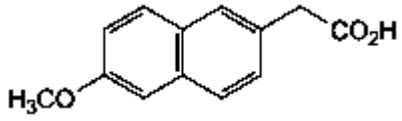
F. ethyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate,



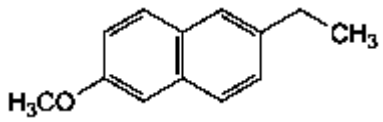
G. (2*R*)-2-(6-methoxynaphthalen-2-yl)propanoic acid ((*R*)-enantiomer),



H. 6-methoxynaphthalen-2-ol,



I. (6-methoxynaphthalen-2-yl)acetic acid,



J. 2-ethyl-6-methoxynaphthalene,

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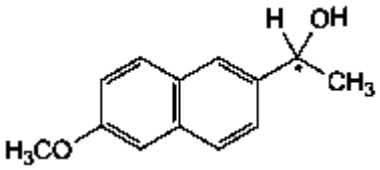
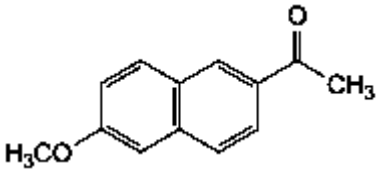
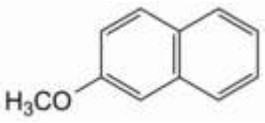


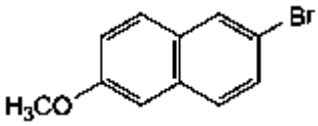
K. (1*RS*)-1-(6-methoxynaphthalen-2-yl)ethanol,



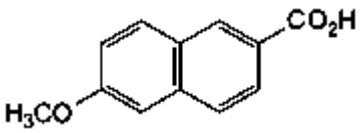
L. 1-(6-methoxynaphthalen-2-yl)ethanone,



M. 2-methoxynaphthalene (nerolin),



N. 2-bromo-6-methoxynaphthalene,



O. 6-methoxynaphthalene-2-carboxylic acid (6-methoxy-2-naphthoic acid).

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Naproxen Gastro-resistant Tablets

General Notices

Gastro-resistant Naproxen Tablets

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Naproxen Gastro-resistant Tablets contain Naproxen. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of naproxen, $C_{14}H_{14}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove the coating from a number of tablets and powder the uncoated cores. Extract a quantity of the powdered tablets containing 0.2 g of Naproxen with 20 mL of *methanol*, shake for 15 minutes, filter, evaporate the filtrate and dry the residue at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of naproxen *(RS 244)*.

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1. The solutions should be protected from light.

Prepare a phosphate buffer pH 7.4 by dissolving 2.62 g of *sodium dihydrogen orthophosphate monohydrate* and 11.5 g of *anhydrous disodium hydrogen orthophosphate* in sufficient *water* to produce 1000 mL and adjusting the pH to 7.4, with either 0.1M *sodium hydroxide* or 0.1M *hydrochloric acid*, if necessary.

First stage

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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(1) After 2 hours, withdraw a 10-mL sample of the medium, filter through a 5-µm filter and measure the *absorbance* of the filtrate, Appendix II B, diluted with the dissolution medium, if necessary, at 332 nm using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *naproxen BPCRS* in the phosphate buffer pH 7.4.

DETERMINATION OF CONTENT

Calculate the total content of naproxen, $C_{14}H_{14}O_3$, in the medium using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

LIMITS

The amount of naproxen released is not more than 5% of the stated amount.

Final stage

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Replace the 0.1M *hydrochloric acid* in the vessel with 900 mL of the phosphate buffer pH 7.4, previously held at 36.5° to 37.5°.

PROCEDURE

(1) After 45 minutes, withdraw a 10-mL sample of the medium and filter. Immediately measure the *absorbance* of the filtrate, Appendix II B, diluted with the phosphate buffer pH 7.4, if necessary, at 332 nm using the phosphate buffer pH 7.4 in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *naproxen BPCRS* in the phosphate buffer pH 7.4.

DETERMINATION OF CONTENT

Calculate the total content of naproxen, $C_{14}H_{14}O_3$, in the medium using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

LIMITS

The amount of naproxen released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be freshly prepared and protected from light.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 30 mg of Naproxen with 40 mL of the mobile phase, dilute with sufficient mobile phase to produce 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Further dilute 1 volume of this solution to 10 volumes with the mobile phase.

(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil 120-3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 50°.

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(e) Use an autosampler temperature of 8°.

(f) Use a detection wavelength of 230 nm.

(g) Inject 20 µL of each solution.

(h) Allow the chromatography to proceed for 10 times the retention time of naproxen.

MOBILE PHASE

42 volumes of *acetonitrile* and 58 volumes of 0.01M *potassium dihydrogen orthophosphate* previously adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to naproxen (retention time about 2 minutes) are: impurity O, about 0.8; impurity K, about 0.9; impurity L, about 1.5 and impurity N, about 5.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2;

in the chromatogram obtained with solution (2), the *signal-to-noise* ratio of the peak due to naproxen is at least 50.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks corresponding to impurities L, N and O using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the following correction factors: L, 3.5 and O, 1.8.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.16%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be protected from light.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Naproxen with 10 mL of *water*. Add 80 mL of *acetonitrile* and further mix. Dilute to produce 100 mL with *acetonitrile*. Dilute 1 volume of the filtrate to 100 volumes with the mobile phase and filter.

(2) 0.001% w/v of *naproxen BPCRS* in the mobile phase.

(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2.

DETERMINATION OF CONTENT

Calculate the content of naproxen, $C_{14}H_{14}O_3$, in the tablets from the chromatograms obtained and using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

STORAGE

Naproxen Gastro-resistant Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Naproxen.

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Naproxen Oral Suspension

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Naproxen Oral Suspension is a suspension of Naproxen in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of naproxen, $C_{14}H_{14}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Filter a quantity of the oral suspension containing 0.1 g of Naproxen (Whatman 541 is suitable), wash the residue with two 5-mL aliquots of *water* and allow to dry. Shake the residue with 20 mL of *methanol*, filter the resulting solution through a 0.45-µm nylon filter and evaporate the filtrate to dryness. Dry the residue at 105° for 30 minutes. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of naproxen *(RS 244)*.

TESTS

Acidity

pH, 2.4 to 5.0, Appendix V L.

Dissolution

Carry out the test for dissolution described under *dissolution test for tablets and capsules*, Appendix XII B1. The solutions should be protected from light.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a phosphate buffer, prepared in the following manner, at a temperature of 37°, as the medium. Dissolve 2.62 g of *sodium dihydrogen orthophosphate monohydrate* and 11.50 g of *anhydrous disodium hydrogen orthophosphate* in sufficient *water* to produce 1 L, and adjusting the pH to 7.4 with either 0.1M *sodium hydroxide* or 0.1M *hydrochloric acid* if necessary.

PROCEDURE

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(1) Shake the container containing the oral suspension being examined and accurately remove 5 mL. Introduce the dose to the medium in the dissolution vessel. After 15 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 332 nm, Appendix II B, using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *naproxen BPCRS* in the dissolution medium, using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of naproxen, $C_{14}H_{14}O_3$, in the medium from the absorbances obtained and using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

LIMITS

The amount of naproxen released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be freshly prepared and protected from light.

(1) Mix with the aid of ultrasound a quantity of the oral suspension containing 30 mg of Naproxen with 40 mL of the mobile phase, dilute to produce 50 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Further dilute 1 volume of this solution to 10 volumes with the mobile phase.
(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil 120-3 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use an autosampler temperature of 8°.
(f) Use a detection wavelength of 230 nm.
(g) Inject 20 µL of each solution.
(h) Allow the chromatography to proceed for 10 times the retention time of naproxen.

MOBILE PHASE

42 volumes of *acetonitrile* and 58 volumes of 0.01M *potassium dihydrogen orthophosphate* previously adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to naproxen (retention time about 2 minutes) are: impurity O, about 0.8; impurity K, about 0.9; impurity L, about 1.5 and impurity N, about 5.6.

SYSTEM SUITABILITY

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The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2;

in the chromatogram obtained with solution (2), the *signal-to-noise* ratio of the peak due to naproxen is at least 50.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks corresponding to impurities L, N and O using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the following correction factors: L, 3.5 and O, 1.8.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.16%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be protected from light.

(1) Mix with the aid of ultrasound a weighed quantity of the oral suspension containing 0.1 g of Naproxen with 80 mL of the mobile phase, dilute with sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of the filtrate to 100 volumes with the mobile phase.
(2) 0.001% w/v of *naproxen BPCRS* in the mobile phase.
(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{14}H_{14}O_3$, weight in volume, using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

STORAGE

Naproxen Oral Suspension should be protected from light.

IMPURITIES

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The impurities limited by the requirements of this monograph include those listed under Naproxen.

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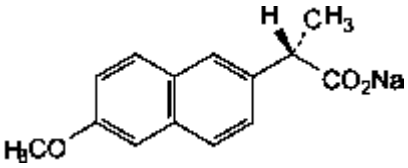
Naproxen Sodium

General Notices

(Ph. Eur. monograph 1702)



$C_{14}H_{13}O_3Na$ 252.2 *26159-34-2*

Ph Eur

DEFINITION

Sodium (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, freely soluble or soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C, D.

Second identification: A, B, D.

A. Specific optical rotation (2.2.7): -17.0 to -14.7 (dried substance).

Dissolve 0.50 g in a 4.2 g/L solution of *sodium hydroxide R* and dilute to 25.0 mL with the same solution.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

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Test solution Dissolve 40.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *methanol R*.

Spectral range 230-350 nm.

Absorption maxima At 262 nm, 271 nm, 316 nm and 331 nm.

Specific absorbance at the absorption maxima:

— at 262 nm: 207 to 227;

— at 271 nm: 200 to 220;

— at 316 nm: 56 to 68;

— at 331 nm: 72 to 84.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dissolve 50 mg in 5 mL of *water R*. Add 1 mL of *dilute sulfuric acid R* and 5 mL of *ethyl acetate R*. Shake vigorously. Allow the 2 layers to separate. Evaporate the upper layer to dryness and subsequently dry at 60 °C for 15 min. Record the spectrum using the residue.

Comparison *naproxen CRS*.

D. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 1.25 g in *water R* and dilute to 25 mL with the same solvent.

pH (*2.2.3*)

7.0 to 9.8.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Test solution Dissolve 25.0 mg of the substance to be examined in 15 mL of *water R* and add 1 mL of *hydrochloric acid R*. Shake with 2 quantities, each of 10 mL, of *ethyl acetate R*, combine the upper layers and evaporate to dryness under reduced pressure. Dissolve the residue in 50.0 mL of *tetrahydrofuran R*. Dilute 2.0 mL of this solution to 20.0 mL with the mobile phase.

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Reference solution (a) Dilute 2.5 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *racemic naproxen CRS* in 10 mL of *tetrahydrofuran R* and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel π-acceptor/π-donor for chiral separations R* (5 µm) (*S*,*S*);

— *temperature*: 25 °C.

Mobile phase *glacial acetic acid R*, *acetonitrile R*, *2-propanol R*, *hexane R* (5:50:100:845 *V/V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 263 nm.

Injection 20 µL.

Run time 1.5 times the retention time of naproxen (retention time = about 5 min).

System suitability Reference solution (b):

— *resolution*: minimum 3 between the peaks due to impurity G and naproxen.

Limit:

— *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Test solution Dissolve 12 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 6 mg of *bromomethoxynaphthalene R* (impurity N), 6.0 mg of *naproxen impurity L CRS* and 6 mg of *(1RS)-1-(6-methoxynaphthalen-2-yl)ethanol R* (impurity K) in *acetonitrile R* and dilute to 10 mL with the same solvent. To 1 mL of the solution add 1 mL of the test solution and dilute to 50 mL with the mobile phase. Dilute 1 mL of this solution to 20 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm);

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— *temperature*: 50 °C.

Mobile phase Mix 42 volumes of *acetonitrile R* and 58 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 1.5 times the retention time of impurity N.

Relative retention With reference to naproxen (retention time = about 2.5 min): impurity K = about 0.9; impurity L = about 1.4; impurity N = about 5.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.2 between the peaks due to impurity K and naproxen.

Limits:

— *impurity L*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.200 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.22 mg of $C_{14}H_{13}O_3Na$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

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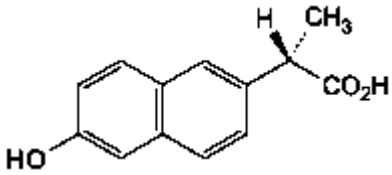
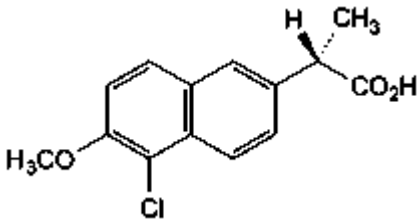
Specified impurities G, L.

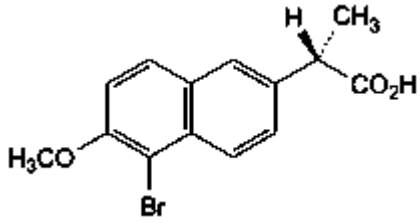
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, H, I, J, K, M, N.



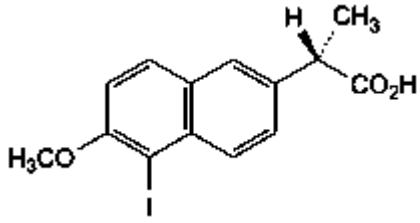
A. (2*S*)-2-(6-hydroxynaphthalen-2-yl)propanoic acid,



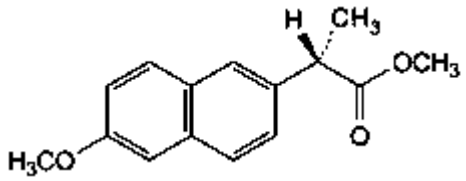
B. (2*S*)-2-(5-chloro-6-methoxynaphthalen-2-yl)propanoic acid,



C. (2*S*)-2-(5-bromo-6-methoxynaphthalen-2-yl)propanoic acid,



D. (2*S*)-2-(5-iodo-6-methoxynaphthalen-2-yl)propanoic acid,



E. methyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate,

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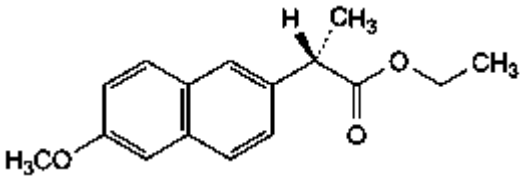
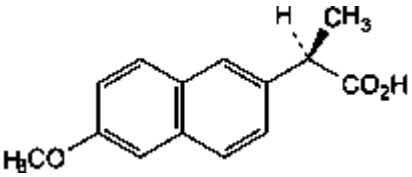
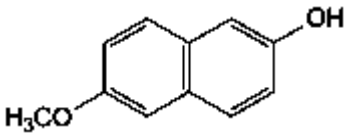


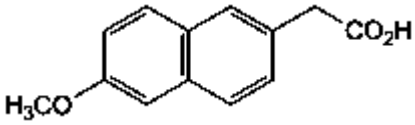
F. ethyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate,



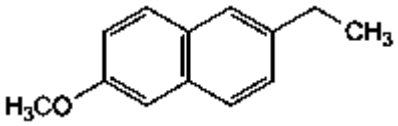
G. (2*R*)-2-(6-methoxynaphthalen-2-yl)propanoic acid,



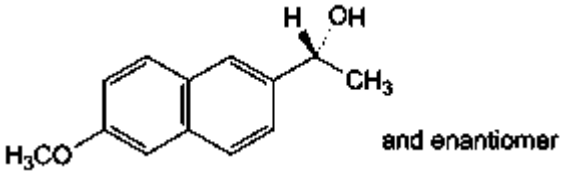
H. 6-methoxynaphthalen-2-ol,



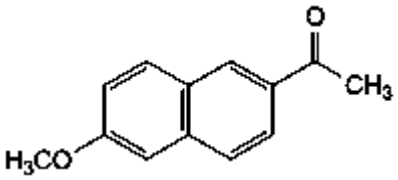
I. (6-methoxynaphthalen-2-yl)acetic acid,



J. 2-ethyl-6-methoxynaphthalene,



K. (1*RS*)-1-(6-methoxynaphthalen-2-yl)ethanol,



L. 1-(6-methoxynaphthalen-2-yl)ethanone,

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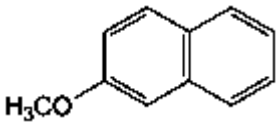
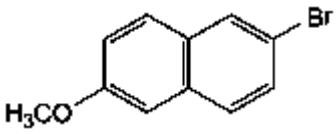


M. 2-methoxynaphthalene (nerolin),



N. 2-bromo-6-methoxynaphthalene.

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Naproxen Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Naproxen Tablets contain Naproxen.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of naproxen, $C_{14}H_{14}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.2 g of Naproxen with 20 mL of *methanol*, shake for 15 minutes, filter, evaporate the filtrate and dry the residue at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of naproxen *(RS 244)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1. The solutions should be protected from light.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a phosphate buffer, prepared in the following manner, at a temperature of 37°, as the medium. Dissolve 2.62 g of *sodium dihydrogen orthophosphate monohydrate* and 11.50 g of *anhydrous disodium hydrogen orthophosphate* in sufficient *water* to produce 1 L and adjust to pH 7.4, if necessary, with either 0.1M *sodium hydroxide* or 0.1M *hydrochloric acid*.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 332 nm, Appendix II B using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *naproxen BPCRS* in dissolution medium, using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of naproxen, $C_{14}H_{14}O_3$, in the medium using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

LIMITS

The amount of naproxen released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be freshly prepared and protected from light.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 30 mg of Naproxen with 40 mL of the mobile phase, dilute with sufficient mobile phase to produce 50 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Further dilute 1 volume of this solution to 10 volumes with the mobile phase.
(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil 120-3 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use an autosampler temperature of 8°.
(f) Use a detection wavelength of 230 nm.
(g) Inject 20 µL of each solution.
(h) Allow the chromatography to proceed for 10 times the retention time of naproxen.

MOBILE PHASE

42 volumes of *acetonitrile* and 58 volumes of 0.01M *potassium dihydrogen orthophosphate* previously adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to naproxen (retention time about 2 minutes) are: impurity O, about 0.8; impurity K, about 0.9; impurity L, about 1.5 and impurity N, about 5.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2;

in the chromatogram obtained with solution (2), the *signal-to-noise* ratio of the peak due to naproxen is at least 50.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks corresponding to impurities L, N and O using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the following correction factors: L, 3.5 and O, 1.8.

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In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.16%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be protected from light.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Naproxen with 80 mL of the mobile phase, dilute with sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of the filtrate to 100 volumes with the mobile phase.
(2) 0.001% w/v of *naproxen BPCRS* in the mobile phase.
(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2.

DETERMINATION OF CONTENT

Calculate the content of naproxen, $C_{14}H_{14}O_3$, in the tablets from the chromatograms obtained and using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

STORAGE

Naproxen Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Naproxen.

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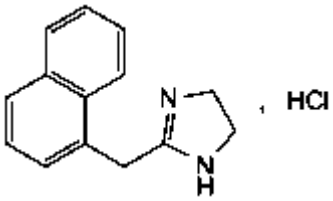
Naphazoline Hydrochloride

General Notices

(Ph. Eur. monograph 0730)



$C_{14}H_{15}ClN_2$ 246.7 *550-99-2*

Action and use

Alpha-adrenoceptor agonist.

Ph Eur

DEFINITION

2-(Naphthalen-1-ylmethyl)-4,5-dihydro-1*H*-imidazole hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

mp

About 259 °C, with decomposition.

IDENTIFICATION

First identification: B.

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Second identification: A, C.

A. Dissolve 50.0 mg in *0.01 M hydrochloric acid* and dilute to 250.0 mL with the same acid. Dilute 25.0 mL of the solution to 100.0 mL with *0.01 M hydrochloric acid*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows 4 absorption maxima, at 270 nm, 280 nm, 287 nm and 291 nm. The ratios of the absorbances measured at the maxima at 270 nm, 287 nm and 291 nm to that measured at the maximum at 280 nm are 0.82 to 0.86, 0.67 to 0.70 and 0.65 to 0.69, respectively.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *naphazoline hydrochloride CRS*.

C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 20 mL of solution S add 0.2 mL of *0.01 M sodium hydroxide* and 0.1 mL of *methyl red solution R*. The solution is yellow. Not more than 0.6 mL of *0.01 M hydrochloric acid* is required to change the colour of the solution to red.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *1-naphthylacetic acid R* in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *naphazoline impurity A CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (4 µm) with a pore size of 6 nm.

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Mobile phase Dissolve 1.1 g of *sodium octanesulfonate R* in a mixture of 5 mL of *glacial acetic acid R*, 300 mL of *acetonitrile R* and 700 mL of *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 3 times the retention time of naphazoline.

Retention time Naphazoline = about 14 min.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to naphazoline and impurity B.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 24.67 mg of $C_{14}H_{15}ClN_2$.

STORAGE

Protected from light.

IMPURITIES

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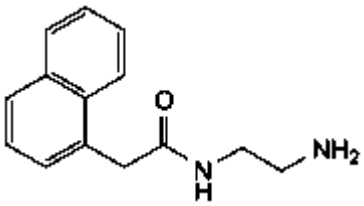
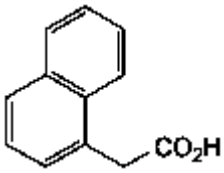
Specified impurities A.

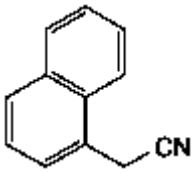
Other detectable impurities: B, C, D.



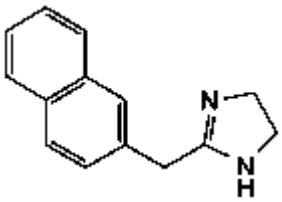
A. *N*-(2-aminoethyl)-2-(naphthalen-1-yl)acetamide (naphthylacetylethylenediamine),



B. (naphthalen-1-yl)acetic acid (1-naphthylacetic acid),



C. (naphthalen-1-yl)acetonitrile (1-naphthylacetonitrile),



D. 2-(naphthalen-2-ylmethyl)-4,5-dihydro-1*H*-imidazole (β-naphazoline).

Ph Eur

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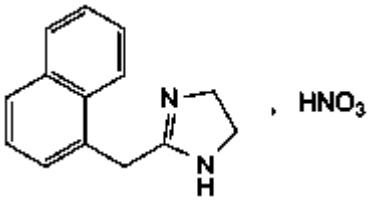
Naphazoline Nitrate

General Notices

(Ph. Eur. monograph 0147)



$C_{14}H_{15}N_3O_3$ 273.3 *5144-52-5*

Action and use

Alpha-adrenoceptor agonist.

Ph Eur

DEFINITION

2-(Naphthalen-1-ylmethyl)-4,5-dihydro-1*H*-imidazole nitrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 167 °C to 170 °C.

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B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *0.01 M hydrochloric acid* and dilute to 250.0 mL with the same acid. Dilute 25.0 mL of the solution to 100.0 mL with *0.01 M hydrochloric acid*.

Spectral range 230-350 nm.

Absorption maximum At 270 nm, 280 nm, 287 nm and 291 nm.

Absorbance ratio:

— A_{270}/A_{280} = 0.82 to 0.86,

— A_{291}/A_{280} = 0.65 to 0.69.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *naphazoline nitrate CRS*.

D. Dissolve 45 mg of the substance to be examined in 2 mL of *water R*. Add 1 mL of *sulfuric acid R*. Shake carefully and allow to cool. Add 1 mL of *ferrous sulfate solution R2* dropwise along the walls of the container. At the junction of the 2 liquids, a brown colour develops.

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R*, warming gently, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

pH (2.2.3)

5.0 to 6.5 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *1-naphthylacetic acid R* in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *naphazoline impurity A CRS* in the mobile phase and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

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Reference solution (c) Dilute 2.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm,

— *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (4 µm) with a pore size of 6 nm.

Mobile phase Dissolve 1.1 g of *sodium octanesulfonate R* in a mixture of 5 mL of *glacial acetic acid R*, 300 mL of *acetonitrile R* and 700 mL of *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 3 times the retention time of naphazoline.

Relative retention With reference to naphazoline (retention time = about 14 min): impurity A = about 0.76; impurity D = about 1.24; impurity B = about 1.27; impurity C = about 2.8.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to naphazoline and impurity B.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peak due to the nitrate ion.

Chlorides (2.4.4)

Maximum 330 ppm, determined on solution S.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.200 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 27.33 mg of $C_{14}H_{15}N_3O_3$.

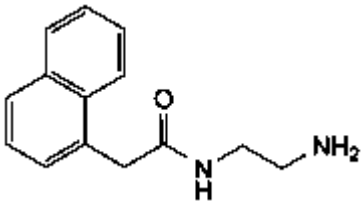
STORAGE

Protected from light.

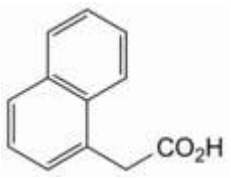
IMPURITIES

Specified impurities A.

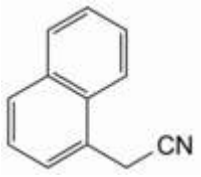
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D.



A. *N*-(2-aminoethyl)-2-(naphthalen-1-yl)acetamide (naphthylacetylethylenediamine),



B. (naphthalen-1-yl)acetic acid (1-naphthylacetic acid),



C. (naphthalen-1-yl)acetonitrile (1-naphthylacetonitrile),

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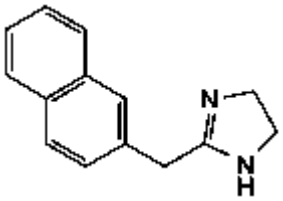

D. 2-(naphthalen-2-ylmethyl)-4,5-dihydro-1*H*-imidazole (β-naphazoline).

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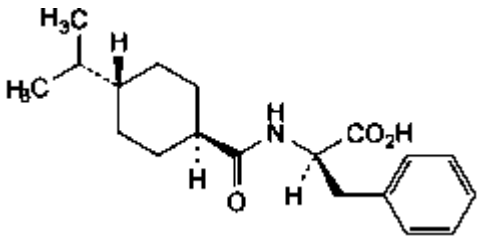
Nateglinide

General Notices

(Ph. Eur. monograph 2575)



$C_{19}H_{27}NO_3$ 317.4 *105816-04-4*

Action and use

Stimulates insulin release; treatment of diabetes mellitus.

Ph Eur

DEFINITION

N-[[*trans*-4-(1-Methylethyl)cyclohexyl]carbonyl]-D-phenylalanine.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Carry out either tests A, B or tests B, C.

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A. Specific optical rotation (2.2.7): -40.0 to -36.5 (dried substance).

Dissolve 0.200 g in a 4 g/L solution of *sodium hydroxide R* and dilute to 20.0 mL with the same solution.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *nateglinide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Test B for related substances (see Tests).

TESTS

Related substances

A. Impurity A and unspecified impurities. Liquid chromatography (2.2.29).

Test solution Dissolve 60.0 mg of the substance to be examined in 1 mL of *acetonitrile R1* and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 3.0 mg of *nateglinide impurity A CRS* in 1 mL of *acetonitrile R1* and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 3 mg of the substance to be examined in 1 mL of *acetonitrile R1*, add 4.0 mL of reference solution (a) and dilute to 10 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.05 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a 7.8 g/L solution of *sodium dihydrogen phosphate monohydrate R* previously adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 100 µL of the test solution and reference solutions (b), (c) and (d).

Run time 5 times the retention time of nateglinide.

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Relative retention With reference to nateglinide (retention time = about 7 min): impurity A = about 0.5.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity A and nateglinide.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.10 per cent);

— *sum of unspecified impurities*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent).

B. Impurity B. Liquid chromatography (2.2.29).

Test solution Dissolve 0.200 g of the substance to be examined in *methanol R2* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *nateglinide impurity B CRS* in *methanol R2* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 0.10 g of the substance to be examined in *methanol R2*. Add 1.0 mL of reference solution (a) and dilute to 10.0 mL with *methanol R2*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: urea type silica gel for chiral chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Dissolve 0.77 g of *ammonium acetate R* in *methanol R2* and dilute to 1000 mL with the same solvent.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 1.5 times the retention time of nateglinide.

Relative retention With reference to nateglinide (retention time = about 21 min): impurity B = about 0.9.

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System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to nateglinide.

Limit:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent).

C. Impurities C and D. Liquid chromatography (2.2.29).

Sodium phosphate buffer Dissolve 8.5 g of *anhydrous disodium hydrogen phosphate R* in 950 mL of *water R*. Adjust to pH 7.5 with *phosphoric acid R* and dilute to 1000 mL with *water R*.

Test solution Dissolve 50.0 mg of the substance to be examined in 25 mL of *methanol R2* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *phenylalanine CRS* (impurity D) and 5 mg of *nateglinide impurity C CRS* in *methanol R2* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 20 mg of the substance to be examined in 10 mL of *methanol R2*, add 1.0 mL of reference solution (a) and dilute to 20.0 mL with sodium phosphate buffer.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (e) Dissolve 50.0 mg of *nateglinide CRS* in 25 mL of *methanol R2* and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 6.0 mm;

— *stationary phase*: *polymethacrylate gel R* (6 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R2*, sodium phosphate buffer (45:55 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 1.4 times the retention time of nateglinide.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and D.

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Relative retention With reference to nateglinide (retention time = about 18 min): impurity D = about 0.2; impurity C = about 0.9.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to nateglinide.

Limits:

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.2 per cent).

Limits:

— *total for impurities A, B, C, D and sum of unspecified impurities*: maximum 0.5 per cent;

— *disregard limit for impurities A, B, C and D*: 0.05 per cent for each impurity.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in test C for related substances with the following modification.

Injection Test solution and reference solution (e).

Calculate the percentage content of $C_{19}H_{27}NO_3$ taking into account the assigned content of *nateglinide CRS*.

IMPURITIES

Specified impurities *A, B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, G.*

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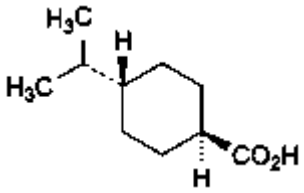
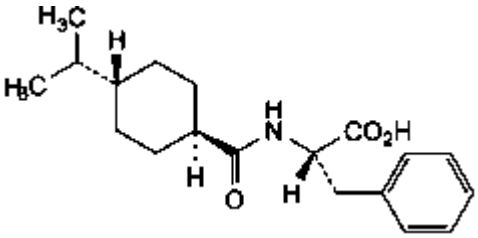
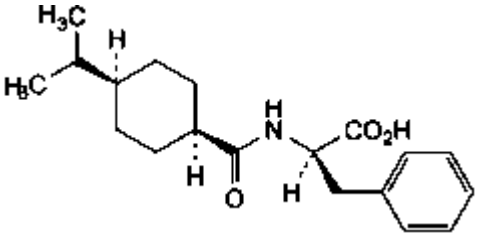


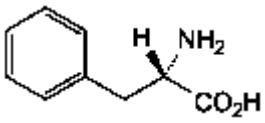
A. *trans*-4-(1-methylethyl)cyclohexanecarboxylic acid,



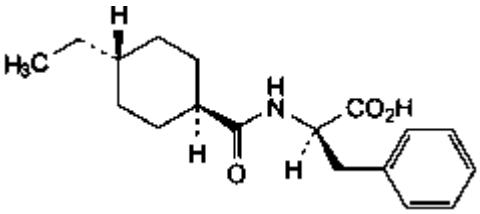
B. *N*-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-L-phenylalanine (L-phenylalanine isomer),



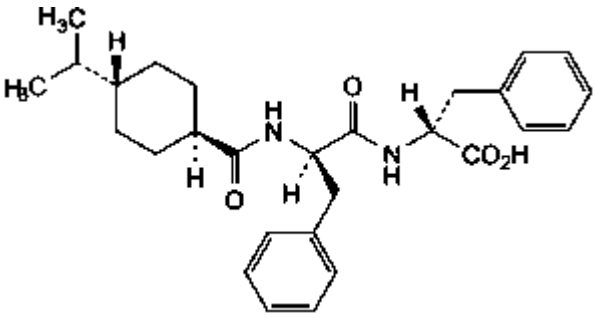
C. *N*-[[*cis*-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanine (*cis*-isomer),



D. (2*S*)-2-amino-3-phenylpropanoic acid (phenylalanine),



E. *N*-[(*trans*-4-ethylcyclohexyl)carbonyl]-D-phenylalanine,



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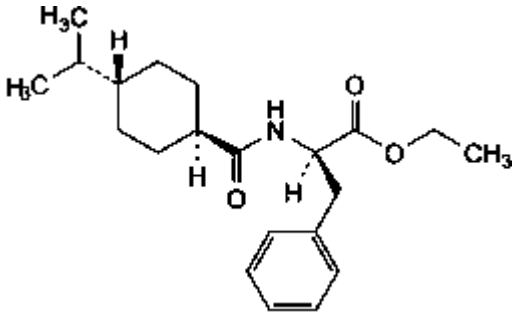
F. *N*-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanyl-D-phenylalanine,



G. ethyl *N*-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalaninate.

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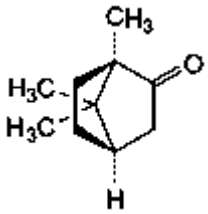
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Natural Camphor

General Notices

(D-Camphor, Ph. Eur. monograph 1400)



$C_{10}H_{16}O$ 152.2 *464-49-3*

Ph Eur

DEFINITION

(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one.

CHARACTERS

Appearance

White or almost white, crystalline powder or friable, crystalline masses.

Highly volatile even at room temperature.

Solubility

Slightly soluble in water, very soluble in ethanol (96 per cent) and in light petroleum, freely soluble in fatty oils, very slightly soluble in glycerol.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Specific optical rotation (see Tests).

B. Melting point (2.2.14): 175 °C to 179 °C.

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C. Infrared absorption spectrophotometry (2.2.24).

Comparison racemic camphor CRS.

D. Dissolve 1.0 g in 30 mL of methanol R. Add 1.0 g of hydroxylamine hydrochloride R and 1.0 g of anhydrous sodium acetate R. Boil under a reflux condenser for 2 h. Allow to cool and add 100 mL of water R. Filter, wash the precipitate obtained with 10 mL of water R and recrystallise from 10 mL of a mixture of 4 volumes of alcohol R and 6 volumes of water R. The crystals, dried *in vacuo*, melt (2.2.14) at 118 °C to 121 °C.

TESTS

Carry out the weighings and dissolution rapidly.

Solution S

Dissolve 2.50 g in 10 mL of alcohol R and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of phenolphthalein solution R1. The solution is colourless. Not more than 0.2 mL of 0.1 M sodium hydroxide is required to change the colour of the indicator.

Specific optical rotation (2.2.7)

+ 41.0 to + 44.0, determined on solution S.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 2.50 g of the substance to be examined in heptane R and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with heptane R.

Reference solution (b) Dilute 10.0 mL of reference solution (a) to 20.0 mL with heptane R.

Reference solution (c) Dissolve 0.50 g of borneol R in heptane R and dilute to 25.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with heptane R.

Reference solution (d) Dissolve 50 mg of linalol R and 50 mg of bornyl acetate R in heptane R and dilute to 100.0 mL with the same solvent.

Column:

— *size*: *l* = 30 m, Ø = 0.25 mm,

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— *stationary phase*: *macrogol 20 000 R* (0.25 µm).

Carrier gas *helium for chromatography R*.

Split ratio 1:70.

Flow rate 45 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	50
	10 - 35	50 → 100
	35 - 45	100 → 200
	45 - 55	200
Injection port		220
Detector		250

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution (d).

— *resolution*: minimum 3.0 between the peaks due to bornyl acetate and to linalol.

Limits:

— *borneol*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent),

— *any other impurity*: not more than half of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *total of other impurities*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (4.0 per cent),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Halogens

Maximum 100 ppm.

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Dissolve 1.0 g in 10 mL of *2-propanol R* in a distillation flask. Add 1.5 mL of *dilute sodium hydroxide solution R* and 50 mg of *nickel-aluminium alloy R*. Heat on a water-bath until the *2-propanol R* has evaporated. Allow to cool and add 5 mL of *water R*. Mix and filter through a wet filter previously washed with *water R* until free from chlorides. Dilute the filtrate to 10.0 mL with *water R*. To 5.0 mL of the solution, add *nitric acid R* dropwise until the precipitate which forms is redissolved and dilute to 15 mL with *water R*. The solution complies with the limit test for chlorides (*2.4.4*).

Residue on evaporation (*2.8.9*)

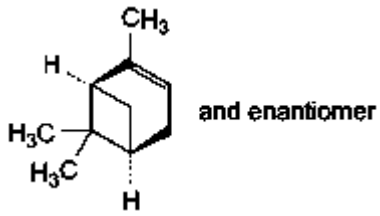
Maximum 0.05 per cent.

Evaporate 2.0 g on a water-bath and dry in an oven at 100-105 °C for 1 h. The residue weighs a maximum of 1 mg.

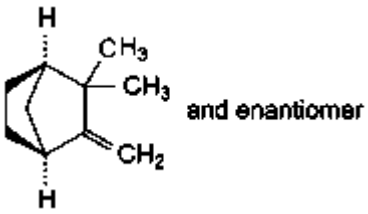
Water

Dissolve 1 g in 10 mL of *light petroleum R*. The solution is clear (*2.2.1*).

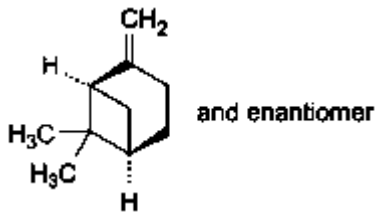
IMPURITIES



A. 2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (α-pinene),



B. 2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane (camphene),



C. 6,6-dimethyl-2-methylenebicyclo[3.1.1]heptane (β-pinene),

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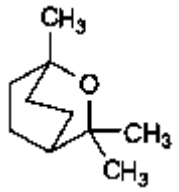
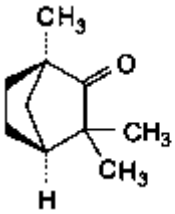
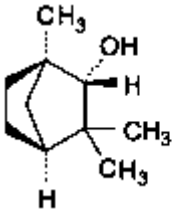


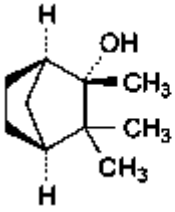
D. 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane (cineole),



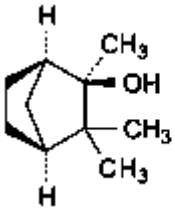
E. 1,3,3-trimethylbicyclo[2.2.1]heptan-2-one (fenchone),



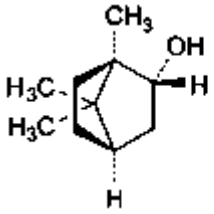
F. *exo*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (fenchol),



G. *exo*-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (camphene hydrate),



H. *endo*-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (methylcamphenilol),



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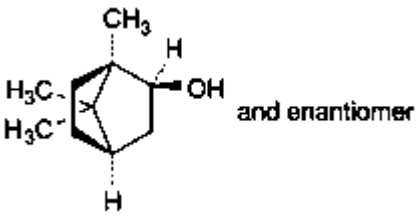
I. *exo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (*exo*-borneol),



and enantiomer

J. *endo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (*endo*-borneol).

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Natural Vitamin A Ester Concentrate

General Notices

DEFINITION

Natural Vitamin A Ester Concentrate consists of a natural ester or a mixture of natural esters of retinol or of a solution of the ester or mixture of esters in Arachis Oil or other suitable vegetable oil. It contains in 1 g not less than 485,000 IU of vitamin A and not less than 97.0% of the number of IU of vitamin A stated on the label. It may contain a suitable antioxidant or mixture of antioxidants.

CHARACTERISTICS

A yellow oil or a mixture of oil and crystalline material which yields a homogeneous yellow oil on warming.

Solubility

Practically insoluble in *water*; soluble or partly soluble in *ethanol (96%)*; miscible with *ether* and with petroleum spirit.

IDENTIFICATION

A. Dissolve a quantity containing 10 IU in a mixture of 100 parts of *absolute ethanol* and 1 part of *hydrochloric acid*. The *light absorption*, Appendix II B, of the solution immediately after preparation exhibits a single maximum at 326 nm. Heat the solution in a water bath for 30 seconds and cool rapidly. The *light absorption* in the range 300 to 400 nm exhibits a low maximum or inflection at 332 nm and sharp maxima at 348, 367 and 389 nm.

B. Dissolve a quantity containing 30 IU in 1 mL of *chloroform* and add 10 mL of *antimony trichloride solution*. A transient bright blue colour is produced immediately.

TESTS

Acid value

Not more than 2.0, Appendix X B.

Peroxide value

Place 1 g in a boiling tube (20 cm × 2.5 cm) and dissolve in 20 mL of a mixture of 2 volumes of *glacial acetic acid* and 1 volume of *ethanol-free chloroform*. Add 1 g of finely powdered *potassium iodide* and pass a rapid current of *oxygen-free nitrogen* through the mixture for 1 minute. Stopper the tube loosely, partly immerse in boiling water for 30 seconds and then in water at 80° for 2 minutes, tighten the stopper and cool rapidly. Transfer the contents to a flask containing 25 mL of a freshly prepared 1% w/v solution of *potassium iodide*, rinse the tube with a further 25 mL of the potassium iodide solution, shake the combined solution and rinsings and titrate with 0.01M *sodium thiosulfate VS*. Repeat the procedure without the concentrate. The difference between the titrations does not exceed 1.4 mL.

Retinol

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Carry out the method for *descending paper chromatography*, Appendix III E, using a mixture of 70 volumes of *1,4-dioxan*, 15 volumes of *methanol* and 15 volumes of *water* containing 1% w/v of *butylated hydroxyanisole* in the bottom of the tank and as the mobile phase. Saturate the paper with a 10% w/v solution of *liquid paraffin* in *petroleum spirit (boiling range, 40° to 60°)* and dry without the aid of heat. Apply separately to the impregnated paper 5 µL and 10 µL of each of the following freshly prepared solutions. For solution (1) dissolve sufficient of the concentrate in *petroleum spirit (boiling range, 40° to 60°)* to yield a solution containing 16,150 to 17,850 IU per mL. For solution (2) mix a quantity of the concentrate containing not less than 500 IU of vitamin A and not more than 1 g of fat with 30 mL of *absolute ethanol* and 3 mL of a 50% w/w solution of *potassium hydroxide*. Boil gently under a reflux condenser in a current of *oxygen-free nitrogen* for 30 minutes, cool rapidly and add 30 mL of water. Transfer the hydrolysate to a separating funnel using three 50 mL quantities of *ether* and extract the vitamin A by shaking for 1 minute. After complete separation discard the aqueous layer and wash the extract with four 50 mL quantities of *water*, mixing very cautiously during the first two washes to avoid the formation of emulsions. Evaporate the separated extract to about 5 mL and remove the remaining solvent in a current of *oxygen-free nitrogen* without the application of heat. Dissolve the residue in sufficient *petroleum spirit (boiling range, 40° to 60°)* to produce a solution of retinol containing about 340 IU per mL.

Develop until the solvent front approaches the bottom of the paper. Examine the dried paper under *ultraviolet light (365 nm)*. The fluorescence of any spot corresponding to retinol in the chromatograms obtained with solution (1) is not more intense than that of the spot in the corresponding chromatogram obtained with solution (2).

ASSAY

Carry out the test as rapidly as possible, avoiding exposure to actinic light and air, oxidising agents, oxidation catalysts (e.g. copper and iron) and acids.

Examine by *ultraviolet absorption spectrophotometry*, Appendix II B (Method A). If method A is found not to be valid, examine by *liquid chromatography*, Appendix III D (Method B).

Method A

Test solution To a quantity of the substance being examined containing 50,000 IU in a round-bottomed flask, add 3 mL of a freshly prepared 50% w/w solution of *potassium hydroxide* and 30 mL of *absolute ethanol*. Boil under a reflux condenser in a current of *nitrogen* for 30 minutes. Cool rapidly and add 30 mL of *water*. Extract with four 50 mL quantities of *ether* discarding the lower layer after complete separation. Wash the combined upper layers with four 50 mL quantities of *water* and evaporate to dryness under a gentle current of *nitrogen* at a temperature not exceeding 30° or in a rotary evaporator at a temperature not exceeding 30° under reduced pressure (water ejector). Dissolve the residue in sufficient *propan-2-ol* to give an expected concentration of vitamin A equivalent to 10 to 15 IU per mL.

Measure the *absorbances*, Appendix II B, of the solution at 300 nm, 310 nm, 325 nm and 334 nm and at the wavelength of maximum absorption with a suitable spectrophotometer in 1-cm specially matched cells, using *propan-2-ol* as the compensation liquid.

Calculate the content of vitamin A, as all-*trans*-retinol, in IU per gram from the expression:

$$A_{325} \times \frac{1830}{100m} \times V$$

where A_{325} = absorbance at 325 nm,

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m	=	mass of the substance to be examined in grams,
V	=	total volume of solution containing 10 IU to 15 IU of vitamin A per mL,
1830	=	conversion factor for the specific absorbance of all-*trans*-retinol in IU.

The above expression can be used only if A_{325} has a value of not greater than $A_{325,\ corr}$ / 0.970 where $A_{325,\ corr}$ is the corrected *absorbance* at 325 nm and is given by the equation:

$A_{325,\ corr} = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$

where *A* designates the absorbance at the wavelength indicated by the subscript.

If A_{325} has a value greater than $A_{325,\ corr}$ / 0.970, calculate the content of vitamin A from the expression:

$$A_{325,corr} \times \frac{1830}{100m} \times V$$

The assay is not valid unless:

(a) the wavelength of maximum absorption lies between 323 nm and 327 nm and

(b) the *absorbance* at 300 nm relative to that at 325 nm is at most 0.73.

Method B

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare solution (1) as follows. To a quantity of the substance being examined containing 50,000 IU in a round-bottomed flask, add 5 mL of a freshly prepared 10% w/v solution of *ascorbic acid* and 10 mL of a freshly prepared 80% w/v solution of *potassium hydroxide* and 100 mL of *ethanol (96%)*. Boil under a reflux condenser on a water bath for 15 minutes. Add 100 mL of a 1% w/v solution of *sodium chloride* and cool. Transfer the solution to a 500 mL separating funnel rinsing the round-bottomed flask with about 75 mL of a 1% w/v solution of *sodium chloride* and then with 150 mL of a mixture of equal volumes of *petroleum spirit (boiling range, 40° to 60°)* and *ether*. Shake for 1 minute. When the layers have separated completely, discard the lower layer and wash the upper layer, first with 50 mL of a 3% w/v solution of *potassium hydroxide* in a 10% v/v solution of *ethanol (96%)* and then with three 50 mL quantities of a 1% w/v solution of *sodium chloride*. Filter the upper layer through 5 g of *anhydrous sodium sulfate* on a fast filter paper into a 250 mL flask suitable for a rotary evaporator. Wash the funnel with 10 mL of fresh extraction mixture, filter and combine the upper layers. Distil them at a temperature not exceeding 30° under reduced pressure (water ejector) and fill with *nitrogen* when evaporation is completed. Alternatively evaporate the solvent under a gentle current of *nitrogen* at a temperature not exceeding 30°. Dissolve the residue in *propan-2-ol*, transfer to a 25 mL volumetric flask and dilute to 25 mL with *propan-2-ol*. Gentle heating in an ultrasonic bath may be required. For solution (2) prepare a solution of *retinyl acetate EPCRS* in *propan-2-ol R1* so that 1 mL contains about 1000 IU of all-*trans*-retinol.

The exact concentration of solution (2) is assessed by ultraviolet absorption spectrophotometry, Appendix II B. Dilute solution (2) with *propan-2-ol R1* to a presumed concentration of 10 IU per mL to 15 IU per mL and measure the *absorbance* at 326 nm in matched 1-cm cells using *propan-2-ol R1* as the compensation liquid.

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Calculate the content of vitamin A in IU per mL of solution (2) from the following expression, taking into account the assigned content of *retinyl acetate EPCRS*:

$$A_{326} \times \frac{1900 \times V_2}{100 \times V_1}$$

where	A_{326}	=	*absorbance* at 326 nm,
	V_2	=	volume of the diluted solution,
	V_1	=	volume of solution (2) used,
	1900	=	conversion factor for the specific absorbance of *retinyl acetate EPCRS* in IU.

For solution (3) proceed as described for solution (1) but use 2 mL of solution (2) in place of the substance being examined.

The exact concentration of solution (3) is assessed by *ultraviolet absorption spectrophotometry*, Appendix II B. Dilute solution (3) with *propan-2-ol R1* to a presumed concentration of 10 IU per mL to 15 IU per mL of all-*trans*-retinol and measure the absorbance at 325 nm in matched 1 cm cells using *propan-2-ol R1* as the compensation liquid.

Calculate the content of all-*trans*-retinol in IU per millilitre of solution (3) from the expression:

$$A_{325} \times \frac{1830 \times V_4}{100 \times V_3}$$

where	A_{325}	=	*absorbance* at 325 nm,
	V_3	=	volume of the diluted solution,
	V_4	=	volume of solution (3) used,
	1830	=	conversion factor for the specific absorbance of all-*trans*-retinol in IU.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm to 10 µm), (b) as mobile phase at a flow rate of 1 mL per minute a mixture of 3 volumes of *water* and 97 volumes of *methanol*, (c) a detection wavelength of 325 nm, (d) a 10 µL loop injector and (e) an electronic integrator.

Inject in triplicate solution (1) and solution (3). The retention time of all-*trans*-retinol is 5 minute ± 1 minute.

The assay is not valid unless (a) the chromatogram obtained with solution (1) shows a peak corresponding to that of all-*trans*-retinol in the chromatogram obtained with solution (3), (b) when using the method of standard additions to solution (1) there is greater than 95% recovery of the added *retinyl acetate EPCRS*, and (c) the recovery of all-*trans*-retinol in solution (3) as assessed by direct absorption spectrophotometry is greater than 95%.

Calculate the content of vitamin A using the following expression:

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$$A_1 \times \frac{C \times V}{A_2} \times \frac{1}{m}$$

where	A_1	=	area of the peak corresponding to all-*trans*-retinol in the chromatogram obtained with solution (1),
	A_2	=	area of the peak corresponding to all-*trans*-retinol in the chromatogram obtained with solution (3),
	C	=	concentration of *retinyl acetate EPCRS* in solution (2) as assessed prior to the saponification in International Units per mL (1000 IU per mL),
	V	=	volume of solution (2) treated,
	m	=	mass of the substance being examined in solution (1).

STORAGE

Vitamin A Ester Concentrate (Natural) should be kept in an airtight container, protected from light and stored at a temperature of 8° to 15°. Once the container has been opened its contents should be used as soon as possible; any part of the contents not used at once should be protected by an atmosphere of an inert gas.

LABELLING

The label states (1) the number of IU (Units) of vitamin A per g; (2) the name of the ester or esters; (3) the name and proportion of the principal excipients; (4) the method of restoring the solution if partial crystallisation has occurred.

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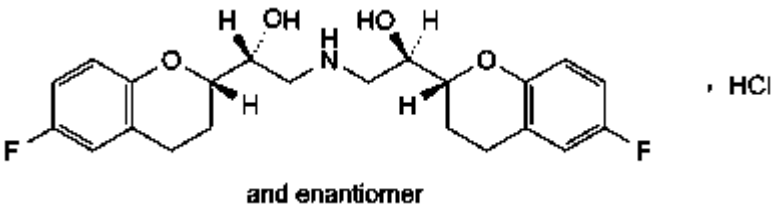
Nebivolol Hydrochloride

General Notices

(Ph. Eur. monograph 2775)



and enantiomer

$C_{22}H_{26}ClF_2NO_4$ 441.9 *152520-56-4*

Action and use

Beta-adrenoceptor antagonist.

Ph Eur

DEFINITION

(1*RS*)-1-[(2*RS*)-6-Fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-[[(2*RS*)-2-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]ethan-1-ol hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystalline powder.

Solubility

Very slightly soluble in water, sparingly soluble in methanol, very slightly soluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *nebivolol hydrochloride CRS*.

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B. Dissolve 20 mg in 20 mL of *methanol R* and add 1 mL of *silver nitrate solution R1*. Shake and allow to stand. A curdled, white precipitate is formed. Remove the supernatant and suspend the precipitate in 5 mL of *dilute nitric acid R*. The precipitate does not dissolve. Add 20 mL of *ammonia R* and shake well. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

TESTS

Impurity D

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 3.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 20.0 mL with *methanol R*.

Reference solution (b) Dissolve the contents of a vial of *nebivolol impurity D CRS* in 1 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *diethylamine R*, *ethanol (96 per cent) R* (0.1:99.9 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 3 times the retention time of nebivolol isomer 1.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurity D.

Relative retention With reference to nebivolol isomer 1 (retention time = about 14 min): nebivolol isomer 2 = about 1.3; impurity D (isomer 1) = about 1.9; impurity D (isomer 2) = about 2.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity D (isomer 1) and impurity D (isomer 2).

Calculation of percentage content:

— use the concentration of nebivolol hydrochloride (both isomers) in reference solution (a).

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Limit:

— *impurity D*: maximum 0.3 per cent for the sum of the 2 isomers.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of nebivolol hydrochloride CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of nebivolol for peak identification CRS (containing impurity A) in 1 mL of the solvent mixture.

Reference solution (d) Dissolve the contents of a vial of nebivolol impurity B CRS in 1 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped phenylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, 3.4 g/L solution of tetrabutylammonium hydrogen sulfate R (5:95 *V/V*);

— *mobile phase B*: water for chromatography R, acetonitrile R (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	76	24
18 - 30	76 → 65	24 → 35
30 - 45	65	35

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

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Injection 10 µL of test solution (a) and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram supplied with *nebivolol for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity B.

Relative retention With reference to nebivolol (retention time = about 19 min): impurity A = about 0.8; impurity B = about 1.1.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to nebivolol and impurity B.

Calculation of percentage content:

— for each impurity, use the concentration of nebivolol hydrochloride in reference solution (a).

Limits:

— *impurities A, B*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	74	26
15 - 20	74 → 30	26 → 70
20 - 25	30	70

Flow rate 1.2 mL/min.

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Injection 20 µL of test solution (b) and reference solution (b).

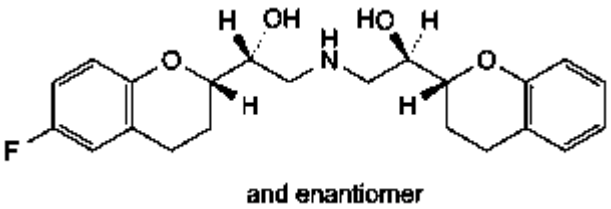
Retention time Nebivolol = about 12 minutes.

Calculate the percentage content of $C_{22}H_{26}ClF_2NO_4$ taking into account the assigned content of *nebivolol hydrochloride CRS*.

IMPURITIES

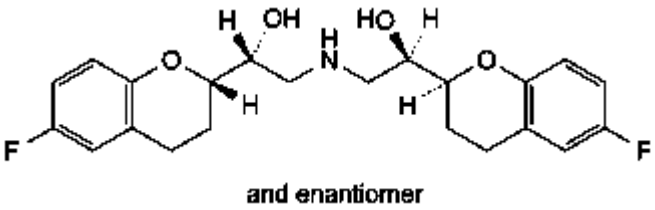
Specified impurities *A, B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



and enantiomer

A. (1*RS*)-1-[(2*RS*)-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-[[(2*RS*)-2-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]ethan-1-ol,



and enantiomer

B. (1*RS*,1′*RS*)-2,2′-azanediylbis[1-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]ethan-1-ol],

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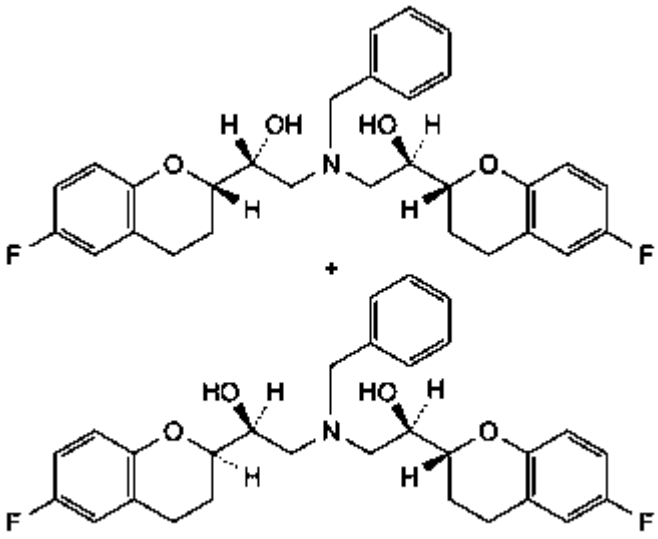
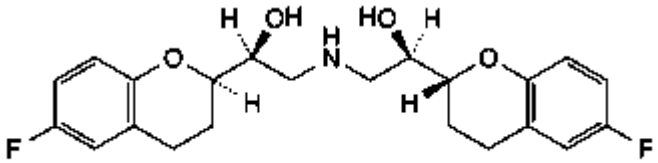


and their enantiomers

C. (1*RS*)-2-[benzyl[(2*RS*)-2-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]-1-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]ethan-1-ol and (1*RS*)-2-[benzyl[(2*SR*)-2-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]-1-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]ethan-1-ol,



and enantiomer

D. (1*RS*)-1-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-[[(2*SR*)-2-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]ethan-1-ol.

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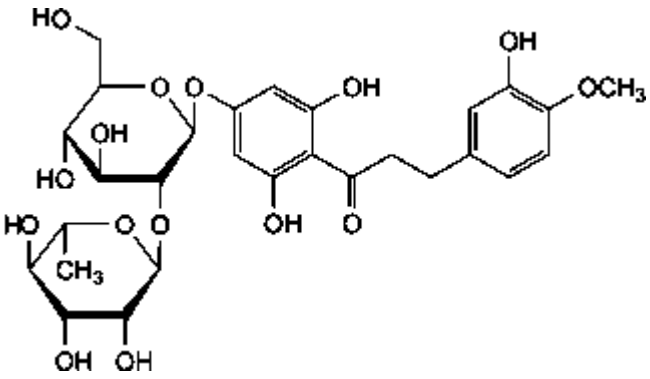
Neohesperidin-Dihydrochalcone

General Notices

(Ph. Eur. monograph 1547)



$C_{28}H_{36}O_{15}$ 613 *20702-77-6*

Ph Eur

DEFINITION

1-[4-[[2-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,6-dihydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl)propan-1-one.

Content

96.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Practically insoluble in water, freely soluble in dimethyl sulfoxide, soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *neohesperidin-dihydrochalcone CRS*.

B. Examine the chromatograms obtained in the assay.

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Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_4 (2.2.2, *Method II*).

Dissolve 0.25 g in *methanol R* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.10 g of the substance to be examined in *dimethyl sulfoxide R* and dilute to 50.0 mL with the same solvent.

Test solution (b) Dilute 10.0 mL of test solution (a) to 20.0 mL with *dimethyl sulfoxide R*.

Reference solution (a) Dissolve 50.0 mg of *neohesperidin-dihydrochalcone CRS* in *dimethyl sulfoxide R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dissolve 4.0 mg of *neohesperidin-dihydrochalcone impurity B CRS* in *dimethyl sulfoxide R* and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with *dimethyl sulfoxide R*.

Reference solution (d) In order to prepare *in situ* impurity F and impurity G, suspend 0.10 g of the substance to be examined in 10.0 mL of a 100 g/L solution of *sulfuric acid R*. Heat the sample for 5 min on a water-bath. Dilute immediately 1.0 mL of the resulting solution to 50.0 mL with *dimethyl sulfoxide R*.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm,

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (4 µm) with a carbon loading of 7 per cent,

— *temperature*: 30 °C.

Mobile phase Mix 20 volumes of *acetonitrile R* and 80 volumes of a solution prepared by adding 5.0 mL of *glacial acetic acid R* to 1000.0 mL of *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 282 nm.

Injection 10 µL; inject test solution (a) and reference solutions (a), (b), (c) and (d).

Run time 5 times the retention time of neohesperidin-dihydrochalcone which is about 10 min.

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Relative retention With reference to neohesperidin-dihydrochalcone: impurity B = about 0.4; impurity D = about 0.7; impurity F = about 1.2; impurity G = about 3.7.

System suitability:

— *resolution*: minimum of 2.5 between the first peak (neohesperidin-dihydrochalcone) and the second peak (impurity F) in the chromatogram obtained with reference solution (d),

— chromatogram obtained with reference solution (a) is similar to the chromatogram provided with *neohesperidin-dihydrochalcone CRS*.

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent),

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (2 per cent),

— *any other impurity*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent),

— *total of all impurities apart from impurity B*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.5 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (*2.5.12*)

Maximum 12.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances.

Injection 10 µL; inject test solution (b) and reference solutions (a) and (d).

System suitability:

— *resolution*: minimum of 2.5 between the first peak (neohesperidin-dihydrochalcone) and the second peak (impurity F) in the chromatogram obtained with reference solution (d),

— *repeatability*: reference solution (a).

Calculate the percentage content of $C_{28}H_{36}O_{15}$ using the chromatogram obtained with reference solution (a) and the stated content of $C_{28}H_{36}O_{15}$ in *neohesperidin-dihydrochalcone CRS*, correcting for the water content of the substance to be examined.

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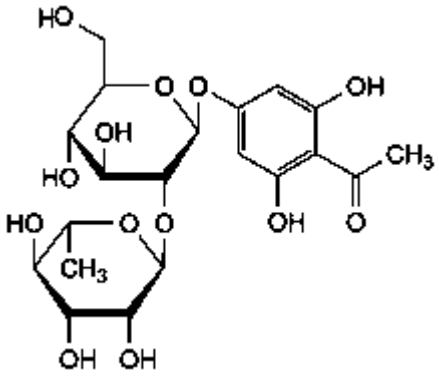
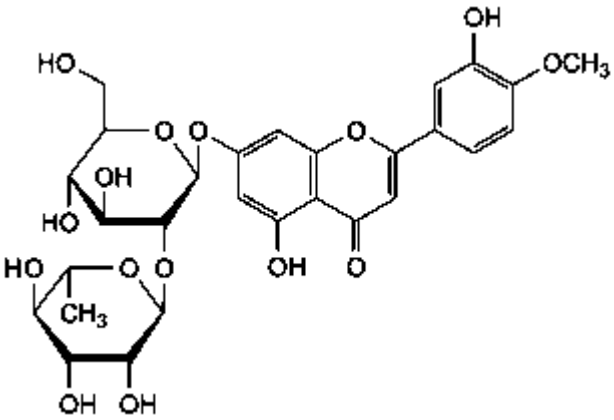
STORAGE

Protected from light.

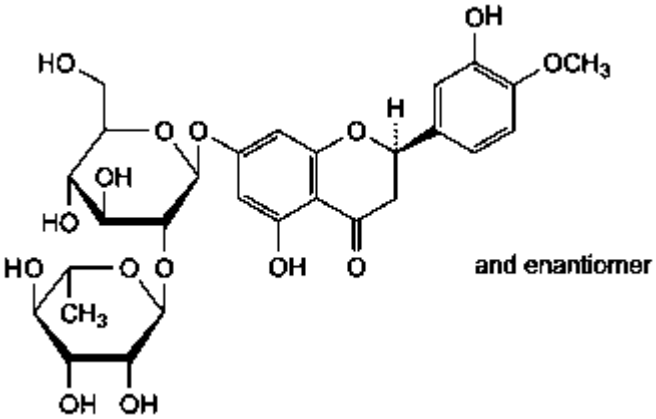
IMPURITIES



A. 1-[4-[[2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,6-dihydroxyphenyl]ethanone (phloroacetophenone neohesperidoside),



B. 7-[[2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one (neodiosmin),



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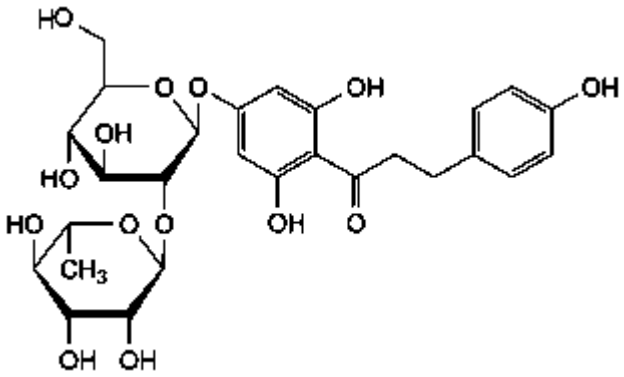
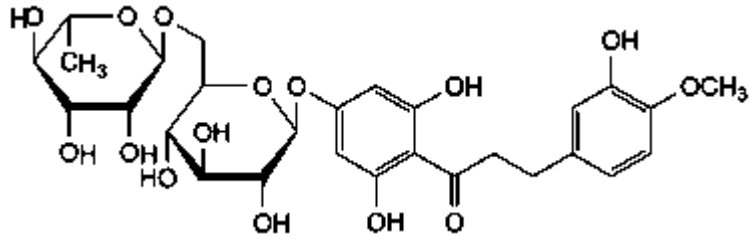
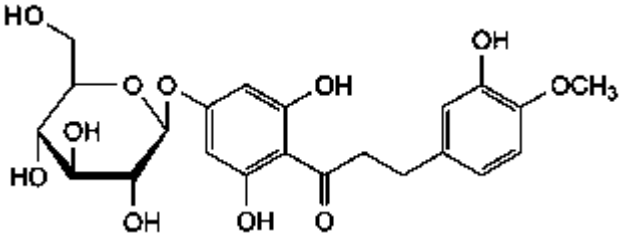
C. (2*RS*)-7-[[2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (neohesperidin),



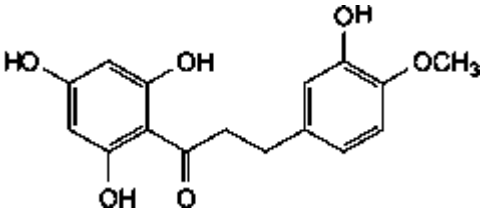
D. 1-[4-[[2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,6-dihydroxyphenyl]-3-(4-hydroxyphenyl)propan-1-one (naringin-dihydrochalcone),



E. 1-[4-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,6-dihydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl)propan-1-one (hesperidin-dihydrochalcone),



F. 1-[4-(β-D-glucopyranosyloxy)-2,6-dihydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl)propan-1-one (hesperetin-dihydrochalcone 7′-glucoside),



G. 3-(3-hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one (hesperetin-dihydrochalcone).

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Neomycin Eye Drops

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Neomycin Eye Drops are a sterile solution of Neomycin Sulfate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) A volume of the eye drops containing 3.5 IU.

(2) 0.5% w/v of *neomycin sulfate EPCRS* in *water*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply all of solution (1) and 1 µL of each of solutions (2) and (3).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with a 1% w/v solution of *ninhydrin* in *butan-1-ol* and heat at 105° for 2 minutes.

MOBILE PHASE

20 volumes of *chloroform*, 40 volumes of 13.5M *ammonia* and 60 volumes of *methanol*.

CONFIRMATION

The principal red spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) and the principal red spot in the chromatogram obtained with solution (3) appears as a single spot.

B. Yield the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Neamine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

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(1) A volume of the eye drops containing 3.5 IU.

(2) The same volume of *water* containing 0.1 µg of *neamine EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel H*.

(b) Use the mobile phase as described below.

(c) Apply all of solutions (1) and (2).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, heat at 110° for 10 minutes and spray the hot plate with a solution prepared immediately before use by diluting *sodium hypochlorite solution* with *water* to contain 0.5% w/v of available chlorine. Dry in a current of cold air until a sprayed area of the plate below the line of application gives not more than a very faint blue colour with one drop of a 0.5% w/v solution of *potassium iodide* in *starch mucilage*; avoid prolonged exposure to cold air. Spray the plate with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*.

MOBILE PHASE

A freshly prepared 3.85% w/v solution of *ammonium acetate*.

CONFIRMATION

Any spot corresponding to neamine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Neomycin C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the eye drops with 0.02M *sodium tetraborate* to contain 700 IU per mL. To 0.5 mL of this solution add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol*, heat in a water bath at 60° for 1 hour and cool; dilute the solution to 25 mL with the mobile phase, allow to stand and use the clear lower layer.

(2) Add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol* to 0.5 mL of a 0.10% w/v solution of *neomycin sulfate EPCRS* in 0.02M *sodium tetraborate*, heat in a water bath at 60° for 1 hour and cool; dilute the solution to 25 mL with the mobile phase, allow to stand and use the clear lower layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Nucleosil 100-5 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 350 nm.

(f) Inject 10 µL of each solution.

(g) Record the chromatograms for 1.4 times the retention time of the peak due to neomycin B.

MOBILE PHASE

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Mix 97 mL of *tetrahydrofuran*, 1.0 mL of *water* and 0.5 mL of *glacial acetic acid* with sufficient of a 2.0% v/v solution of *absolute ethanol* in *ethanol-free chloroform* to produce 250 mL. Pass the mobile phase through the column for several hours before injecting the solutions.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (2) shows a principal peak due to neomycin B and a major *secondary peak* due to neomycin C with a retention time relative to neomycin B of about 0.6;

the *column efficiency*, determined using the peak due to neomycin B in the chromatogram obtained with solution (2), should be not less than 13,000 *theoretical plates* per metre.

LIMITS

In the chromatogram obtained with solution (1) the area of the peak corresponding to neomycin C is not less than 3% and not more than 15% of the sum of the areas of the peaks corresponding to neomycin B and neomycin C.

ASSAY

Dilute a quantity containing 3500 IU to 50 mL with sterile *phosphate buffer pH 8.0*; dilute 10 mL of the resulting solution to 100 mL with the same solvent and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU per mL.

STORAGE

Neomycin Eye Drops should be protected from light.

LABELLING

The strength is stated as the number of IU (Units) per mL.

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Neomycin Eye Ointment

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Neomycin Eye Ointment is a sterile preparation containing Neomycin Sulfate in a suitable basis.

The eye ointment complies with the requirements stated under Eye Preparations and with the following requirements.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the eye ointment containing 14,000 IU in 100 mL of *chloroform*, extract with 5 mL of *water* and use the aqueous extract.

(2) 0.4% w/v of *neomycin sulfate EPCRS* in *water*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with a 1% w/v solution of *ninhydrin* in *butan-1-ol* and heat at 105° for 2 minutes.

MOBILE PHASE

20 volumes of *chloroform*, 40 volumes of 13.5M *ammonia* and 60 volumes of *methanol*.

CONFIRMATION

The principal red spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) and the principal red spot in the chromatogram obtained with solution (3) appears as a single spot.

TESTS

Neamine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

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(1) Disperse a quantity containing 14,000 IU in 20 mL of *chloroform*, shake gently with 8 mL of *water*, allow the layers to separate and use the aqueous layer.

(2) 0.005% w/v of *neamine EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel H*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, heat at 110° for 10 minutes and spray the hot plate with a solution prepared immediately before use by diluting *sodium hypochlorite solution* with *water* to contain 0.5% w/v of available chlorine. Dry in a current of cold air until a sprayed area of the plate below the line of application gives not more than a very faint blue colour with one drop of a 0.5% w/v solution of *potassium iodide* in *starch mucilage*; avoid prolonged exposure to cold air. Spray the plate with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*.

MOBILE PHASE

A freshly prepared 3.85% w/v solution of *ammonium acetate*.

CONFIRMATION

Any spot corresponding to neamine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Neomycin C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the eye ointment containing 3500 IU in 20 mL of *petroleum spirit (boiling range, 120° to 160°)*, add 5 mL of 0.02 M *sodium tetraborate*, shake, separate the aqueous layer and centrifuge. To 0.5 mL of the aqueous layer add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol*, heat in a water bath at 60° for 1 hour and cool; dilute the solution to 25 mL with the mobile phase, allow to stand and use the clear lower layer.

(2) Add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol* to 0.5 mL of a 0.10% w/v solution of *neomycin sulfate EPCRS* in 0.02M *sodium tetraborate*, heat in a water bath at 60° for 1 hour and cool; dilute the solution to 25 mL with the mobile phase, allow to stand and use the clear lower layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Nucleosil 100-5 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 350 nm.

(f) Inject 10 µL of each solution.

(g) Record the chromatograms for 1.4 times the retention time of the peak due to neomycin B.

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MOBILE PHASE

Mix 97 mL of *tetrahydrofuran*, 1.0 mL of *water* and 0.5 mL of *glacial acetic acid* with sufficient of a 2.0% v/v solution of *absolute ethanol* in *ethanol-free chloroform* to produce 250 mL. Pass the mobile phase through the column for several hours before injecting the solutions.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (2) shows a principal peak due to neomycin B and a major *secondary peak* due to neomycin C with a retention time relative to neomycin B of about 0.6;

the *column efficiency*, determined using the peak due to neomycin B in the chromatogram obtained with solution (2), should be not less than 13,000 *theoretical plates* per metre.

LIMITS

In the chromatogram obtained with solution (1) the area of the peak corresponding to neomycin C is not less than 3% and not more than 15% of the sum of the areas of the peaks corresponding to neomycin B and neomycin C.

ASSAY

Dissolve a quantity containing 3500 IU in 25 mL of *chloroform*, extract with four 20-mL quantities of sterile *phosphate buffer pH 8.0*, combine the extracts and add sufficient of the buffer solution to produce 100 mL. Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU per g.

LABELLING

The strength is stated as the number of IU (Units) per g.

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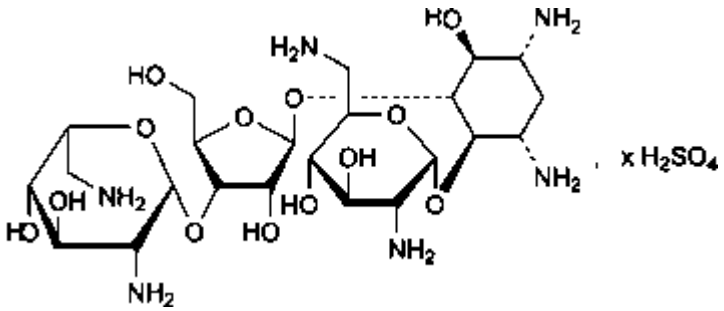
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Neomycin Sulfate

General Notices

Neomycin Sulphate

(Ph. Eur. monograph 0197)



$C_{23}H_{46}N_6O_{13},xH_2SO_4$ 615 (base)

Action and use

Aminoglycoside antibacterial.

Preparations

Dexamethasone and Neomycin Ear Spray

Hydrocortisone and Neomycin Cream

Hydrocortisone Acetate and Neomycin Ear Drops

Hydrocortisone Acetate and Neomycin Eye Drops

Hydrocortisone Acetate and Neomycin Eye Ointment

Neomycin Eye Drops

Neomycin Eye Ointment

Neomycin Tablets

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DEFINITION

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Mixture of sulfates of substances produced by the growth of certain selected strains of *Streptomyces fradiae*, the main component being the sulfate of 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-D-streptamine (neomycin B).

Content

Minimum of 680 IU/mg (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic.

Solubility

Very soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Examine the chromatograms obtained in the test for related substances.

Results:

— the retention time of the principal peak in the chromatogram obtained with the test solution is approximately the same as that of the principal peak in the chromatogram obtained with reference solution (e);

— it complies with the limits given for impurity C.

B. It gives reaction (a) of sulfates (*2.3.1*).

TESTS

pH (*2.2.3*)

5.0 to 7.5.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 53.5 to + 59.0 (dried substance).

Dissolve 1.00 g in *water R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

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Reference solution (a) Dissolve 25.0 mg of framycetin sulfate CRS in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve the contents of a vial of neamine CRS (corresponding to 0.5 mg) in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (e) Dissolve 10 mg of neomycin sulfate CRS in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 25 °C.

Mobile phase Mix 20.0 mL of trifluoroacetic acid R, 6.0 mL of carbonate-free sodium hydroxide solution R and 500 mL of water R, allow to equilibrate, dilute to 1000 mL with water R and degas.

Flow rate 0.7 mL/min.

Post-column solution carbonate-free sodium hydroxide solution R diluted 1 in 25 previously degassed, which is added pulse-less to the column effluent using a 375 µL polymeric mixing coil.

Flow rate 0.5 mL/min.

Detection Pulsed amperometric detector with a gold indicator electrode, a silver-silver chloride reference electrode and a stainless steel auxiliary electrode which is the cell body, held at respectively 0.00 V detection, + 0.80 V oxidation and -0.60 V reduction potentials, with pulse durations according to the instrument used.

Injection 10 µL; inject the test solution and the reference solutions (b), (c), (d) and (e).

Run time 1.5 times the retention time of neomycin B.

Relative retention With reference to neomycin B (retention time = about 10 min): impurity A = about 0.65; impurity C = about 0.9; impurity G = about 1.1.

System suitability:

— resolution: minimum of 2.0 between the peaks due to impurity C and to neomycin B in the chromatogram obtained with reference solution (e); if necessary, adjust the volume of the carbonate-free sodium hydroxide solution in the mobile phase;

— signal-to-noise ratio: minimum 10 for the principal peak in the chromatogram obtained with reference solution (c).

Limits:

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— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (2.0 per cent);

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (15.0 per cent) and not less than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (5.0 per cent);

— *total of other impurities*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (15.0 per cent);

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent).

Sulfate

27.0 per cent to 31.0 per cent (dried substance).

Dissolve 0.250 g in 100 mL of *water R* and adjust the solution to pH 11 using *concentrated ammonia R*. Add 10.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate* adding 50 mL of *alcohol R* when the colour of the solution begins to change, continuing the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of SO_4.

Loss on drying (*2.2.32*)

Maximum 8.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.0 g.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *neomycin sulfate for microbiological assay CRS* as the chemical reference substance.

STORAGE

In an airtight container, protected from light.

IMPURITIES

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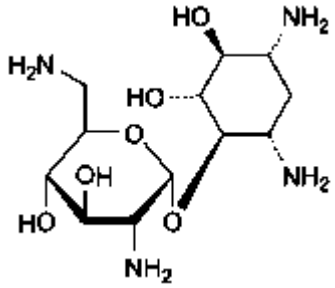
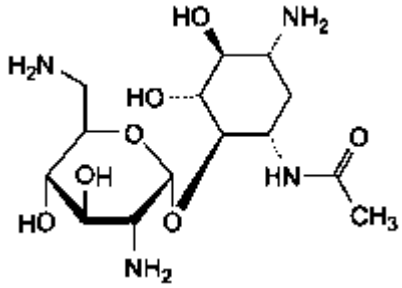
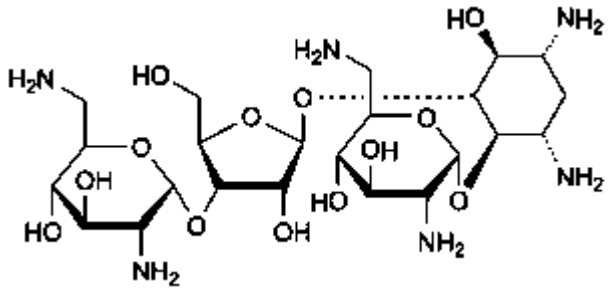


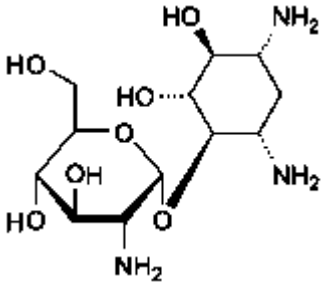
A. 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine (neamine or neomycin A-LP),



B. 3-*N*-acetyl-2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine (3-acetylneamine),



C. 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-β-D-ribofuranosyl]-D-streptamine (neomycin C),



D. 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine (paromamine or neomycin D),

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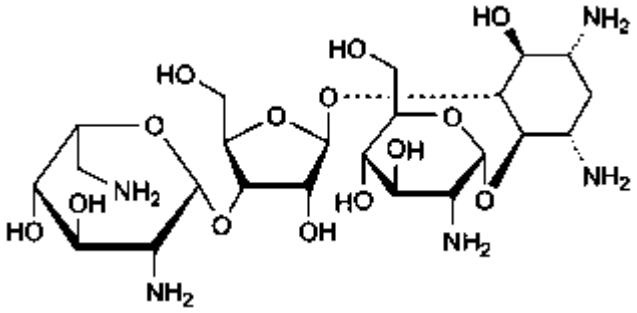
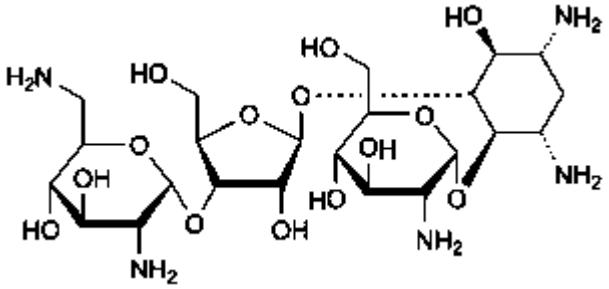
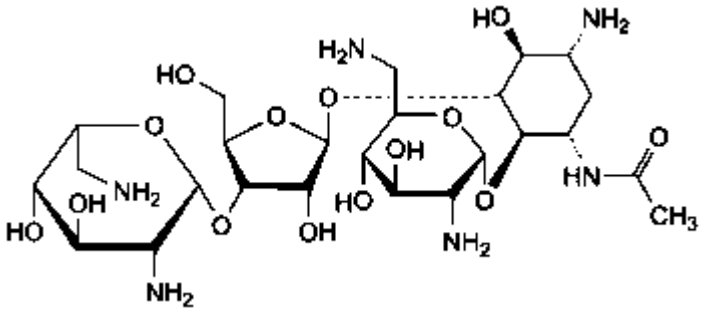


E. 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-2-deoxy-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-D-streptamine (paromomycin I or neomycin E),



F. 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-2-deoxy-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-β-D-ribofuranosyl]-D-streptamine (paromomycin II or neomycin F),



G. 3-*N*-acetyl-2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-D-streptamine (neomycin B-LP).

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Neomycin Tablets

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Neomycin Tablets contain Neomycin Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 70,000 IU with 25 mL of *water* and filter.

(2) 0.4% w/v of *neomycin sulfate EPCRS* in *water*.

(3) Mix equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with a 1% w/v solution of *ninhydrin* in *butan-1-ol* and heat at 105° for 2 minutes.

MOBILE PHASE

20 volumes of *chloroform*, 40 volumes of 13.5M *ammonia* and 60 volumes of *methanol*.

CONFIRMATION

The principal red spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) and the principal red spot in the chromatogram obtained with solution (3) appears as a single compact spot.

B. The powdered tablets yield the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Neamine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

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(1) Add 5 mL of *water* to a quantity of the powdered tablets containing 7000 IU, shake for 5 minutes and filter.

(2) 0.004% w/v of *neamine EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel H*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, heat at 110° for 10 minutes and spray the hot plate with a solution prepared immediately before use by diluting *sodium hypochlorite solution* with *water* to contain 0.5% w/v of available chlorine. Dry in a current of cold air until a sprayed area of the plate below the line of application gives not more than a very faint blue colour with one drop of a 0.5% w/v solution of *potassium iodide* in *starch mucilage*; avoid prolonged exposure to cold air. Spray the plate with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*.

MOBILE PHASE

A freshly prepared 3.85% w/v solution of *ammonium acetate*.

CONFIRMATION

Any spot corresponding to neamine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Neomycin C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 17,500 IU with 20 mL of 0.02M *sodium tetraborate*, dilute to 25 mL with the same solvent, mix and centrifuge. To 0.5 mL of this solution add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol*, heat in a water bath at 60° for 1 hour and cool; dilute the solution to 25 mL with the mobile phase, allow to stand and use the clear lower layer.

(2) Add 1.5 mL of a freshly prepared 2% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *methanol* to 0.5 mL of a 0.10% w/v solution of *neomycin sulfate EPCRS* in 0.02M *sodium tetraborate*, heat in a water bath at 60° for 1 hour and cool; dilute the solution to 25 mL with the mobile phase, allow to stand and use the clear lower layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Nucleosil 100-5 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 350 nm.

(f) Inject 10 µL of each solution.

(g) Record the chromatograms for 1.4 times the retention time of the peak due to neomycin B.

MOBILE PHASE

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Mix 97 mL of *tetrahydrofuran*, 1.0 mL of *water* and 0.5 mL of *glacial acetic acid* with sufficient of a 2.0% v/v solution of *absolute ethanol* in *ethanol-free chloroform* to produce 250 mL. Pass the mobile phase through the column for several hours before injecting the solutions.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (2) shows a principal peak due to neomycin B and a major *secondary peak* due to neomycin C with a retention time relative to neomycin B of about 0.6;

the *column efficiency*, determined using the peak due to neomycin B in the chromatogram obtained with solution (2), should be not less than 13,000 *theoretical plates* per metre.

LIMITS

In the chromatogram obtained with solution (1) the area of the peak corresponding to neomycin C is not less than 3% and not more than 15% of the sum of the areas of the peaks corresponding to neomycin B and neomycin C.

ASSAY

Weigh and powder 20 tablets. Transfer an accurately weighed quantity of the powder containing 15,000 IU to a flask containing 150 mL of sterile *phosphate buffer pH 8.0* and add sufficient of the buffer solution to produce 250 mL. Allow to stand, dilute 10 mL of the clear supernatant liquid to 100 mL with the buffer solution and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated number of IU.

STORAGE

Neomycin Tablets should be protected from light and stored at a temperature not exceeding 30°.

LABELLING

The quantity of active ingredient is stated in terms of the number of IU (Units).

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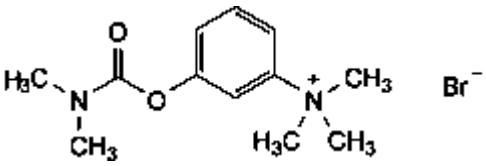
Neostigmine Bromide

General Notices

(Ph. Eur. monograph 0046)



$C_{12}H_{19}BrN_2O_2$ 303.2 *114-80-7*

Action and use

Cholinesterase inhibitor.

Preparation

Neostigmine Tablets

Ph Eur

DEFINITION

3-[(Dimethylcarbamoyl)oxy]-*N*,*N*,*N*-trimethylanilinium bromide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

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Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20 mg in *0.5 M sulfuric acid* and dilute to 100 mL with the same acid.

Spectral range 230-350 nm.

Absorption maxima At 260 nm and 266 nm.

Specific absorbance at the absorption maxima:

— at 260 nm: about 16;

— at 266 nm: about 14.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *neostigmine bromide CRS*.

C. To 50 mg add 0.4 g of *potassium hydroxide R* and 2 mL of *ethanol (96 per cent) R* and heat on a water-bath for 3 min, replacing the evaporated ethanol (96 per cent). Cool and add 2 mL of *water R* and 2 mL of *diazobenzenesulfonic acid solution R1*. An orange-red colour develops.

D. It gives the reactions of bromides (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of *3-dimethylaminophenol R* (impurity B) in 50 mL of the mobile phase. Dilute 1 mL of the solution to 200 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *neostigmine impurity A CRS* in 1 mL of reference solution (b).

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Reference solution (d) Mix 1 mL of the mobile phase and 1 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase To 710 mL of a 3.6 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 3.2 with *phosphoric acid R*, add 4.3 g of *sodium dodecyl sulfate R* and 290 mL of *acetonitrile R1*.

Flow rate 1.6 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL of the test solution and reference solutions (a), (c) and (d).

Run time Twice the retention time of neostigmine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to neostigmine (retention time = about 20 min): impurity B = about 0.56; impurity A = about 0.61.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities B and A in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 25 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— for each impurity, use the concentration of neostigmine bromide in reference solution (a);

— *correction factor*: multiply the peak area of impurity B by 0.5.

Limits:

— *impurity B*: maximum 0.01 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to impurity B.

Sulfates (*2.4.13*)

Maximum 200 ppm, determined on solution S.

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Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.225 g in 2 mL of *anhydrous formic acid R*. Add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 30.32 mg of $C_{12}H_{19}BrN_2O_2$.

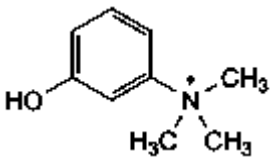
STORAGE

In an airtight container, protected from light.

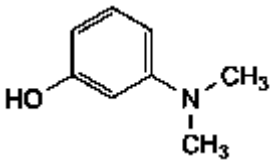
IMPURITIES

Specified impurities B.

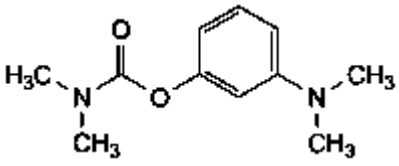
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C.



A. 3-hydroxy-*N*,*N*,*N*-trimethylanilinium,



B. 3-(dimethylamino)phenol,



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C. 3-(dimethylamino)phenyl dimethylcarbamate.

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Neostigmine Injection

General Notices

Action and use

Cholinesterase inhibitor.

DEFINITION

Neostigmine Injection is a sterile solution of Neostigmine Metilsulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of neostigmine metilsulfate, $C_{13}H_{22}N_2O_6S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dilute, if necessary, a volume of the injection containing 2.5 mg of Neostigmine Metilsulfate to 5 mL with *water*, shake with three 10-mL quantities of *ether* and discard the ether extracts. The *light absorption* of the aqueous solution, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 260 nm and 266 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the injection diluted, if necessary, with *water* to produce a solution containing 0.05% w/v of Neostigmine Metilsulfate.

(2) 0.05% w/v of *neostigmine metilsulfate EPCRS*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

5 volumes of *water*, 10 volumes of *formic acid*, 35 volumes of *methanol* and 50 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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The principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot.

C. To 1 mL add 0.5 mL of 5M *sodium hydroxide* and evaporate to dryness on a water bath. Heat rapidly on an oil bath to about 250° and maintain at this temperature for about 30 seconds. Cool, dissolve the residue in 1 mL of *water*, cool in ice and add 1 mL of *diazobenzenesulfonic acid solution*. An orange-red colour is produced.

TESTS

Acidity

pH, 4.5 to 6.5, Appendix V L.

(3-Hydroxy)trimethylanilinium methyl sulfate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the injection diluted, if necessary, with *water* to contain 0.05% w/v of Neostigmine Metilsulfate.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(3) Add 0.05 mL of 5M *sodium hydroxide* to 1 mL of solution (1) and allow to stand for 5 minutes. Add 0.1 mL of 5M *hydrochloric acid* and use immediately.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher 60 RP-select B is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A 0.0015M solution of *sodium heptanesulfonate* in a mixture of 15 volumes of *acetonitrile* and 85 volumes of 0.05M *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the principal peak has a retention time of about 6.8 minutes (neostigmine metilsulfate) and there is a peak with a relative retention time of about 0.5 ((3-hydroxy)trimethylanilinium methylsulfate).

LIMITS

In the chromatogram obtained with solution (1):

Identify any peak due to (3-hydroxy)trimethylanilinium methylsulfate using the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1):

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the area of the peak due to (3-hydroxy)trimethylanilinium methylsulfate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Dilute a quantity containing 25 mg of Neostigmine Metilsulfate to 50 mL with *water*. Measure the *absorbance* of the resulting solution at the maximum at 260 nm, Appendix II B. Calculate the content of $C_{13}H_{22}N_2O_6S$ taking 14.35 as the value of A(1%, 1 cm) at the maximum at 260 nm.

STORAGE

Neostigmine Injection should be protected from light.

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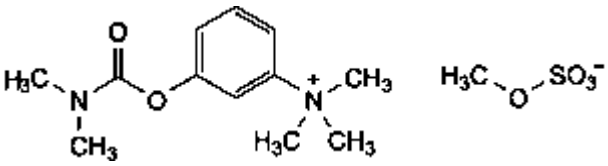
Neostigmine Metilsulfate

General Notices

(Ph. Eur. monograph 0626)



$C_{13}H_{22}N_2O_6S$ 334.4 *51-60-5*

Action and use

Cholinesterase inhibitor.

Preparation

Neostigmine Injection

Ph Eur

DEFINITION

3-[(Dimethylcarbamoyl)oxy]-*N,N,N*-trimethylanilinium methyl sulfate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

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Second identification: A, B, D, E.

A. Melting point (2.2.14): 144 °C to 149 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in *0.5 M sulfuric acid* and dilute to 100 mL with the same acid.

Spectral range 230-350 nm.

Absorption maxima 261 nm and 267 nm.

Resolution (2.2.25): minimum 1.9 for the absorbance ratio.

Absorbance ratio A_{267}/A_{261} = 0.84 to 0.87.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *neostigmine metilsulfate CRS*.

D. To 50 mg add 0.4 g of *potassium hydroxide R* and 2 mL of *ethanol (96 per cent) R* and heat on a water-bath for 3 min, replacing the evaporated ethanol (96 per cent). Cool and add 2 mL of *water R* and 2 mL of *diazobenzenesulfonic acid solution R1*. An orange-red colour develops.

E. Dissolve 0.1 g in 5 mL of *distilled water R* and add 1 mL of *barium chloride solution R1*. No precipitate is formed. Add 2 mL of *hydrochloric acid R* and heat in a water-bath for 10 min. A fine, white precipitate is formed.

TESTS

Solution S

Dissolve 2.5 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 4.0 mL of solution S add 6.0 mL of *water R* and 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Add 0.3 mL of *0.01 M sodium hydroxide*; the solution becomes red. Add 0.4 mL of *0.01 M hydrochloric acid*; the solution becomes colourless. Add 0.1 mL of *methyl red solution R*; the solution becomes red or yellowish-red.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of *3-dimethylaminophenol R* (impurity B) in 50 mL of the mobile phase. Dilute 1 mL of the solution to 200 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *neostigmine impurity A CRS* in 1 mL of reference solution (b).

Reference solution (d) Mix 1 mL of the mobile phase and 1 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase To 710 mL of a 3.6 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 3.2 with *phosphoric acid R*, add 4.3 g of *sodium dodecyl sulfate R* and 290 mL of *acetonitrile for chromatography R*.

Flow rate 1.6 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL of the test solution and reference solutions (a), (c) and (d).

Run time Twice the retention time of neostigmine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to neostigmine (retention time = about 20 min): impurity B = about 0.56; impurity A = about 0.61.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities B and A in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 25 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 0.5;

— for each impurity, use the concentration of neostigmine metilsulfate in reference solution (a).

Limits:

— *impurity B*: maximum 0.01 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

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— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent, except for impurity B.

Sulfates (*2.4.13*)

Maximum 200 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 150 mL of *water R* and add 100 mL of *dilute sodium hydroxide solution R*. Distil, collecting the distillate in 40 mL of a 40 g/L solution of *boric acid R* until the total volume in the collecting vessel is about 250 mL. Titrate the solution in the collecting vessel with *0.1 M hydrochloric acid*, using 0.25 mL of *methyl red mixed solution R* as indicator. Carry out a blank test.

1 mL of *0.1 M hydrochloric acid* is equivalent to 33.44 mg of $C_{13}H_{22}N_2O_6S$.

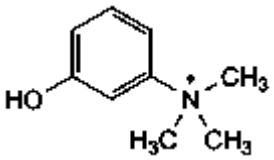
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C.



A. 3-hydroxy-*N*,*N*,*N*-trimethylanilinium,

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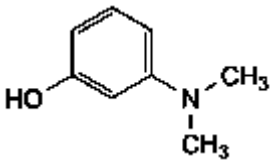
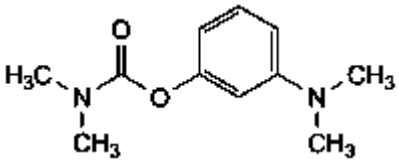


B. 3-(dimethylamino)phenol,



C. 3-(dimethylamino)phenyl dimethylcarbamate.

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Neostigmine Tablets

General Notices

Action and use

Cholinesterase inhibitor.

DEFINITION

Neostigmine Tablets contain Neostigmine Bromide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of neostigmine bromide, $C_{12}H_{19}BrN_2O_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Triturate a quantity of the powdered tablets containing 60 mg of Neostigmine Bromide with two 5 mL quantities of hot *chloroform* and filter. Evaporate the filtrate to dryness on a water bath, extract the residue with 5 mL of hot *water*, cool and filter. To 0.1 mL of the filtrate add 0.5 mL of 5M *sodium hydroxide* and evaporate to dryness on a water bath. Heat quickly in an oil bath to about 250° and maintain at this temperature for about 30 seconds. Cool, dissolve the residue in 1 mL of *water*, cool in ice and add 1 mL of *diazobenzenesulfonic acid solution*. A cherry-red colour is produced.

B. The aqueous filtrate obtained in text A yields the reactions characteristic *of bromides*, Appendix VI.

ASSAY

Weigh and powder 20 tablets. Transfer a quantity of the powder containing 0.15 g of Neostigmine Bromide to a semi-micro ammonia-distillation apparatus, add 20 mL of a 50% w/v solution of *sodium hydroxide* and 0.5 mL of a 2% solution of *octan-2-ol* in *liquid paraffin*. Pass a current of steam through the mixture, collect the distillate in 50 mL of *0.01M sulfuric acid VS* until the total volume is about 200 mL and titrate the excess of acid with *0.02M sodium hydroxide VS* using *methyl red solution* as indicator. Repeat the operation without the powdered tablets. The difference between the titrations represents the amount of acid required to neutralise the dimethylamine produced. Each mL of *0.01M sulfuric acid VS* is equivalent to 6.064 mg of $C_{12}H_{19}BrN_2O_2$.

STORAGE

Neostigmine Tablets should be protected from light.

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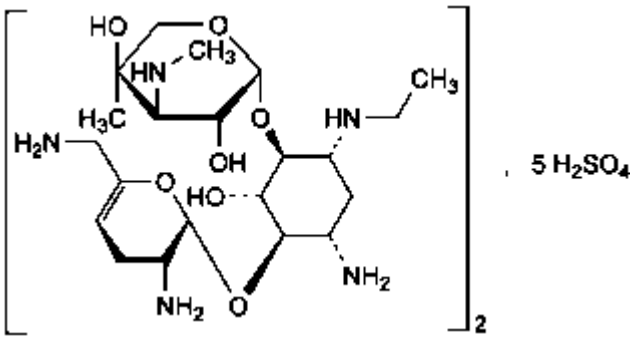
Netilmicin Sulfate

General Notices

Netilmicin Sulphate

(Ph. Eur. monograph 1351)



$C_{42}H_{92}N_{10}O_{34}S_5$ 1442 *56391-57-2*

Action and use

Aminoglycoside antibacterial.

Ph Eur

DEFINITION

Bis[2-deoxy-6-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranosyl)-1-*N*-ethyl-D-streptamine] pentasulfate.

Substance obtained by synthesis from sisomicin.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, very hygroscopic powder.

Solubility

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Very soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

B. It gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 0.80 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 400 nm is not greater than 0.08.

pH (2.2.3)

3.5 to 5.5 for solution S.

Related substances

Liquid chromatography (2.2.29). *Perform weighing steps as quickly as possible and immediately after opening the sample container.*

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *netilmicin sulfate for LC assay CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 25.0 mg of *sisomicin sulfate CRS* (impurity A) in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (c) Dissolve 25.0 mg of *1-N-ethylgaramine sulfate CRS* (impurity B) in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (d) Dilute 0.6 mL of reference solution (a), 1.0 mL of reference solution (b) and 1.0 mL of reference solution (c) to 50.0 mL with the mobile phase.

Reference solution (e) Dissolve 5.0 mg of *netilmicin for peak identification CRS* (containing impurities E and F) in the mobile phase and dilute to 2.5 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase Solution in *carbon dioxide-free water R* containing 0.3 g/L of *sodium octanesulfonate R*, 20 g/L of *anhydrous sodium sulfate R1*, 20 mL/L of *tetrahydrofuran R* and 50 mL/L of *0.2 M potassium dihydrogen phosphate R*, adjusted to pH 3.0 with a 22.5 g/L solution of *phosphoric acid R*; degas.

Flow rate 1.0 mL/min.

Post-column solution Mixture of 1 volume of *carbonate-free sodium hydroxide solution R* and 24 volumes of previously degassed *carbon dioxide-free water R*, which is added pulse-free to the column effluent using a 375 µL polymeric mixing coil.

Flow rate of post-column solution 0.3 mL/min.

Detection Pulsed amperometric detector or equivalent with a gold indicator electrode, a silver-silver chloride reference electrode and a stainless steel auxiliary electrode which is the cell body, held at respectively + 0.05 V detection, + 0.75 V oxidation and - 0.15 V reduction potentials, with pulse durations according to the instrument used.

Injection 20 µL of the test solution and reference solutions (d) and (e).

Run time 3 times the retention time of netilmicin.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A and B; use the chromatogram supplied with *netilmicin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities E and F.

Relative retention With reference to netilmicin (retention time = about 16 min): impurity B = about 0.4; impurity A = about 0.7; impurity E = about 1.9; impurity F = about 2.1.

System suitability Reference solution (d):

— *resolution*: minimum 10.0 between the peaks due to impurities B and A; minimum 6.0 between the peaks due to impurity A and netilmicin; if necessary, adjust the concentration of sodium octanesulfonate in the mobile phase.

Calculation of percentage contents:

— for impurities A and B, use the concentration of each impurity in reference solution (d);

— for impurities other than A and B, use the concentration of netilmicin sulfate in reference solution (d).

Limits:

— *impurities A, B, E, F*: for each impurity, maximum 1.0 per cent;

— *any other impurity*: for each impurity, maximum 0.3 per cent;

— *total*: maximum 3.0 per cent;

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— *reporting threshold*: 0.1 per cent.

Sulfate

31.5 per cent to 35.0 per cent (dried substance).

Dissolve 0.12 g in 100 mL of *water R* and adjust the solution to pH 11 using *concentrated ammonia R*. Add 30.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate* adding 50 mL of *ethanol (96 per cent) R* when the colour of the solution begins to change and continue the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of SO_4.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 0.500 g by drying at 110 °C under high vacuum for 3 h.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 0.5 g.

ASSAY

Liquid chromatography (*2.2.29*). *Perform weighing steps as quickly as possible and immediately after opening the sample container.*

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution Dissolve the contents of a vial of *netilmicin sulfate for LC assay CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase Solution in *carbon dioxide-free water R* containing 0.15 g/L of *sodium octanesulfonate R*, 20 g/L of *anhydrous sodium sulfate R1*, 20 mL/L of *2-methyl-2-propanol R* and 50 mL/L of *0.2 M potassium dihydrogen phosphate R*, adjusted to pH 3.0 with *dilute phosphoric acid R*; degas.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL.

Run time 1.3 times the retention time of netilmicin.

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Retention time Netilmicin = about 4 min.

Calculate the percentage content of $C_{42}H_{92}N_{10}O_{34}S_5$ taking into account the assigned content of *netilmicin sulfate for LC assay CRS*.

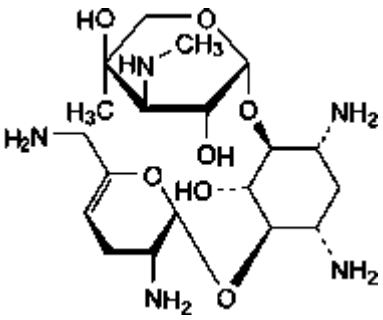
STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

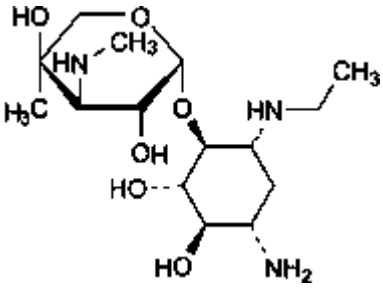
IMPURITIES

Specified impurities *A, B, E, F.*

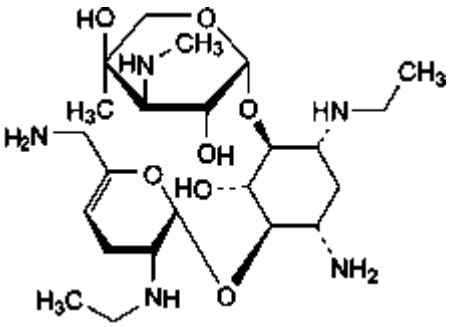
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D.*



A. 2-deoxy-4-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-6-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranosyl)-L-streptamine (sisomicin),



B. 2-deoxy-6-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-1-*N*-ethyl-D-streptamine (1-*N*-ethylgaramine),



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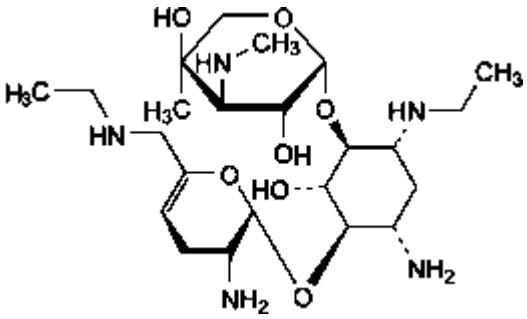
C. 4-*O*-[6-amino-2,3,4,6-tetradeoxy-2-(ethylamino)-α-D-*glycero*-hex-4-enopyranosyl]-2-deoxy-6-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-1-*N*-ethyl-D-streptamine (2′-*N*-ethylnetilmicin),



D. 4-*O*-[2-amino-2,3,4,6-tetradeoxy-6-(ethylamino)-α-D-*glycero*-hex-4-enopyranosyl]-2-deoxy-6-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-1-*N*-ethyl-D-streptamine (6′-*N*-ethylnetilmicin),

E. unknown structure,

F. unknown structure.

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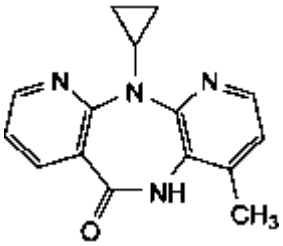
Nevirapine

General Notices

Anhydrous Nevirapine

(Ph. Eur. monograph 2255)



$C_{15}H_{14}N_4O$ 266.3 *129618-40-2*

Action and use

Non-nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Preparations

Nevirapine Tablets

Nevirapine Prolonged-release Tablets

Ph Eur

DEFINITION

11-Cyclopropyl-4-methyl-5,11-dihydro-6*H*-dipyrido [3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Practically insoluble in water, sparingly soluble or slightly soluble in methylene chloride, slightly soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *anhydrous nevirapine CRS*.

B. Loss on drying (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 24.0 mg of the substance to be examined in a mixture of 4 mL of *acetonitrile R* and 80 mL of the mobile phase and sonicate until dissolution is complete. Dilute to 100.0 mL with the mobile phase.

Test solution (b) Dilute 3.0 mL of test solution (a) to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Add 2.0 mL of the mobile phase to a vial of *nevirapine for peak identification CRS* (containing impurities A, B and C), mix and sonicate for 1 min.

Reference solution (c) Dissolve 24.0 mg of *anhydrous nevirapine CRS* in a mixture of 4 mL of *acetonitrile R* and 80 mL of the mobile phase and sonicate until complete dissolution. Dilute to 100.0 mL with the mobile phase. Dilute 3.0 mL of this solution to 25.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped amidohexadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 20 volumes of *acetonitrile R* and 80 volumes of a 2.88 g/L solution of *ammonium dihydrogen phosphate R*, previously adjusted to pH 5.0 using *dilute sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL of test solution (a) and reference solutions (a) and (b).

Run time 10 times the retention time of nevirapine.

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Identification of impurities Use the chromatogram supplied with *nevirapine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to nevirapine (retention time = about 8 min): impurity B = 0.7; impurity A = 1.5; impurity C = 2.8.

System suitability Reference solution (b):

— *resolution*: minimum 5 between the peaks due to impurity B and nevirapine.

Limits:

— *impurities A, B, C*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

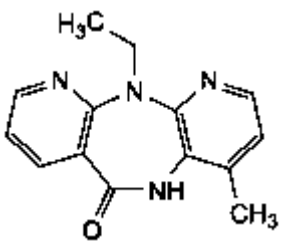
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 25 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{15}H_{14}N_4O$ from the declared content of *anhydrous nevirapine CRS*.

IMPURITIES

Specified impurities *A, B, C.*



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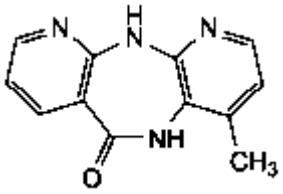
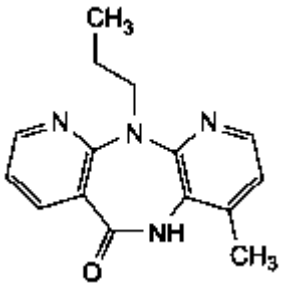
A. 11-ethyl-4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-b:2′,3′-*e*][1,4]diazepin-6-one,



B. 4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-b:2′,3′-*e*][1,4]diazepin-6-one,



C. 4-methyl-11-propyl-5,11-dihydro-6*H*-dipyrido[3,2-b:2′,3′-*e*][1,4]diazepin-6-one.

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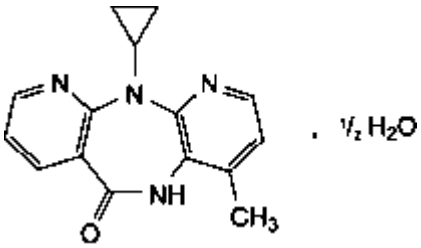
Nevirapine Hemihydrate

General Notices

(Ph. Eur. monograph 2479)



$C_{15}H_{14}N_4O,½H_2O$ 275.3 *220988-26-1*

Action and use

Non-nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Preparation

Nevirapine Oral Suspension

Ph Eur

DEFINITION

11-Cyclopropyl-4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one hemihydrate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, slightly soluble in methanol and in methylene chloride.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *nevirapine hemihydrate CRS*.

B. Water (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in *methanol R* and sonicate until dissolution is complete. Dilute to 50.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Add 1 mL of *methanol R* to a vial of *nevirapine for peak identification CRS* (containing impurities A, B and C), mix and sonicate for 1 min.

Reference solution (c) Dissolve 20.0 mg of *anhydrous nevirapine CRS* in *methanol R* and sonicate until dissolution is complete. Dilute to 50.0 mL with *methanol R*.

Column:

— *size*: *l* = 50 mm, Ø = 2.1 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (1.8 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.77 g of *ammonium acetate R* in 900 mL of *water for chromatography R*, adjust to pH 5.6 with *acetic acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 – 1.35	90	10
1.35 – 3.85	90 → 67	10 → 33
3.85 – 6.70	67 → 60	33 → 40

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
6.70 – 7.65	60	40

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 282 nm.

Injection 2.0 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *nevirapine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to nevirapine (retention time = about 3 min): impurity B = about 0.9; impurity A = about 1.2; impurity C = about 1.3.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to impurity B and nevirapine and minimum 5.0 between the peaks due to nevirapine and impurity A in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.7 for the peak due to nevirapine in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— for each impurity, use the concentration of nevirapine hemihydrate in reference solution (a).

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

3.1 per cent to 3.9 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

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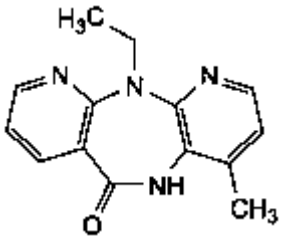
Injection 2.0 µL of the test solution and reference solution (c).

Calculate the percentage content of $C_{15}H_{14}N_4O$ taking into account the assigned content of *anhydrous nevirapine CRS*.

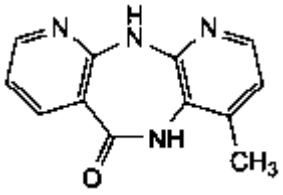
IMPURITIES

Specified impurities *A, B, C.*

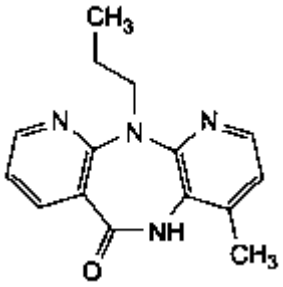
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



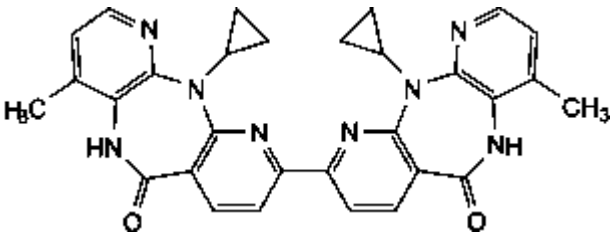
A. 11-ethyl-4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one,



B. 4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one,



C. 4-methyl-11-propyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one,



D. 11,11′-dicyclopropyl-4,4′-dimethyl-5,5′,11,11′-tetrahydro-6*H*,6′*H*-9,9′-bidipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepine-6,6′-dione.

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Nevirapine Oral Suspension

General Notices

Action and use

Non-nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Nevirapine Oral Suspension is a suspension of Nevirapine Hemihydrate in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of nevirapine, $C_{15}H_{14}N_4O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 190 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 25 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: equal volumes of *ethanol* and *water*.

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(1) Shake the oral suspension for 30 seconds and place a volume equivalent to one dose into each dissolution vessel. After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm Nylon filter is suitable). Use the filtered medium, diluted with the dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.0056% w/v of nevirapine.

(2) 1.4% w/v of *nevirapine BPCRS* in solution A. Dilute with the dissolution medium to produce a solution containing 0.0056% w/v of *nevirapine BPCRS*.

(3) 0.5% w/v of *nevirapine BPCRS* and 0.75% w/v of *methyl parahydroxybenzoate* in solution A. Dilute with the dissolution medium to produce a solution containing 0.004% w/v of *nevirapine BPCRS* and 0.006% w/v of *methyl parahydroxybenzoate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

23 volumes of *acetonitrile R1* and 77 volumes of *water R1*.

When the chromatograms are recorded under the prescribed conditions the retention time of nevirapine is about 5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nevirapine and methyl parahydroxybenzoate is at least 5.0.

DETERMINATION OF CONTENT

Calculate the total content of nevirapine, $C_{15}H_{14}N_4O$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{14}N_4O$ in *nevirapine BPCRS*.

LIMITS

The amount of nevirapine released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the oral suspension containing the equivalent of 60 mg of nevirapine in 40 mL of *methanol*, and dilute to 200 mL with *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Dissolve the contents of a vial of *nevirapine for peak identification EPCRS* in 2 mL of *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (3.5 µm) (Zorbax SB-CN is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Solution B: Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 950 mL of *water*, and adjust to pH 3.0 with *orthophosphoric acid*. Dilute to 1000 mL with *water* and filter through a 0.45-µm membrane filter.

Mobile phase A: 3 volumes of *acetonitrile* and 97 volumes of solution B.

Mobile phase B: 24 volumes of *acetonitrile* and 76 volumes of solution B.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-33	100→0	0→100	linear gradient
33-34	0→100	100→0	linear gradient
34-42	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nevirapine (retention time about 23 minutes) are: impurity B, about 0.9; impurity A, about 1.1; impurity C, about 1.2

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and nevirapine is at least 1.7.

the *resolution* between the peaks due to nevirapine and impurity A is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a weighed quantity of the oral suspension containing the equivalent of 60 mg of nevirapine in 40 mL of *methanol*, and dilute to 200 mL with *water*.

(2) 0.25% w/v of *nevirapine BPCRS* in *methanol*. Dilute 3 volumes to 25 volumes with *water*.

(3) Dissolve the contents of a vial of *nevirapine for peak identification EPCRS* in 2 mL of *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and nevirapine is at least 1.7.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of nevirapine, $C_{15}H_{14}N_4O$, weight in volume, using the declared content of $C_{15}H_{14}N_4O$ in *nevirapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nevirapine Hemihydrate.

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Nevirapine Prolonged-release Tablets

General Notices

Nevirapine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Non-nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Nevirapine Prolonged-release Tablets contain Nevirapine. They are formulated so that the active ingredient is released over a period of several hours.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Nevirapine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

Content of nevirapine, $C_{15}H_{14}N_4O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 190 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Nevirapine with 80 mL of *methanol* and dilute to 100 mL with *methanol*. Filter through a 0.45-µm membrane filter and dilute 1 volume of the filtrate to 2 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 1 volume of this solution to 5 volumes with the mobile phase.

(3) Dissolve the contents of a vial of *nevirapine for peak identification EPCRS* in 2 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped amidohexadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-ABZ is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow chromatography to proceed for 4 times the retention time of nevirapine.

MOBILE PHASE

Solution B: Dissolve 2.88 g of *ammonium dihydrogen orthophosphate* in 1000 mL of *water*, adjusted to pH 5.0 with 1M *sodium hydroxide*.

15 volumes of *acetonitrile* and 85 volumes of solution B.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nevirapine (retention time of about 13 minutes) are: impurity B, about 0.7; impurity A, 1.5; impurity C, about 2.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and nevirapine is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Nevirapine with 120 mL of *methanol*. Add 40 mL of *water* and further mix. Dilute to 200 mL with *methanol*, mix and centrifuge. Dilute 1 volume of the supernatant liquid to 50 volumes with *methanol (80%)* and filter through a 0.45-µm membrane filter.

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(2) 0.002% w/v solution of *nevirapine BPCRS* in *methanol (80%)*.

(3) Dissolve the contents of a vial of *nevirapine for peak identification EPCRS* in 2 mL of *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 10°.

(f) Use a detection wavelength of 214 nm.

(g) Inject 20 µL of each solution.

MOBILE PHASE

23 volumes of *acetonitrile R1* and 77 volumes of *water R1*.

When the chromatograms are recorded under the prescribed conditions the retention time of nevirapine is about 4 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and nevirapine is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of nevirapine, $C_{15}H_{14}N_4O$, in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{14}N_4O$ in *nevirapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nevirapine.

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Nevirapine Tablets

General Notices

Action and use

Non-nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Nevirapine Tablets contain Nevirapine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nevirapine, $C_{15}H_{14}N_4O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 25 mg of Nevirapine with 10 mL of *dichloromethane* and filter through a sintered-glass funnel. Using a glass syringe, pass the filtrate through a 0.45-µm PTFE syringe filter and dry the residue at 105° for 1 hour. Triturate the dried residue with 0.2 g of *potassium bromide*. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of nevirapine (*RS 507*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use as the medium 900 mL of a phosphate buffer, at a temperature of 37°, prepared in the following manner. Mix 3.9 mL of *orthophosphoric acid* and 5.73 g of *sodium dihydrogen orthophosphate monohydrate*, and dilute to 1000 mL with *water*. If necessary, adjust the pH to 2.0 using *orthophosphoric acid*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm Nylon filter is suitable). Use the filtered medium, diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.0011% w/v of Nevirapine.

(2) 0.054% w/v of *nevirapine BPCRS* in *ethanol (96%)*. Dilute 1 volume to 50 volumes with dissolution medium.

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(3) Dissolve the contents of a vial of *nevirapine for peak identification EPCRS* in 2 mL of the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Nova-pak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

23 volumes of *acetonitrile R1* and 77 volumes of *water R1*.

When the chromatograms are recorded under the prescribed conditions the retention time of nevirapine is about 4 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and nevirapine is at least 3.0.

DETERMINATION OF CONTENT

Calculate the total content of nevirapine, $C_{15}H_{14}N_4O$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{14}N_4O$ in *nevirapine BPCRS*.

LIMITS

The amount of nevirapine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Nevirapine with 40 mL of *acetonitrile* and 20 mL of the mobile phase. Dilute to 200 mL with the mobile phase and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 1 volume of this solution to 5 volumes with the mobile phase.

(3) Dissolve the contents of a vial of *nevirapine for peak identification EPCRS* in 2 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped amidohexadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-ABZ is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

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(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow chromatography to proceed for 4 times the retention time of nevirapine.

MOBILE PHASE

15 volumes of *acetonitrile* and 85 volumes of a 0.288% w/v solution of *ammonium dihydrogen orthophosphate* previously adjusted to pH 5.0 using *dilute sodium hydroxide solution*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nevirapine (retention time about 13 minutes) are: impurity B, about 0.7; impurity A, 1.5; impurity C, about 2.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and nevirapine is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A.

Solution A: equal volumes of *ethanol* and *water*.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Nevirapine with 150 mL, and dilute to 200 mL. Mix and centrifuge a portion of the solution. Dilute 1 volume of the supernatant liquid to 50 volumes, filter through a membrane filter (nominal pore size 0.45 µm), and use the filtrate.

(2) 0.002% w/v solution of *nevirapine BPCRS*.

(3) Dissolve the contents of a vial of *nevirapine for peak identification EPCRS* in 2 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and nevirapine is at least 3.0.

DETERMINATION OF CONTENT

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Calculate the content of nevirapine, $C_{15}H_{14}N_4O$, in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{14}N_4O_4$ in *nevirapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nevirapine.

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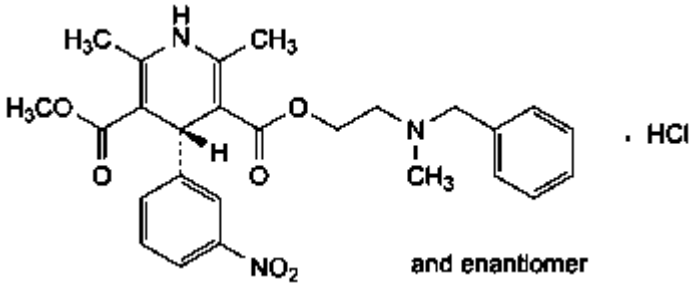
Nicardipine Hydrochloride

General Notices

(Ph. Eur. monograph 2776)



$C_{26}H_{30}ClN_3O_6$ 516.0 *54527-84-3*

Action and use

Calcium channel blocker.

Ph Eur

DEFINITION

2-[Benzyl(methyl)amino]ethyl methyl (4*RS*)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow or pale greenish-yellow, crystalline powder.

Solubility

Slightly soluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *nicardipine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Dissolve 30 mg in 10 mL of *water R* and shake vigorously. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of *nicardipine for system suitability CRS* (containing impurities A, B and C) in 2 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.5 g/L solution of *perchloric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 4 times the retention time of nicardipine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to nicardipine (retention time = about 8 min): impurity B = about 0.5; impurity A = about 0.8; impurity C = about 2.1.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and nicardipine.

Calculation of percentage contents:

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— for each impurity, use the concentration of nicardipine hydrochloride in reference solution (a).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurities A, C*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

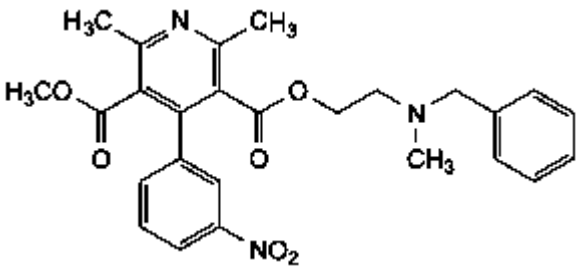
1 mL of *0.1 M sodium hydroxide* is equivalent to 51.60 mg of $C_{26}H_{30}ClN_3O_6$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. 2-[benzyl(methyl)amino]ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate,

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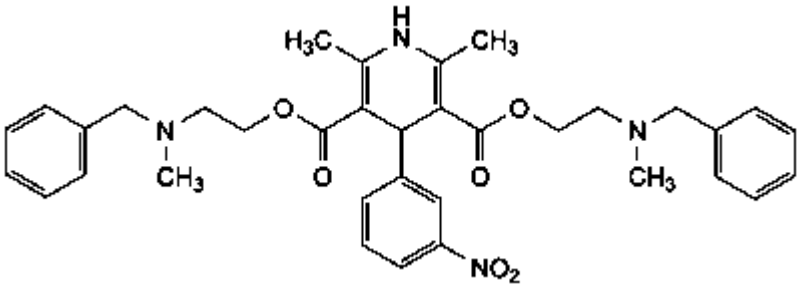
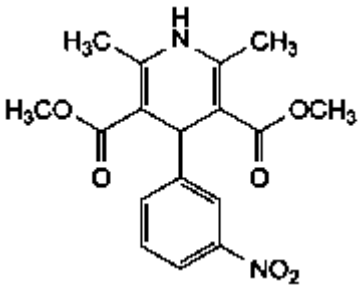


B. bis[2-[benzyl(methyl)amino]ethyl] 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate,



C. dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

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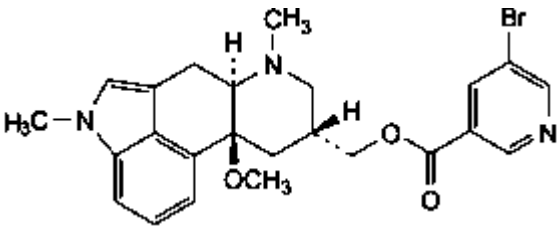
Nicergoline

General Notices

(Ph. Eur. monograph 1998)



$C_{24}H_{26}BrN_3O_3$ 484.4 *27848-84-6*

Action and use

Ergot derivative.

Ph Eur

DEFINITION

[(6a*R*,9*R*,10a*S*)-10a-Methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Fine to granular, white or yellowish powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, C.

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Second identification: A, B, D.

A. Specific optical rotation (2.2.7): + 4.8 to + 5.8 (anhydrous substance).

Dissolve 0.50 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *ethanol (96 per cent) R*.

Spectral range 220-350 nm.

Absorption maximum At 288 nm.

Absorption minimum At 251 nm.

Specific absorbance at the absorption maximum 175 to 185 (anhydrous substance).

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *nicergoline CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *ethanol (96 per cent) R*, evaporate to dryness and record new spectra using the residues.

D. Dissolve 2 mg in 2 mL of *sulfuric acid R*. A blue colour develops.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (2.2.2, *Method II*).

Dissolve 0.5 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 2.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 2 mg of *nicergoline for system suitability CRS* (containing impurities A, B, C, D, F and H) in *acetonitrile R* and dilute to 2 mL with the same solvent.

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Reference solution (c) Dissolve 5.0 mg of *nicergoline impurity D CRS* in *acetonitrile R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 50.0 mL with *acetonitrile R*.

Reference solution (d) Dissolve the contents of a vial of *nicergoline for peak identification CRS* (containing impurity I) in 1 mL of *acetonitrile R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *solution A*: dissolve 34.02 g of *potassium dihydrogen phosphate R* in 930 mL of *water for chromatography R* and dilute to 1000 mL with *water for chromatography R* (buffer solution); dissolve 21.21 g of *tetrabutylammonium hydrogen sulfate R* in 225 mL of the buffer solution and dilute to 250.0 mL with the same solution; adjust to pH 7.5 with a 300 g/L solution of *potassium hydroxide R*;

— *mobile phase A*: mix 2.0 mL of solution A with 300 mL of *acetonitrile R* and 700 mL of *water for chromatography R*;

— *mobile phase B*: mix 2.0 mL of solution A with 300 mL of *water for chromatography R* and 700 mL of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 30	100 → 70	0 → 30
30 - 40	70 → 0	30 → 100
40 - 50	0	100

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 288 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *nicergoline for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, F and H; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity I.

Relative retention With reference to nicergoline (retention time = about 34 min): impurity D = about 0.06; impurity C = about 0.1; impurity B = about 0.6; impurity H = about 0.8; impurity A = about 0.96; impurity F = about 1.1; impurity I = about 1.2.

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System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and nicergoline.

Calculation of percentage contents:

— for impurity D, use the concentration of impurity D in reference solution (c);

— for impurities other than D, use the concentration of nicergoline in reference solution (a).

Limits:

— *impurity B*: maximum 0.8 per cent;

— *impurity A*: maximum 0.5 per cent;

— *impurity H*: maximum 0.3 per cent;

— *impurities C, D, F, I*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.2 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *acetone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Titrate to the 1st point of inflexion.

1 mL of *0.1 M perchloric acid* is equivalent to 48.44 mg of $C_{24}H_{26}BrN_3O_3$.

IMPURITIES

Specified impurities *A, B, C, D, F, H, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, G, J.*

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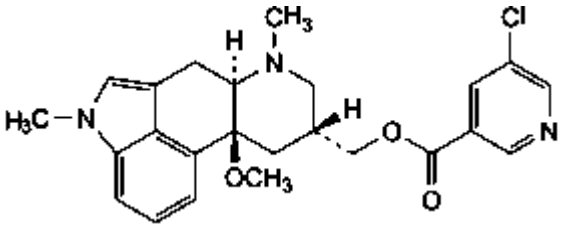
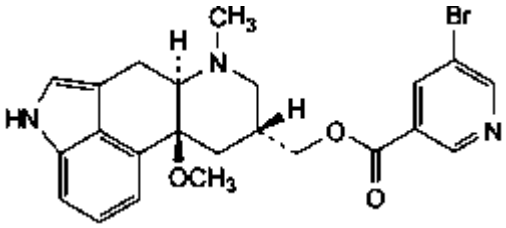
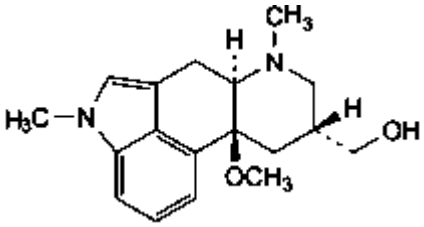


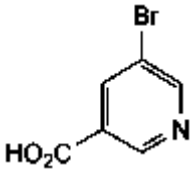
A. [(6a*R*,9*R*,10a*S*)-10a-methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-chloropyridine-3-carboxylate (chloronicergoline),



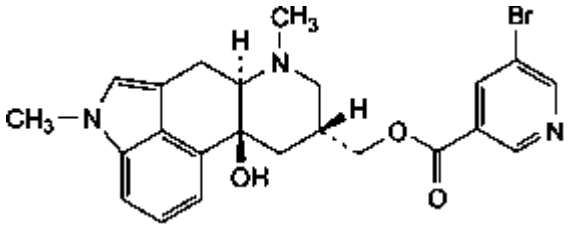
B. [(6a*R*,9*R*,10a*S*)-10a-methoxy-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate (1-desmethylnicergoline),



C. [(6a*R*,9*R*,10a*S*)-10a-methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methanol,



D. 5-bromopyridine-3-carboxylic acid,



E. [(6a*R*,9*R*,10a*S*)-10a-hydroxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate,

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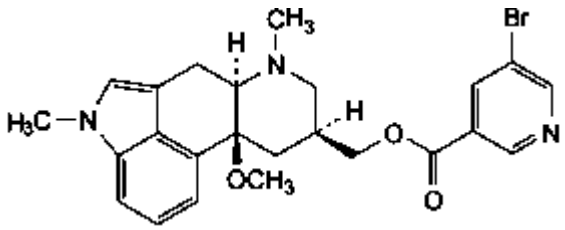
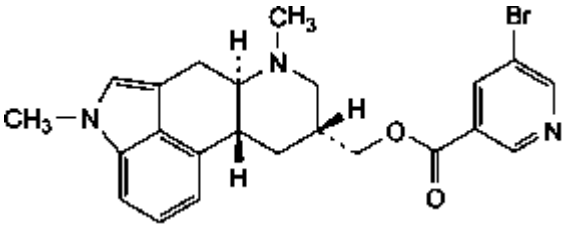
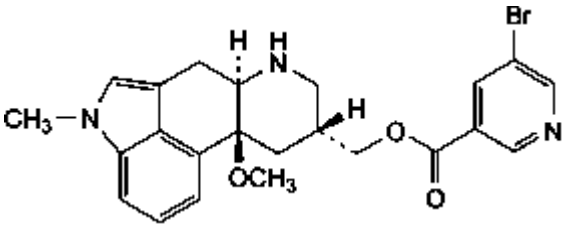


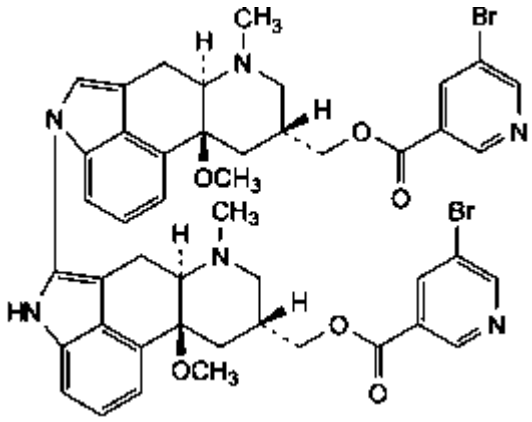
F. [(6a*R*,9*S*,10a*S*)-10a-methoxy-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate (isonicergoline),



G. [(6a*R*,9*R*,10a*R*)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate,



H. [(6a*R*,9*R*,10a*S*)-10a-methoxy-4-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]methyl 5-bromopyridine-3-carboxylate (6-desmethylnicergoline),



I. [(6a*R*,6a′*R*,9*R*,9′*R*,10a*S*,10a′*S*)-9′-[[[(5-bromopyridin-3-yl)carbonyl]oxy]methyl]-10a,10a′-dimethoxy-7,7′-dimethyl-4′,6′,6a,6a′,7,7′,8,8′,9,9′,10,10′,10a,10a′-tetradecahydro-6*H*-4,5′-biindolo[4,3-*fg*]quinoline-9-yl]methyl 5-bromopyridine-3-carboxylate,

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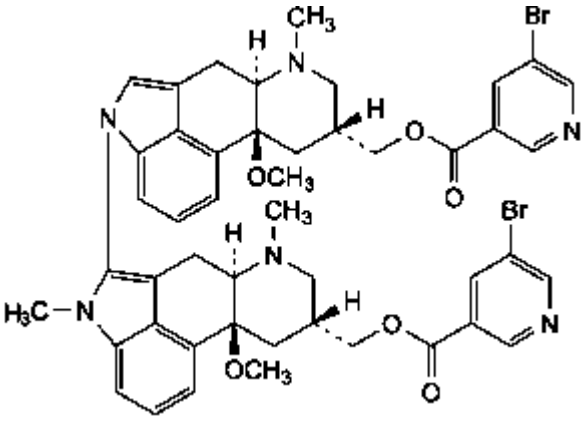

J. [(6a*R*,6a′*R*,9*R*,9′*R*,10a*S*,10a′*S*)-9′-[[[(5-bromopyridin-3-yl)carbonyl]oxy]methyl]-10a,10a′-dimethoxy-4′,7,7′-trimethyl-4′,6′,6a,6a′,7,7′,8,8′,9,9′,10,10′,10a,10a′-tetradecahydro-6*H*-4,5′-biindolo[4,3-*fg*]quinoline-9-yl]methyl 5-bromopyridine-3-carboxylate.

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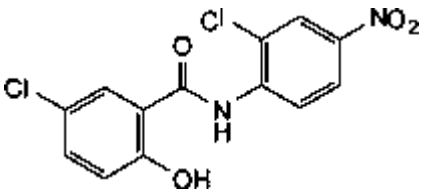
Niclosamide

General Notices

Anhydrous Niclosamide

(Ph. Eur. monograph 0679)



$C_{13}H_8Cl_2N_2O_4$ 327.1 *50-65-7*

Action and use

Anthelminthic.

Preparation

Niclosamide Tablets

Ph Eur

DEFINITION

5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellowish-white or yellowish, fine crystals.

Solubility

Practically insoluble in water, sparingly soluble in acetone, slightly soluble in anhydrous ethanol.

IDENTIFICATION

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First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 227 °C to 232 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs prepared using about 0.5 mg of substance and 0.3 g of *potassium bromide R*.

Comparison *anhydrous niclosamide CRS*.

C. To 50 mg add 5 mL of *1 M hydrochloric acid* and 0.1 g of *zinc powder R*, heat in a water-bath for 10 min, cool and filter. To the filtrate add 1 mL of a 5 g/L solution of *sodium nitrite R* and allow to stand for 3 min; add 2 mL of a 20 g/L solution of *ammonium sulfamate R*, shake, allow to stand for 3 min and add 2 mL of a 5 g/L solution of *naphthylethylenediamine dihydrochloride R*. A violet colour is produced.

D. Heat the substance on a copper wire in a non-luminous flame. The flame becomes green.

E. Loss on drying (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R*, heating gently, cool and dilute to 50.0 mL with the same solvent.

Reference solution Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 20.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mixture of equal volumes of *acetonitrile R* and a solution containing 2 g/L of *potassium dihydrogen phosphate R*, 1 g/L of *disodium hydrogen phosphate dodecahydrate R* and 2 g/L of *tetrabutylammonium hydrogen sulfate R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time Twice the retention time of niclosamide.

Limits:

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— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.005 per cent).

5-Chlorosalicylic acid

Maximum 60 ppm.

Test solution To 1.0 g add 15 mL of *water R*, boil for 2 min, cool, filter through a membrane filter (nominal pore size 0.45 µm), wash the filter and dilute the combined filtrate and washings to 20.0 mL with *water R*.

Reference solution Dissolve 30 mg of *5-chlorosalicylic acid R* in 20 mL of *methanol R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

To 10.0 mL of the test solution and to 10.0 mL of the reference solution add separately 0.1 mL of *ferric chloride solution R2*. Any violet colour in the test solution is not more intense than that in the reference solution.

2-Chloro-4-nitroaniline

Maximum 100 ppm.

Test solution To 0.250 g add 5 mL of *methanol R*, heat to boiling, cool, add 45 mL of *1 M hydrochloric acid*, heat again to boiling, cool, filter and dilute the filtrate to 50.0 mL with *1 M hydrochloric acid*.

Reference solution Dissolve 50 mg of *2-chloro-4-nitroaniline R* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 20.0 mL with *1 M hydrochloric acid*.

To 10.0 mL of the test solution and to 10.0 mL of the reference solution add separately 0.5 mL of a 5 g/L solution of *sodium nitrite R* and allow to stand for 3 min. Add 1 mL of a 20 g/L solution of *ammonium sulfamate R*, shake, allow to stand for 3 min and add 1 mL of a 5 g/L solution of *naphthylethylenediamine dihydrochloride R*. Any pinkish-violet colour in the test solution is not more intense than that in the reference solution.

Chlorides (*2.4.4*)

Maximum 500 ppm.

To 2 g add a mixture of 1.2 mL of *acetic acid R* and 40 mL of *water R*, boil for 2 min, cool and filter. Dilute 2 mL of the filtrate to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.3000 g in 80 mL of a mixture of equal volumes of *acetone R* and *methanol R*. Titrate with 0.1 M tetrabutylammonium hydroxide, determining the end-point potentiometrically (*2.2.20*).

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 32.71 mg of $C_{13}H_8Cl_2N_2O_4$.

STORAGE

In an airtight container, protected from light.

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Niclosamide Chewable Tablets

General Notices

Niclosamide Tablets

Action and use

Antihelminthic.

DEFINITION

Niclosamide Chewable Tablets contain Niclosamide or Niclosamide Monohydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous niclosamide, $C_{13}H_8Cl_2N_2O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Heat a quantity of the powdered tablets containing 0.5 g of anhydrous niclosamide with 25 mL of hot *ethanol (96%)*, filter while hot and evaporate the filtrate to dryness on a water bath. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of niclosamide *(RS 245)*. If the spectra are not concordant heat a suitable quantity of the residue at 120° for 1 hour and prepare a new spectrum.

TESTS

2-Chloro-4-nitroaniline

Boil a quantity of the powdered tablets containing 0.10 g of anhydrous niclosamide with 20 mL of *methanol* for 2 minutes, cool, add sufficient 1M *hydrochloric acid* to produce 50 mL and filter. To 10 mL of the filtrate add 0.5 mL of a 0.5% w/v solution of *sodium nitrite* and allow to stand for 10 minutes. Add 1 mL of a 2% w/v solution of *ammonium sulfamate*, shake, allow to stand for 10 minutes and add 1 mL of a 0.5% w/v solution of N-*(1-naphthyl)ethylenediamine dihydrochloride*. Any colour produced is not more intense than that obtained by treating 20 mL of a solution in *methanol* containing 10 µg of *2-chloro-4-nitroaniline* at the same time and in the same manner, beginning at the words ‘add sufficient 1M *hydrochloric acid*…’ (100 ppm).

5-Chlorosalicylic acid

Boil a quantity of the powdered tablets containing 0.50 g of anhydrous niclosamide with 10 mL of *water* for 2 minutes, cool, filter through a membrane filter (pore size 0.45 µm is suitable) (solution A).

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Dissolve 30 mg of *5-chlorosalicylic acid* in 20 mL *methanol* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 100 volumes with *water* (solution B).

Separately add 0.1 mL of *iron(III) chloride solution R1* to 10 mL of solution A and to 10 mL of solution B. Any red or violet colour produced in solution A is not more intense than that obtained in solution B (60 ppm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of anhydrous niclosamide with 80 mL of *methanol* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with *acetonitrile*.
(3) Dilute 1 volume of solution (2) to 10 volumes with *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of a solution containing 0.2% w/v of *potassium dihydrogen orthophosphate*, 0.2% w/v of *tetrabutylammonium hydrogen sulfate* and 0.1% w/v of *disodium hydrogen orthophosphate*.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out Method II for *non-aqueous titration*, Appendix VIII A, using a quantity of the powdered tablets containing 0.3 g of anhydrous niclosamide dissolved in 60 mL of *dimethylformamide*, 0.1M *tetrabutylammonium hydroxide VS* as titrant and determining the end point potentiometrically. Each mL of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 32.71 mg of $C_{13}H_8Cl_2N_2O_4$.

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STORAGE

Niclosamide Tablets should be protected from light.

LABELLING

The label states that the tablets should be chewed before swallowing.

When the active ingredient is Niclosamide Monohydrate the quantity is stated in terms of the equivalent amount of anhydrous niclosamide.

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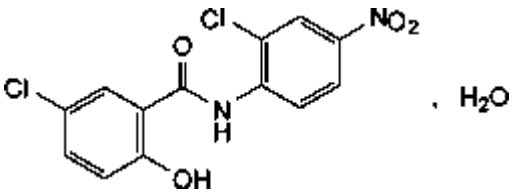
Niclosamide Monohydrate

General Notices

(Ph. Eur. monograph 0680)



$C_{13}H_8Cl_2N_2O_4,H_2O$ 345.1

Action and use

Anthelminthic.

Preparation

Niclosamide Tablets

Ph Eur

DEFINITION

5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide monohydrate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellowish, fine crystals.

Solubility

Practically insoluble in water, sparingly soluble in acetone, slightly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: B, E.

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Second identification: A, C, D, E.

A. Melting point (2.2.14): 227 °C to 232 °C, determined after drying at 100-105 °C for 4 h.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Dry the substance to be examined at 100-105 °C for 4 h and examine as discs prepared using about 0.5 mg of substance and 0.3 g of *potassium bromide R*.

Comparison *anhydrous niclosamide CRS*.

C. To 50 mg add 5 mL of *1 M hydrochloric acid* and 0.1 g of *zinc powder R*, heat in a water-bath for 10 min, cool and filter. To the filtrate add 1 mL of a 5 g/L solution of *sodium nitrite R* and allow to stand for 3 min; add 2 mL of a 20 g/L solution of *ammonium sulfamate R*, shake, allow to stand for 3 min and add 2 mL of a 5 g/L solution of *naphthylethylenediamine dihydrochloride R*. A violet colour is produced.

D. Heat the substance on a copper wire in a non-luminous flame. The flame becomes green.

E. Loss on drying (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R*, heating gently, cool and dilute to 50.0 mL with the same solvent.

Reference solution Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 20.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mixture of equal volumes of *acetonitrile R* and a solution containing 2 g/L of *potassium dihydrogen phosphate R*, 1 g/L of *disodium hydrogen phosphate dodecahydrate R* and 2 g/L of *tetrabutylammonium hydrogen sulfate R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time Twice the retention time of niclosamide.

Limits:

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent);

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— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.005 per cent).

5-Chlorosalicylic acid

Maximum 60 ppm.

Test solution To 1.0 g add 15 mL of *water R*, boil for 2 min, cool, filter through a membrane filter (nominal pore size 0.45 µm), wash the filter and dilute the combined filtrate and washings to 20.0 mL with *water R*.

Reference solution Dissolve 30 mg of *5-chlorosalicylic acid R* in 20 mL of *methanol R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

To 10.0 mL of the test solution and to 10.0 mL of the reference solution add separately 0.1 mL of *ferric chloride solution R2*. Any violet colour produced in the test solution is not more intense than that in the reference solution.

2-Chloro-4-nitroaniline

Maximum 100 ppm.

Test solution To 0.250 g add 5 mL of *methanol R*, heat to boiling, cool, add 45 mL of *1 M hydrochloric acid*, heat again to boiling, cool, filter and dilute the filtrate to 50.0 mL with *1 M hydrochloric acid*.

Reference solution Dissolve 50 mg of *2-chloro-4-nitroaniline R* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 20.0 mL with *1 M hydrochloric acid*.

To 10.0 mL of the test solution and to 10.0 mL of the reference solution add separately 0.5 mL of a 5 g/L solution of *sodium nitrite R* and allow to stand for 3 min. Add 1 mL of a 20 g/L solution of *ammonium sulfamate R*, shake, allow to stand for 3 min and add 1 mL of a 5 g/L solution of *naphthylethylenediamine dihydrochloride R*. Any pinkish-violet colour produced in the test solution is not more intense than that in the reference solution.

Chlorides (*2.4.4*)

Maximum 500 ppm.

To 2 g add a mixture of 1.2 mL of *acetic acid R* and 40 mL of *water R*, boil for 2 min, cool and filter. Dilute 2 mL of the filtrate to 15 mL with *water R*.

Loss on drying (*2.2.32*)

4.5 per cent to 6.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.3000 g in 80 mL of a mixture of equal volumes of *acetone R* and *methanol R*. Titrate with 0.1 M tetrabutylammonium hydroxide, determining the end-point potentiometrically (*2.2.20*).

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 32.71 mg of $C_{13}H_8Cl_2N_2O_4$.

STORAGE

Protected from light.

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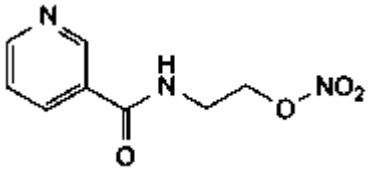
Nicorandil

General Notices

(Ph. Eur. monograph 2332)



$C_8H_9N_3O_4$ 211.2 *65141-46-0*

Action and use

Potassium channel opener.

Preparation

Nicorandil Tablets

Ph Eur

DEFINITION

2-[(Pyridin-3-ylcarbonyl)amino]ethyl nitrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *nicorandil CRS*.

TESTS

pH (*2.2.3*)

5.5 to 7.0.

Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *nicorandil impurity A CRS* in the mobile phase using sonication and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm).

Mobile phase *trifluoroacetic acid R*, *triethylamine R*, *tetrahydrofuran R*, *water R* (3:5:10:982 *V/V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 1.5 times the retention time of nicorandil.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to nicorandil (retention time = about 19 min): impurity A = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity A and nicorandil.

Calculation of percentage contents:

— for each impurity, use the concentration of nicorandil in reference solution (b).

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Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Sulfates (*2.4.13*)

Maximum 100 ppm.

Dissolve 5.000 g in 30 mL of *ethanol (50 per cent V/V) R*, add 1 mL of *dilute hydrochloric acid R* and dilute to 50.0 mL with *distilled water R*.

Water (*2.5.32*)

Maximum 0.5 per cent.

Dissolve 0.300 g in a suitable solvent and dilute to 1.0 mL with the same solvent. Inject 0.400 mL of the solution through the septum.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

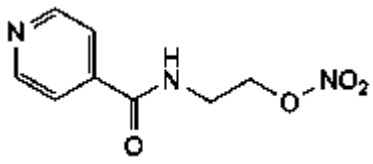
1 mL of *0.1 M perchloric acid* is equivalent to 21.12 mg of $C_8H_9N_3O_4$.

STORAGE

At a temperature of 2 °C to 8 °C.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



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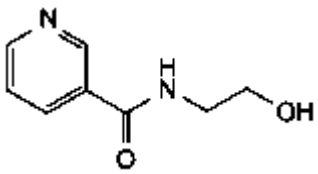
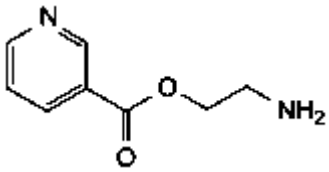
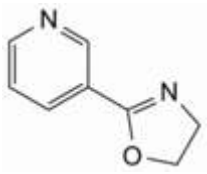
A. 2-[(pyridin-4-ylcarbonyl)amino]ethyl nitrate,



B. *N*-(2-hydroxyethyl)pyridine-3-carboxamide,



C. 2-aminoethyl pyridine-3-carboxylate,



D. 3-(4,5-dihydro-1,3-oxazol-2-yl)pyridine.

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Nicorandil Tablets

General Notices

Action and use

Potassium channel opener; vasodilator.

DEFINITION

Nicorandil Tablets contain Nicorandil.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nicorandil, $C_8H_9N_3O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

Solvent A: 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

(1) Dissolve a quantity of the powdered tablets containing 10 mg of Nicorandil in solvent A and mix with the aid of ultrasound. Add sufficient solvent A to produce a solution containing 0.1% w/v of Nicorandil and filter.

(2) 0.1% w/v of *nicorandil BPCRS* in *methanol*.

(3) 0.1% w/v each of *nicorandil BPCRS* and *nicotinamide BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *methanol*, 4 volumes of *dichloromethane* and 5 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes, withdraw a sample of the medium and filter (a 0.45-µm PTFE filter is suitable). Use the filtrate, diluted with dissolution medium if necessary, to give a solution expected to contain 0.0011% w/v of Nicorandil.
(2) 0.0011% w/v of *nicorandil BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC pack ODS AQ is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 40 µL of each solution.

MOBILE PHASE

Add 1.5 volumes of *trifluoroacetic acid* to 965 volumes of *water*. Separately mix 2 volumes of *triethylamine*, 10 volumes of *tetrahydrofuran* and 25 volumes of *methanol*. Mix the 2 solutions together.

When the chromatograms are recorded under the prescribed conditions the retention time of nicorandil is about 11 minutes.

DETERMINATION OF CONTENT

Calculate the total content of nicorandil, $C_8H_9N_3O_4$, in the medium from the chromatograms obtained and using the declared content of $C_8H_9N_3O_4$ in *nicorandil BPCRS*.

LIMITS

The amount of nicorandil released is not less than 80% (Q) of the stated amount.

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared immediately before use.

Solution A: 7 volumes of *methanol* and 93 volumes of *water*.

(1) To a quantity of the powdered tablets containing 0.1 g of Nicorandil, add 4 mL of *water* and 28 mL of *methanol* and shake. Add sufficient *water* to produce 100 mL and filter (a 0.45-µm membrane filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.0004% w/v of *nicorandil impurity standard BPCRS* in solution A.

(4) Heat approximately 40 mg of *nicorandil BPCRS* for 2 hours at 70°. Allow to cool and dissolve a quantity of the material in sufficient solution A to produce a 0.8% w/v solution (generation of impurities 2, D, 4, 5 and 6).

(5) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC pack ODS AQ is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Add 1.5 volumes of *trifluoroacetic acid* to 965 volumes of *water*. Separately mix 2 volumes of *triethylamine*, 10 volumes of *tetrahydrofuran* and 25 volumes of *methanol*. Mix the 2 solutions together.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-45	100	0	isocratic
45-80	100→75	0→25	linear gradient
80-82	75→100	25→0	linear gradient
82-92	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nicorandil (retention time about 14 minutes) are: impurity 1, about 0.27; impurity B (nicorandil amide), about 0.31; impurity 2, about 0.36; impurity D (2-(3-pyridyl) 2-oxazoline), about 0.5; impurity 3, about 0.7; impurity 4, about 1.1; impurity 5, about 1.3 and impurity 6, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless:

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in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 1 (nicotinic acid) and impurity B (nicorandil amide) is at least 1.5;

in the chromatogram obtained with solution (4), the *peak-to-valley ratio* is at least 4.5, where *Hp* is the height above the baseline of the peak due to impurity 4 and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to nicorandil.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity 4 using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity 4 by a correction factor of 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity 4 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A: 7 volumes of *methanol* and 93 volumes of *water*.
(1) To a quantity of the powdered tablets containing 0.1 g of Nicorandil, add 4 mL of *water* and 28 mL of *methanol* and shake. Add sufficient *water* to produce 100 mL and filter (a 0.45-µm PTFE filter is suitable). Dilute 1 volume to 20 volumes with *water*.
(2) 0.005% w/v of *nicorandil BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_9N_3O_4$ in the tablets using the declared content of $C_8H_9N_3O_4$ in *nicorandil BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and D listed under *Nicorandil* and:

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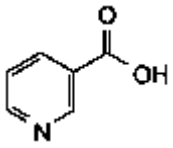
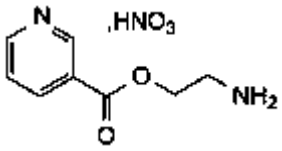
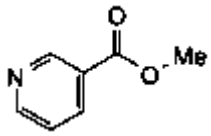


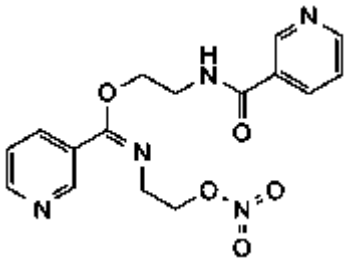
1. pyridine-3-carboxylic acid (nicotinic acid)



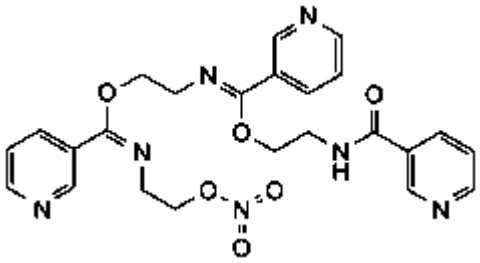
2. 2-aminoethyl pyridine-3-carboxylate nitrate (nicorandil nitrate)



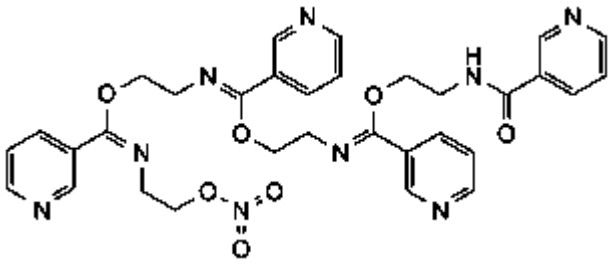
3. methyl pyridine-3-carboxylate (methyl nicotinate)



4. *N*-[2-({*N*-[2-(nitro-oxy)ethyl]pyridin-3-carboximidoyl}oxy)ethyl]pyridine-3-carboxamide (nicorandil dimer)



5. *N*-{2-[{*N*-[2-({*N*-[2-(nitro-oxy)ethyl]pyridin-3-carboximidoyl}oxy)ethyl]pyridin-3-carboximidoyl}oxy]ethyl}pyridine-3-carboxamide (nicorandil trimer)



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6. *N*-{2-[(*N*-{2-[{*N*-[2-({*N*-[2-(nitro-oxy)ethyl]pyridin-3-carboximidoyl}oxy)ethyl]pyridin-3-carboximidoyl}oxy]ethyl}pyridin-3-carboximidoyl)oxy]ethyl}pyridine-3-carboxamide (nicorandil tetramer)

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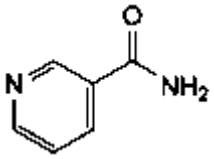
Nicotinamide

General Notices

(Ph. Eur. monograph 0047)



$C_6H_6N_2O$ 122.1 *98-92-0*

Action and use

Component of vitamin B.

Preparations

Nicotinamide Tablets

Vitamins B and C Injection

Ph Eur

DEFINITION

Pyridine-3-carboxamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water and in anhydrous ethanol, slightly soluble in methylene chloride.

IDENTIFICATION

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First identification: B.

Second identification: A, C.

A. Melting point (2.2.14): 128 °C to 131 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *nicotinamide CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in a mixture of equal volumes of *ethanol (96 per cent) R* and *water R* and dilute to 5.0 mL with the same mixture of solvents.

Reference solution Dissolve 5 mg of *nicotinamide CRS* in a mixture of equal volumes of *ethanol (96 per cent) R* and *water R* and dilute to 5.0 mL with the same mixture of solvents.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *ethanol (96 per cent) R*, *methylene chloride R* (4:45:48 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

pH (2.2.3)

6.0 to 7.5 for solution S.

Related substances

Liquid chromatography (2.2.29).

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Test solution Dissolve 0.150 g of the substance to be examined in mobile phase A and dilute to 150.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *isonicotinamide R* (impurity D) in the test solution and dilute to 100.0 mL with the test solution. Dilute 1.0 mL of this solution to 25.0 mL with the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: mix 5.0 mL of *dilute acetic acid R* and 900 mL of *water for chromatography R*, then add 30 mL of *dilute ammonia R3* and 15 mL of *acetonitrile R*; dilute to 1 L with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*, mobile phase A (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	98	2
2 - 16	98 → 0	2 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 264 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to nicotinamide (retention time = about 7 min): impurity D = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity D and nicotinamide.

Calculation of percentage contents:

— for each impurity, use the concentration of nicotinamide in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

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— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* for 18 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

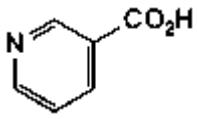
ASSAY

Dissolve 0.100 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

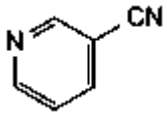
1 mL of *0.1 M perchloric acid* is equivalent to 12.21 mg of $C_6H_6N_2O$.

IMPURITIES

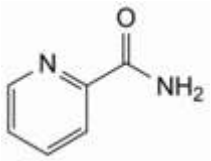
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E.



A. pyridine-3-carboxylic acid (nicotinic acid),



B. pyridine-3-carbonitrile,



C. pyridine-2-carboxamide (picolinamide),

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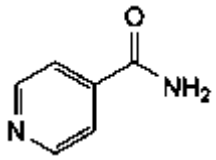
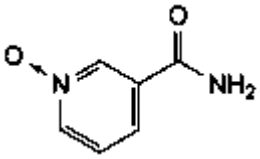


D. pyridine-4-carboxamide (isonicotinamide),



E. pyridine-3-carboxamide 1-oxide (nicotinamide *N*-oxide).

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Nicotinamide Tablets

General Notices

Action and use

Component of vitamin B.

DEFINITION

Nicotinamide Tablets contain Nicotinamide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nicotinamide, $C_6H_6N_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Nicotinamide with 25 mL of *absolute ethanol* for 15 minutes, filter and evaporate the filtrate to dryness on a water bath. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of nicotinamide *(RS 246)*.

B. The *light absorption* of the solution obtained in the Assay, Appendix II B, in the range 230 to 350 nm exhibits a maximum only at 262 nm and two shoulders, at 258 nm and 269 nm.

C. Shake a quantity of the powdered tablets containing 50 mg of Nicotinamide with 50 mL of *water* and filter. To 2 mL of the filtrate add 2 mL of *cyanogen bromide solution* and 3 mL of a 2.5% v/v solution of *aniline* and shake. A yellow colour is produced.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Nicotinamide with 15 mL of *absolute ethanol*, filter, evaporate to dryness on a water bath and dissolve the residue as completely as possible in 1 mL of *absolute ethanol*.

(2) Dilute 1 volume of solution (1) to 400 volumes with *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

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(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *water*, 45 volumes of *ethanol (96%)* and 48 volumes of *chloroform*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 50 mg of Nicotinamide with 50 mL of *ethanol (96%)*, dilute to 100 mL with *ethanol (96%)* and filter. Dilute 5 mL of the filtrate to 100 mL with *ethanol (96%)* and measure the *absorbance* of the resulting solution at the maximum at 262 nm, Appendix II B. Calculate the content of $C_6H_6N_2O$ taking 241 as the value of A(1%, 1 cm) at the maximum at 262 nm.

STORAGE

Nicotinamide Tablets should be protected from light.

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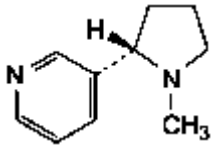
Nicotine

General Notices

(Ph. Eur. monograph 1452)



$C_{10}H_{14}N_2$ 162.2 *54-11-5*

Action and use

Aid to smoking cessation.

Preparations

Nicotine Inhalation Cartridges

Nicotine Nasal Spray

Nicotine Sublingual Tablets

Nicotine Transdermal Patches

Ph Eur

DEFINITION

3-[(2*S*)-1-Methylpyrrolidin-2-yl]pyridine.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Colourless or brownish viscous liquid, volatile, hygroscopic.

Solubility

Soluble in water, miscible with anhydrous ethanol.

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IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of nicotine*.

TESTS

Appearance of solution

Dissolve 1.0 g in *water R* and dilute to 10 mL with the same solvent. The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5, BY_5 or R_5 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

-140 to -152.

Dissolve 1.00 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *nicotine for system suitability CRS* (containing impurities A, B, C, D, E, F and G) in 1.0 mL of *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm).

Mobile phase:

— *mobile phase A*: to 900 mL of *water R*, add 25 mL of a 60 g/L solution of *acetic acid R*, then add 6 mL of *concentrated ammonia R1*. Adjust to pH 10.0 with *dilute ammonia R2* or *dilute acetic acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
3 - 3.01	100 → 95	0 → 5
3.01 - 28	95 → 74	5 → 26
28 - 32	74 → 60	26 → 40

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *nicotine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, F and G.

Relative retention With reference to nicotine (retention time = about 17.8 min): impurity E = about 0.3; impurity C = about 0.55; impurity F = about 0.7; impurity A = about 0.8; impurity D = about 0.86; impurity G = about 0.9; impurity B = about 1.6.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity G and nicotine.

Limits:

— *impurities A, B, C, D, E, F, G*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

ASSAY

Dissolve 60.0 mg in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 8.11 mg of $C_{10}H_{14}N_2$.

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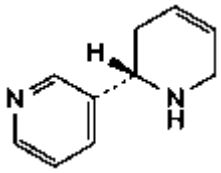
STORAGE

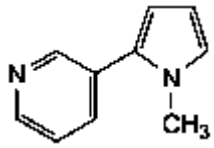
Under nitrogen, in an airtight container, protected from light.

IMPURITIES

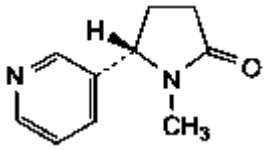
Specified impurities *A, B, C, D, E, F, G.*



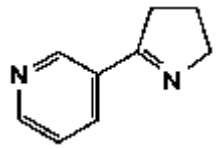
A. (2*S*)-1,2,3,6-tetrahydro-2,3′-bipyridyl (anatabine),



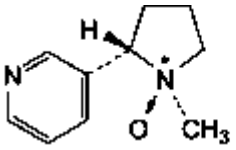
B. 3-(1-methyl-1*H*-pyrrol-2-yl)pyridine (β-nicotyrine),



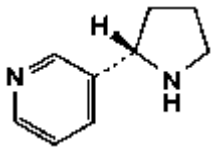
C. (5*S*)-1-methyl-5-(pyridin-3-yl)pyrrolidin-2-one (cotinine),



D. 3-(4,5-dihydro-3*H*-pyrrol-2-yl)pyridine (myosmine),



E. (1*RS*,2*S*)-1-methyl-2-(pyridin-3-yl)pyrrolidine 1-oxide (nicotine *N*′-oxide),



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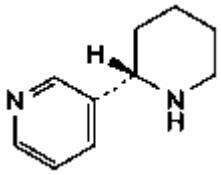
F. 3-[(2*S*)-pyrrolidin-2-yl]pyridine (nornicotine),



G. 3-[(2*S*)-piperidin-2-yl]pyridine (anabasine).

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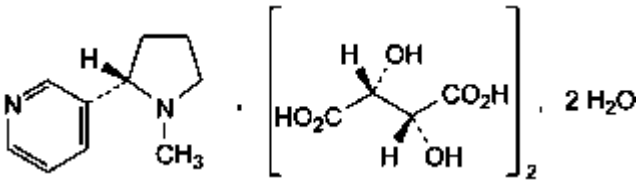
Nicotine Ditartrate Dihydrate

General Notices

(Ph. Eur. monograph 2599)



$C_{18}H_{26}N_2O_{12},2H_2O$ 498.4 *6019-06-3*

Action and use

Aid to smoking cessation.

Ph Eur

DEFINITION

3-[(2*S*)-1-Methylpyrrolidin-2-yl]pyridine bis[(2*R*,3*R*)-2,3-dihydroxybutanedioate] dihydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Soluble in water and in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *nicotine ditartrate dihydrate CRS*.

TESTS

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pH (*2.2.3*)

3.0 to 3.4.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 21.0 to + 23.0.

Dissolve 0.25 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 60 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *nicotine for system suitability CRS* (containing impurities A, B, C, D, E, F and G) in 1.0 mL of *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm).

Mobile phase:

— *mobile phase A*: to 900 mL of *water R* add 25 mL of a 60 g/L solution of *acetic acid R* and 6 mL of *concentrated ammonia R1*; adjust to pH 10.0 with *dilute ammonia R2* or *dilute acetic acid R* and dilute to 1000.0 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 3.01	100 → 95	0 → 5
3.01 - 28	95 → 74	5 → 26
28 - 32	74 → 60	26 → 40

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

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Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *nicotine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, F and G.

Relative retention With reference to nicotine (retention time = about 17.8 min): impurity E = about 0.3; impurity C = about 0.55; impurity F = about 0.7; impurity A = about 0.8; impurity D = about 0.86; impurity G = about 0.9; impurity B = about 1.6.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity G and nicotine.

Limits:

— *impurities A, B, C, D, E, F, G*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

6.5 per cent to 8.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 23.12 mg of $C_{18}H_{26}N_2O_{12}$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

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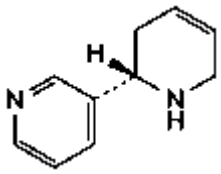
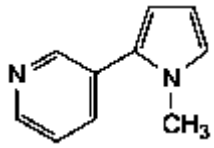
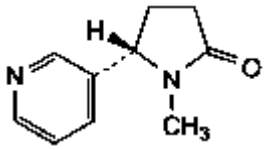


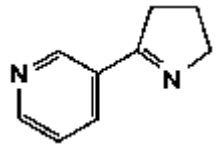
A. (2*S*)-1,2,3,6-tetrahydro-2,3′-bipyridyl (anatabine),



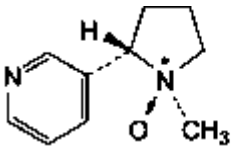
B. 3-(1-methyl-1*H*-pyrrol-2-yl)pyridine (β-nicotyrine),



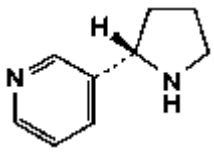
C. (5*S*)-1-methyl-5-(pyridin-3-yl)pyrrolidin-2-one (cotinine),



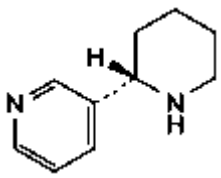
D. 3-(4,5-dihydro-3*H*-pyrrol-2-yl)pyridine (myosmine),



E. (1*RS*,2*S*)-1-methyl-2-(pyridin-3-yl)pyrrolidine 1-oxide (nicotine *N*′-oxide),



F. 3-[(2*S*)-pyrrolidin-2-yl]pyridine (nornicotine),



G. 3-[(2*S*)-piperidin-2-yl]pyridine (anabasine).

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Nicotine Inhalation Cartridges

General Notices

Action and use

Central nervous system stimulant; nicotine replacement therapy.

DEFINITION

Nicotine Inhalation Cartridges are nicotine-impregnated plugs for use with a suitable mouthpiece.

The inhalation cartridges comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of nicotine, $C_{10}H_{14}N_2$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

To a quantity of cartridges containing 20 mg of Nicotine add 10 mL of *chloroform*, extract with the aid of ultrasound, centrifuge for 10 minutes and filter through a 0.7-µm glass filter. Cool the mixture, add two 3-mL quantities of 0.5M *hydrochloric acid* and mix carefully. Centrifuge for 10 minutes. Transfer 5 mL of the aqueous layer to a separating funnel and add sufficient 0.5M *sodium hydroxide* to obtain a pH of 10.5, add 3 mL of *chloroform,* shake and retain the chloroform layer. The *infrared absorption spectrum* of the solution, Appendix II A, is concordant with the *reference spectrum* of nicotine *(RS 452)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) To a quantity of cartridges containing 20 mg of Nicotine add 50 mL of solvent A, extract with the aid of ultrasound and filter through a 0.7-µm glass filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 10 volumes.
(4) 0.04% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XBridge is suitable) fitted with a guard column (3 cm × 4.6 mm) packed with the same material.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Add 25 volumes of 1M *acetic acid* to 1000 volumes of *water*, add 6.2 volumes of 18M *ammonia* and adjust the pH to 10 with 18M *ammonia*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100→95	0→5	linear gradient
3-32	95→60	5→40	linear gradient
32-37	60→100	40→0	linear gradient
37-45	100	0	re-equilibration

In the chromatogram obtained with solution (4):

identify the peaks due to cotinine, myosmine, *cis*-nicotine-1′-oxide and *trans*-nicotine-1′-oxide.

In the chromatogram obtained with solution (1):

identify any peak corresponding to *cis*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5;

identify any peak corresponding to *trans*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to cotinine and *trans*-nicotine-1′-oxide is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to cotinine is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

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the area of any peak corresponding to myosmine is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to *cis*-nicotine-1′-oxide is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

the area of any peak corresponding to *trans*-nicotine-1′-oxide is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0 %);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) To a quantity of cartridges containing 20 mg of Nicotine add 50 mL of solvent A and mix. Dilute 1 volume of the resulting solution to 10 volumes.
(2) 0.0124% w/v of *nicotine ditartrate dihydrate BPCRS*.
(3) 0.004% w/v of *nicotine impurity standard BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cotinine and *trans*-nicotine-1′-oxide is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of nicotine, $C_{10}H_{14}N_2$, in the cartridges using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*. Each mg of $C_{10}H_{14}N_2$ is equivalent to 3.074 mg of $C_{10}H_{14}N_2,C_8H_{12}O_{12},2H_2O$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nicotine.

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Nicotine Nasal Spray

General Notices

Action and use

Central nervous system stimulant; nicotine replacement therapy.

DEFINITION

Nicotine Nasal Spray is a solution of Nicotine containing suitable buffering agents in a suitable container fitted with a suitable nasal delivery system.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of nicotine, $C_{10}H_{14}N_2$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

CHARACTERISTICS

Colourless or brownish solution.

IDENTIFICATION

To a volume of the nasal spray containing 20 mg of Nicotine add 5 mL of *chloroform*, dissolve with the aid of ultrasound and centrifuge for 10 minutes. Cool the mixture, add two 3-mL quantities of 0.5M *hydrochloric acid* and mix carefully. Centrifuge the mixture for 10 minutes. Transfer 5 mL of the aqueous layer to a separating funnel and add sufficient 0.5M *sodium hydroxide* to obtain a pH of 10.5, add 3 mL of *chloroform*, shake and retain the chloroform layer. The *infrared absorption spectrum* of the solution, Appendix II A, is concordant with the *reference spectrum* of nicotine *(RS 452)*.

TESTS

Acidity or alkalinity

pH, 6.7 to 7.3, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

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(1) Dilute a volume of the nasal spray containing 20 mg of Nicotine to 50 mL with solvent A and mix.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.04% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XBridge is suitable) fitted with a guard column (3 cm × 4.6 mm) packed with the same material.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Add 25 volumes of 1M *acetic acid* to 1000 volumes of *water*, add 6.2 volumes of 18M *ammonia* and adjust the pH to 10 with 18M *ammonia*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100→95	0→5	linear gradient
3-32	95→60	5→40	linear gradient
32-37	60→100	40→0	linear gradient
37-45	100	0	re-equilibration

In the chromatogram obtained with solution (4):

identify the peaks due to cotinine, myosmine, *cis*-nicotine-1′-oxide and *trans*-nicotine-1′-oxide.

In the chromatogram obtained with solution (1):

Identify any peak corresponding to *cis*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5;

identify any peak corresponding to *trans*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between *trans*-nicotine-1′-oxide and cotinine is at least 2.0.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to cotinine is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to myosmine is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any peak corresponding to *cis*-nicotine-1′-oxide is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

the area of any peak corresponding to *trans*-nicotine-1′-oxide is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all the *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (5.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate*, the pH of which is adjusted to 2.0 with *orthophosphoric acid* (solvent A).

(1) To a volume of the nasal spray containing 20 mg of Nicotine add 50 mL of solvent A and mix. Dilute 1 volume of the resulting solution to 10 volumes.
(2) 0.0124% w/v of *nicotine ditartrate dihydrate BPCRS* in solvent A.
(3) 0.04% w/v of *nicotine impurity standard BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between *trans*-nicotine-1′-oxide and cotinine is at least 2.0.

DETERMINATION OF CONTENT

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Calculate the total content of $C_{10}H_{14}N_2$ in the nasal spray using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

Each mg of $C_{10}H_{14}N_2$ is equivalent to 3.074 mg of $C_{10}H_{14}N_2,C_8H_{12}O_{12},2H_2O$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nicotine.

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Nicotine Resinate

General Notices

(Ph. Eur. monograph 1792)

96055-45-7

Action and use

Aid to smoking cessation.

Preparation

Nicotine Resinate Medicated Chewing Gum

Ph Eur

DEFINITION

Complex of nicotine (3-[(2*S*)-1-methylpyrrolidin-2-yl]pyridine) with a weak cationic exchange resin.

Content

95.0 per cent to 115.0 per cent of the declared content of nicotine ($C_{10}H_{14}N_2$) stated on the label (dried substance).

It may contain glycerol.

CHARACTERS

Appearance

White or slightly yellowish powder, hygroscopic.

Solubility

Practically insoluble in water.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Shake a quantity of the substance to be examined equivalent to 100 mg of nicotine with a mixture of 10 mL of *dilute ammonia R2*, 10 mL of *water R*, 5 mL of *strong sodium hydroxide solution R* and 20 mL of *hexane R* for 5 min. Transfer the upper layer to a beaker and evaporate to produce an oily residue. Record the spectrum of the oily residue as a thin film between *sodium chloride R* plates.

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Comparison *Ph. Eur. reference spectrum of nicotine*.

B. Nicotine release (see Tests).

TESTS

Nicotine release

Minimum 70 per cent of the content determined under Assay in 10 min.

Transfer an accurately weighed quantity of the substance to be examined, equivalent to about 4 mg of nicotine, to a glass-stoppered test-tube, add 10.0 mL of a 9 g/L solution of *sodium chloride R* previously heated to 37 °C and shake vigorously for 10 min. Immediately filter the liquid through a dry filter paper discarding the 1st millilitre of filtrate. Transfer 1.0 mL of the filtrate to a 20 mL volumetric flask, dilute to 20 mL with *0.1 M hydrochloric acid* and mix. Determine the absorbance (*2.2.25*) at the minima at about 236 nm and 282 nm and at the maximum at 259 nm using 1.0 mL of a 9 g/L solution of *sodium chloride R* diluted to 20 mL with *0.1 M hydrochloric acid* as compensation liquid.

Calculate the percentage of nicotine release using the following expression:

$$\frac{20\times10^{6}\times\left(A_{259}-0.5A_{236}-0.5A_{282}\right)}{323\times C\times m}$$

323	=	specific absorbance of nicotine at 259 nm;
C	=	percentage of nicotine in the substance to be examined determined in the assay;
m	=	mass of the substance to be examined, in milligrams;
A_{236}, A_{259}, A_{282}	=	absorbances of the solution at the wavelength indicated by the subscript.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Weigh a quantity of the substance to be examined, equivalent to 30.0 mg of nicotine, into a glass-stoppered test-tube, add 10.0 mL of *dilute ammonia R2* and shake vigorously for 10 min. Centrifuge for 20 min at about 3000 r/min. To 5.0 mL of the clear solution, add 5 mL of a 60 g/L solution of *acetic acid R* and dilute to 25.0 mL with *water R*.

Reference solution (a) Dissolve the contents of a vial of *nicotine for system suitability CRS* (containing impurities A, B, C, D, E, F and G) in 1.0 mL of *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (c) Dissolve 46.0 mg of *nicotine ditartrate CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm).

Mobile phase:

— *mobile phase A*: to 900 mL of *water R*, add 25 mL of a 60 g/L solution of *acetic acid R*, then add 6 mL of *concentrated ammonia R1*; adjust to pH 10.0 with *dilute ammonia R2* or *dilute acetic acid R* and dilute to 1 L with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 3.01	100 → 95	0 → 5
3.01 - 28	95 → 74	5 → 26
28 - 32	74 → 60	26 → 40

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *nicotine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, F and G.

Relative retention With reference to nicotine (retention time = about 18 min): impurity E = about 0.3; impurity C = about 0.55; impurity F = about 0.7; impurity A = about 0.8; impurity D = about 0.86; impurity G = about 0.9; impurity B = about 1.6.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity G and nicotine.

Limits:

— *impurities A, B, C, D, E, F, G*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

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Maximum 7.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of nicotine ($C_{10}H_{14}N_2$) taking into account the assigned content of $C_{10}H_{14}N_2$ in *nicotine ditartrate CRS*.

STORAGE

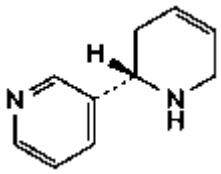
In an airtight container, protected from light.

LABELLING

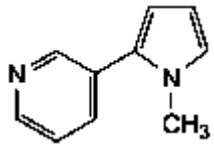
The label states the content of nicotine.

IMPURITIES

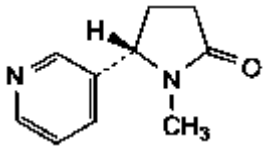
Specified impurities *A, B, C, D, E, F, G.*



A. (2*S*)-1,2,3,6-tetrahydro-2,3′-bipyridine (anatabine),



B. 3-(1-methyl-1*H*-pyrrol-2-yl)pyridine (β-nicotyrine),



C. (5*S*)-1-methyl-5-(pyridin-3-yl)pyrrolidin-2-one (cotinine),

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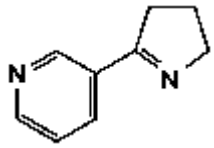
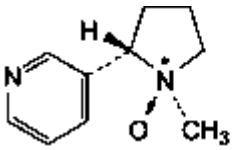
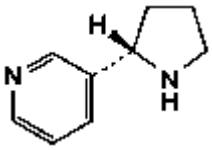


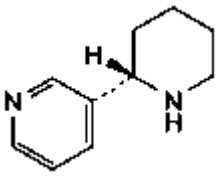
D. 3-(4,5-dihydro-3*H*-pyrrol-2-yl)pyridine (myosmine),



E. (1*RS*,2*S*)-1-methyl-2-(pyridin-3-yl)pyrrolidine 1-oxide (nicotine *N*-oxide),



F. 3-[(2*S*)-pyrrolidin-2-yl]pyridine (nornicotine),



G. 3-[(2*S*)-piperidin-2-yl]pyridine (anabasine).

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Nicotine Resinate Medicated Chewing Gum

General Notices

Action and use

Central nervous system stimulant; nicotine replacement therapy.

DEFINITION

Nicotine Resinate Medicated Chewing Gum contains Nicotine Resinate in a suitable gum basis.

The medicated chewing gum complies with the requirements stated under Medicated Chewing Gums and with the following requirements.

Content of nicotine $C_{10}H_{14}N_2$

90.0 to 113.5% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Cut a quantity of gum containing the equivalent of 20 mg of nicotine into small pieces, place in a centrifuge tube and add 10 mL of *chloroform*. Place in an ultrasonic bath for 30 minutes and centrifuge for 10 minutes. Cool the mixture to 15°, add two 3-mL quantities of 0.5 M *hydrochloric acid* and mix. Centrifuge the mixture for 10 minutes. Transfer 5 mL of the aqueous layer to a separating funnel and add sufficient 0.5M *sodium hydroxide* to obtain a pH of 10.5, add 3 mL of *chloroform*, shake and retain the chloroform layer. The *infrared absorption spectrum* of the solution, Appendix II A, is concordant with the *reference spectrum* of nicotine *(RS 452)*.

TESTS

Dissolution

Carry out the test for *drug release from medicated chewing gum,* Appendix XII B4, using the following conditions.

(1) Use a dissolution medium volume of 20.0 mL prepared from equal volumes of *phosphate buffer solution, pH 7.4* and 0.2% w/v *sodium dodecyl sulfate* at a temperature of 37°, as the medium.
(2) Use a chewing frequency of 60 cycles per minute.
(3) Take samples at 30 minutes.

Insert a whole gum into the chewing chamber and start the chewing process. At the appropriate sampling time withdraw 3 mL of the dissolution medium through a 5-mL syringe. Filter through a 0.4-µm PTFE filter, discard the first 2 mL and use the remaining 1 mL for analysis.

PROCEDURE

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the filtered solution from the chewing chamber.

(2) Dissolve a quantity of *nicotine ditartrate dihydrate BPCRS* in the dissolution medium to produce a solution equivalent to the concentration of the final solution expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XBridge is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 260 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

150 volumes of *acetonitrile*, 425 volumes of 1M *ammonium hydroxide* and 425 volumes of 0.1M *ammonium phosphate*.

DETERMINATION OF CONTENT

Calculate the total content of nicotine, $C_{10}H_{14}N_2$, in the medium using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

LIMITS

The amount of nicotine, $C_{10}H_{14}N_2$, released is not less than 70% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) Transfer a quantity of gum containing the equivalent of 20 mg of nicotine into a separating funnel, add 50 mL of solvent A, 100 mL of *hexane* and shake for at least 45 minutes or until all of the gum has dissolved. Remove the lower aqueous layer and filter through a 0.4-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.04% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* column (3.5 µm) (Waters XBridge is suitable) fitted with a guard column (3 cm × 4.6 mm) packed with the same material.

(b) Use gradient elution using the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Add 25 volumes of 1M *acetic acid* to 1000 volumes with *water*, add 6.2 volumes of 18M *ammonia* and adjust the pH to 10 with 18M *ammonia*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100→95	0→5	linear gradient
3-32	95→60	5→40	linear gradient
32-37	60→100	40→0	linear gradient
37-45	100	0	re-equilibration

In the chromatogram obtained with solution (4):

identify the peaks due to cotinine, myosmine, *cis*-nicotine-1′-oxide and *trans*-nicotine-1′-oxide.

In the chromatogram obtained with solution (1):

identify any peak in the chromatogram corresponding to *cis*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5;

identify any peak in the chromatogram corresponding to *trans*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between *trans*-nicotine-1′-oxide and cotinine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to cotinine is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to myosmine is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to *cis*-nicotine-1′-oxide is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

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the area of any peak corresponding to *trans*-nicotine-1′-oxide is not greater than 4.5 times the area of the principal peak in the chromatogram obtained with solution (2) (4.5%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all *secondary peaks* is not greater than 7.7 times the area of the principal peak in the chromatogram obtained with solution (2) (7.7%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* the pH of which is adjusted to 2.0 with *orthophosphoric acid* (solvent A).

(1) Transfer a quantity of gum containing the equivalent of 20 mg of nicotine into a 500 mL separating flask, add 50 mL of solvent A and 100 mL of *hexane* and shake for at least 45 minutes or until all of the gum has dissolved. Remove the lower aqueous layer and filter through a 0.4-µm filter. Dilute 1 volume of the resulting solution to 10 volumes.

(2) 0.0124% w/v of *nicotine ditartrate dihydrate BPCRS*.

(3) 0.04% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between *trans*-nicotine-1′-oxide and cotinine at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of nicotine, $C_{10}H_{14}N_2$, in the gum using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nicotine Resinate.

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Nicotine Sublingual Tablets

General Notices

Action and use

Central nervous system stimulant; nicotine replacement therapy.

DEFINITION

Nicotine Sublingual Tablets contain Nicotine as a *β-cyclodextrin* complex.

The sublingual tablets comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of nicotine $C_{10}H_{14}N_2$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Mix a quantity of the powdered tablets containing the equivalent of 20 mg of nicotine with 10 mL of *chloroform*. Disperse with the aid of ultrasound for 30 minutes and centrifuge for 10 minutes. Cool the mixture to 15°, add two 3-mL quantities of 0.5M *hydrochloric acid* and mix carefully. Centrifuge the mixture for 10 minutes. Transfer 5 mL of the aqueous layer to a separating funnel and add sufficient 0.5M *sodium hydroxide* to obtain a pH of 10.5, add 3 mL of *chloroform*, shake and retain the chloroform layer. The *infrared absorption spectrum* of the solution, Appendix II A, is concordant with the *reference spectrum* of nicotine *(RS 452)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) To a quantity of the powdered tablets containing the equivalent of 20 mg of nicotine add 50 mL of solvent A, mix with the aid of ultrasound and filter through a 0.7-µm glass filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 10 volumes.
(4) 0.124% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XBridge is suitable) fitted with a guard column (3 cm × 4.6 mm) packed with the same material.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dilute 25 volumes of 1M *acetic acid* to 1000 volumes with *water*, add 6.2 volumes of 18M *ammonia* and adjust the pH to 10 with 18M *ammonia*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100→95	0→5	linear gradient
3-32	95→60	5→40	linear gradient
32-37	60→100	40→0	linear gradient
37-45	100	0	re-equilibration

In the chromatogram obtained with solution (4):

identify the peaks due to cotinine, myosmine, *cis*-nicotine-1′-oxide and *trans*-nicotine-1′-oxide.

In the chromatogram obtained with solution (1):

identify any peak corresponding to *cis*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5;

identify any peak corresponding to *trans*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between cotinine and *trans*-nicotine-1′-oxide is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to cotinine is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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the area of any peak corresponding to myosmine is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any peak corresponding to *cis*-nicotine-1′-oxide is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to *trans*-nicotine-1′-oxide is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all the *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (5.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of nicotine comply with the requirements stated under Oromucosal Preparations using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) To one finely-powdered tablet add 50 mL of solvent A, mix with the aid of ultrasound and filter through a 0.7-µm glass filter.
(2) Prepare a suitable solution of *nicotine ditartrate dihydrate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{14}N_2$ in each tablet using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

Each mg of $C_{10}H_{14}N_2$ is equivalent to 3.074 mg of $C_{10}H_{14}N_2,C_8H_{12}O_{12},2H_2O$.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of nicotine.

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of nicotine.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

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(1) To a quantity of the powdered tablets containing the equivalent of 20 mg of nicotine add 50 mL of solvent A, mix with the aid of ultrasound and filter through a 0.7-µm glass filter. Dilute 2 mL of the resulting solution to 20 mL with solvent A.

(2) 0.0124% w/v of *nicotine ditartrate dihydrate BPCRS*.

(3) 0.0124% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between cotinine and *trans*-nicotine-1′-oxide is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{14}N_2$ in each tablet using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

Each mg of $C_{10}H_{14}N_2$ is equivalent to 3.074 mg of $C_{10}H_{14}N_2,C_8H_{12}O_{12},2H_2O$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nicotine.

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Nicotine Transdermal Patches

General Notices

Action and use

Central nervous system stimulant; nicotine replacement therapy.

DEFINITION

Nicotine Transdermal Patches contain Nicotine in a suitable matrix or reservoir presentation.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of nicotine.

The transdermal patches comply with the requirements stated under Patches and with the following requirements.

Content of nicotine, $C_{10}H_{14}N_2$

90.0 to 110.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Remove the protective liner from a patch, cut into small pieces and place a quantity of the patch containing 20 mg of Nicotine into a centrifuge tube, add 10 mL of *chloroform*, disperse with the aid of ultrasound for 30 minutes, cool and centrifuge for a further 10 minutes. Add 6 mL of 0.5M *hydrochloric acid* and centrifuge for 10 minutes. Transfer 5 mL of the aqueous layer to a separating funnel and adjust the pH to 10.5 with 0.5M *sodium hydroxide*. Extract with 3 mL of *chloroform*, shake and retain the chloroform layer. The *infrared absorption spectrum* of the solution, Appendix II A, is concordant with the *reference spectrum* of nicotine *(RS 452)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 2.0 with *orthophosphoric acid* (solvent A).

(1) Remove the protective liner from a whole patch and cover the exposed surface with a porous material (glass wool or tissue may be suitable). Transfer the whole patch into a separating funnel containing 50 mL of *hexane* and shake for 10 minutes. Ensure that the layers in the patch are separated and shake for a further 10 minutes. Add 20 mL of solvent A and shake for a further 10 minutes. Remove the lower aqueous layer, dilute, if necessary with solvent A to give a concentration of approximately 0.04% w/v and filter through a 0.7-µm glass filter.

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(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.04% w/v of *nicotine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XBridge is suitable) fitted with a guard column (3 cm × 4.6 mm) packed with the same material.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dilute 25 volumes of 1M *acetic acid* to 1000 volumes with *water*, add 6.2 volumes of 18M *ammonia* and adjust the pH to 10 with 18M *ammonia*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100→95	0→5	linear gradient
3-32	95→60	5→40	linear gradient
32-37	60→100	40→0	linear gradient
37-45	100	0	re-equilibration

In the chromatogram obtained with solution (4):

identify the peaks due to cotinine, myosmine, *cis*-nicotine-1′-oxide and *trans*-nicotine-1′-oxide.

In the chromatogram obtained with solution (1):

identify any peak corresponding to *cis*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5;

identify any peak corresponding to *trans*-nicotine-1′-oxide and multiply the area of this peak by a correction factor of 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between cotinine and *trans* nicotine-1′-oxide is at least 2.0.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to cotinine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to myosmine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to *cis*-nicotine-1′-oxide is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to *trans*-nicotine-1′-oxide is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all secondary peaks is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Comply with the requirements stated under Uniformity of content, Appendix XII C3, Test C, with respect to the individual content of each dosage unit and using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A described under Related substances test.

(1) Remove the protective liner from a whole patch and cover the exposed surface with a porous material (glass wool or tissue may be suitable). Transfer a whole patch into a separating funnel containing 50 mL of *hexane* and shake for 10 minutes. Ensure that the layers in the patch are separated and shake for a further 10 minutes. Add sufficient solvent A to produce a concentration of 0.04% w/v of nicotine and shake for a further 10 minutes. Remove the lower aqueous layer and filter through a 0.7-µm glass filter. Dilute 1 volume of the resulting solution to 10 volumes with solvent A.

(2) 0.04% w/v of *nicotine impurity standard BPCRS*.

(3) 0.0124% w/v of *nicotine ditartrate dihydrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between *trans*-nicotine-1′-oxide and cotinine is at least 2.0.

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DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{14}N_2$ in the transdermal patch using the declared content of $C_{10}H_{14}N_2$ in *nicotine ditartrate dihydrate BPCRS*.

Each mg of $C_{10}H_{14}N_2$ is equivalent to 3.074 mg of $C_{10}H_{14}N_2,C_8H_{12}O_{12},2H_2O$.

ASSAY

Use the average of the 10 results obtained in the test for Uniformity of content.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nicotine.

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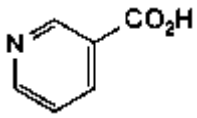
Nicotinic Acid

General Notices

(Ph. Eur. monograph 0459)



$C_6H_5NO_2$ 123.1 *59-67-6*

Action and use

Component of vitamin B.

Preparation

Nicotinic Acid Tablets

Ph Eur

DEFINITION

Pyridine-3-carboxylic acid.

Content

99.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in boiling water and in boiling ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: A, B.

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Second identification: A, C.

A. Melting point (2.2.14): 234 °C to 240 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *nicotinic acid CRS*.

C. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Solvent mixture Dissolve 6.8 g of *potassium dihydrogen phosphate R* in 900 mL of *water R*, adjust to pH 7.0 with *dilute sodium hydroxide solution R* and dilute to 1000 mL with *water R*.

Test solution Dissolve 50 mg in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 25.0 mL with the solvent mixture.

Spectral range 237-262 nm.

Absorption maximum At 262 nm.

Absorption minimum At 237 nm.

Absorbance ratio A_{237}/A_{262} = 0.46 to 0.50.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.120 g of the substance to be examined in 200 µL of *dilute ammonia R1* and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve the contents of a vial of *nicotinic acid impurity mixture CRS* (impurities A and B) in 1.0 mL of mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (4 µm);

— *temperature*: 15 °C.

Mobile phase:

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— *mobile phase A*: dilute 2 mL of *acetic acid R* in 950 mL of *water for chromatography R*, adjust to pH 5.6 with *dilute ammonia R1* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*, *methanol R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 30	100→20	0→80
30 - 35	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *nicotinic acid impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to nicotinic acid (retention time = about 6 min): impurity A = about 2.7; impurity B = about 2.8.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B.

Limits:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dissolve 0.25 g in *water R*, heating on a water-bath, and dilute to 15 mL with the same solvent.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *water R*. Add 0.25 mL of *phenolphthalein solution R*. Titrate with *0.1 M sodium hydroxide* until a pink colour is obtained. Carry out a blank titration.

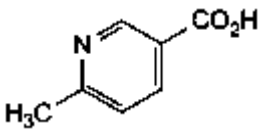
1 mL of *0.1 M sodium hydroxide* is equivalent to 12.31 mg of $C_6H_5NO_2$.

STORAGE

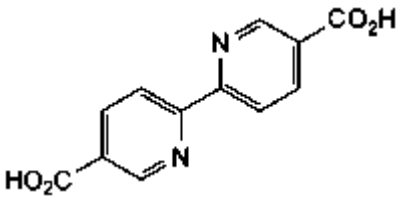
Protected from light.

IMPURITIES

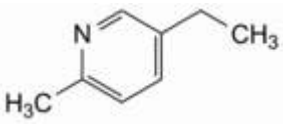
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I.*



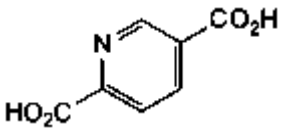
A. 6-methylpyridine-3-carboxylic acid (6-methylnicotinic acid),



B. 2,2′-bipyridine-5,5′-dicarboxylic acid (6,6′-dinicotinic acid),



C. 5-ethyl-2-methylpyridine,



D. pyridine-2,5-dicarboxylic acid,

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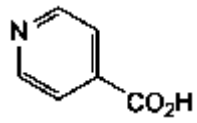
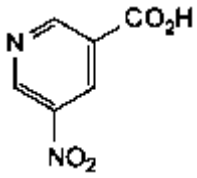
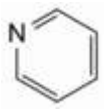


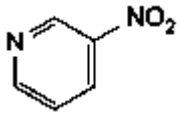
E. pyridine-4-carboxylic acid (isonicotinic acid),



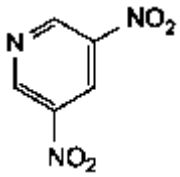
F. 5-nitropyridine-3-carboxylic acid (5-nitronicotinic acid),



G. pyridine,



H. 3-nitropyridine,



I. 3,5-dinitropyridine.

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Nicotinic Acid Tablets

General Notices

Action and use

Component of vitamin B.

DEFINITION

Nicotinic Acid Tablets contain Nicotinic Acid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nicotinic acid, $C_6H_5NO_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 8 volumes of *water*, 45 volumes of *ethanol (96%)* and 48 volumes of *chloroform* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 50 mg of Nicotinic Acid with 50 mL of hot *ethanol (96%)*, filter and allow the filtrate to cool. Solution (2) contains 0.1% w/v of *nicotinic acid* in *ethanol (96%)*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Shake a quantity of the powdered tablets containing 0.1 g of Nicotinic Acid with *ethanol (96%)*, filter and evaporate the filtrate to dryness. To the residue add 10 mg of *citric acid* and 0.15 mL of *acetic anhydride* and heat on a water bath. A reddish-violet colour is produced.

C. Triturate a quantity of the powdered tablets containing 50 mg of Nicotinic Acid with 10 mL of *water* and filter. To 2 mL of the filtrate add 6 mL of *cyanogen bromide solution* and 1 mL of a 2.5% v/v solution of *aniline*. A golden yellow colour is produced.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.3 g of Nicotinic Acid add 40 mL of hot *ethanol (96%)*, previously neutralised to *phenolphthalein solution R1*, and shake. Allow to stand for 15 minutes, swirling occasionally, and then shake for 10 minutes. Filter through absorbent cotton and wash the filter with *ethanol (96%)*. Add 50 mL of *carbon dioxide-free water* and titrate with *0.1M sodium hydroxide VS* using *phenol red solution* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 12.31 mg of $C_6H_5NO_2$.

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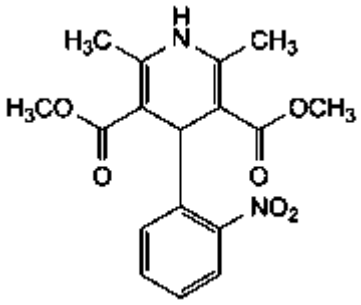
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Nifedipine

General Notices

(Ph. Eur. monograph 0627)



$C_{17}H_{18}N_2O_6$ 346.3 *21829-25-4*

Action and use

Calcium channel blocker.

Preparations

Nifedipine Capsules

Nifedipine Oral Suspension

Nifedipine Prolonged-release Capsules

Nifedipine Prolonged-release Capsules

Nifedipine Prolonged-release Tablets

Ph Eur

DEFINITION

Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

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CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.

When exposed to daylight and to artificial light of certain wavelengths, it readily converts to a nitrosophenylpyridine derivative. Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative.

Prepare solutions immediately before use in the dark or under long-wavelength light (> 420 nm) and protect them from light.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (2.2.14): 171 °C to 175 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *nifedipine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *nifedipine CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ethyl acetate R*, *cyclohexane R* (40:60 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, appearance at 254 nm and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 25 mg in a test tube, add 10 mL of a mixture of 1.5 volumes of *hydrochloric acid R*, 3.5 volumes of *water R* and 5 volumes of *alcohol R* and dissolve with gentle heating. Add 0.5 g of *zinc R* in granules and allow to stand for 5 min with occasional swirling. Filter into a second test tube, add 5 mL of a 10 g/L solution of *sodium nitrite R* to the filtrate and allow to stand for 2 min. Add 2 mL of a 50 g/L solution

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of *ammonium sulfamate R*, shake vigorously with care and add 2 mL of a 5 g/L solution of *naphthylethylenediamine dihydrochloride R*. An intense red colour develops which persists for not less than 5 min.

TESTS

Impurity D and other basic impurities

Transfer 4 g to a 250 mL conical flask and dissolve in 160 mL of *glacial acetic acid R* using an ultrasonic bath. Titrate with *0.1 M perchloric acid* using 0.25 mL of *naphtholbenzein solution R* as indicator until the colour changes from brownish-yellow to green. Not more than 0.48 mL of *0.1 M perchloric acid* is required (0.14 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in 20 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *nifedipine impurity A CRS* in *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *nifedipine impurity B CRS* in *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution (c) Mix 1.0 mL of reference solution (a), 1.0 mL of reference solution (b) and 0.1 mL of the test solution and dilute to 20.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *methanol R*, *water R* (9:36:55 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL; inject the test solution and reference solution (c).

Run time Twice the retention time of nifedipine.

Elution order Impurity A, impurity B, nifedipine.

Retention time Nifedipine = about 15.5 min.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity A and impurity B and minimum 1.5 between the peaks due to impurity B and nifedipine.

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Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent),

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent),

— *any other impurity*: not more than the area of the peak due to nifedipine in the chromatogram obtained with reference solution (c) (0.1 per cent),

— *total*: not more than 0.3 per cent,

— *disregard limit*: 0.1 times the area of the peak due to nifedipine in the chromatogram obtained with reference solution (c) (0.01 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.1300 g in a mixture of 25 mL of *2-methyl-2-propanol R* and 25 mL of *perchloric acid solution R*. Titrate with *0.1 M cerium sulfate* using 0.1 mL of *ferroin R* as indicator, until the pink colour disappears. Titrate slowly towards the end of the titration. Carry out a blank titration.

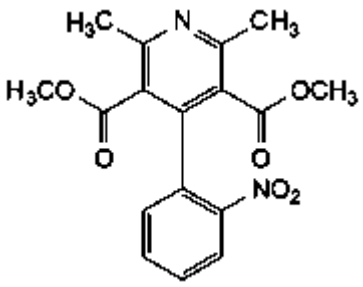
1 mL of *0.1 M cerium sulfate* is equivalent to 17.32 mg of $C_{17}H_{18}N_2O_6$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D.*



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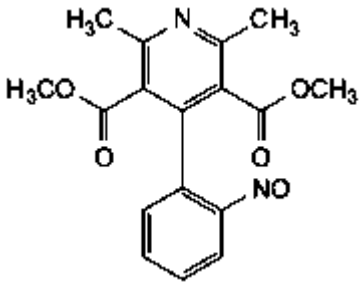
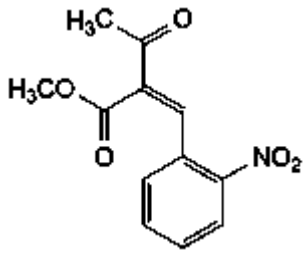
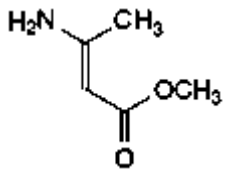
A. dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (nitrophenylpyridine analogue),



B. dimethyl 2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate (nitrosophenylpyridine analogue),



C. methyl 2-(2-nitrobenzylidene)-3-oxobutanoate,



D. methyl 3-aminobut-2-enoate.

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Nifedipine Capsules

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Nifedipine Capsules contain Nifedipine.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of nifedipine, $C_{17}H_{18}N_2O_6$

95.0 to 105.0% of the stated amount.

Carry out all the following procedures in the dark or under long-wavelength light (greater than 420 nm). Prepare solutions immediately before use and protect them from light.

IDENTIFICATION

A. Add a quantity of the contents of the capsules containing 50 mg of Nifedipine to 10 mL of *water* and mix with the aid of ultrasound for 5 minutes, filter (Whatman GF/C paper is suitable), wash the residue with *water* and dry at 110°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of nifedipine *(RS 248)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 40 volumes of *ethyl acetate* and 60 volumes of *cyclohexane* as the mobile phase in an unsaturated tank. Apply separately to the plate 5 µL of each of the following solutions in a mixture of equal volumes of *dichloromethane* and *methanol*. For solution (1) shake a quantity of the contents of the capsules containing 20 mg of Nifedipine with 10 mL of the solvent mixture and filter. Solution (2) contains 0.2% w/v of *nifedipine BPCRS* in the solvent mixture. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) is similar in position, appearance under ultraviolet light and size to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *0.1M hydrochloric acid* and rotate the paddle at 50 revolutions per minute. Withdraw a sample of 10 mL of the medium and measure the *absorbance* of a 2-cm layer of the solution, suitably diluted if necessary, at the maximum at 340 nm, Appendix II B. Measure the *absorbance* of a 2-cm layer of a solution prepared by diluting a 0.025% w/v solution of *nifedipine*

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BPCRS in *methanol* to a suitable volume with the dissolution medium and using the dissolution medium in the reference cell. Calculate the total content of nifedipine, $C_{17}H_{18}N_2O_6$, in the medium from the absorbances obtained and from the declared content of $C_{17}H_{18}N_2O_6$ in *nifedipine BPCRS*.

Nitro- and nitroso-phenylpyridine analogues

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve a quantity of the contents of the capsules containing 20 mg of Nifedipine in 8 mL of *methanol* and dilute to 20 mL with a mixture of 9 volumes of *acetonitrile*, 36 volumes of *methanol* and 55 volumes of *water*. Solution (2) contains 0.0010% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate BPCRS* (nitrophenylpyridine analogue) in a mixture of 5 volumes of *acetonitrile*, 33 volumes of *water* and 62 volumes of *methanol*. Solution (3) contains 0.00050% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate BPCRS* (nitrosophenylpyridine analogue) in a mixture of 5 volumes of *acetonitrile*, 33 volumes of *water* and 62 volumes of *methanol*. For solution (4) dilute 2 volumes of a solution in *methanol* containing 0.25% w/v of *nifedipine BPCRS*, 0.0025% w/v each of the nitrophenylpyridine analogue and nitrosophenylpyridine analogue and 0.0050% w/v of *propyl hydroxybenzoate* to 5 volumes with a mixture of 9 volumes of *acetonitrile*, 36 volumes of *methanol* and 55 volumes of *water*.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable), (b) a mixture of 9 volumes of *acetonitrile*, 36 volumes of *methanol* and 55 volumes of *borate buffer pH 8.0* as the mobile phase with a flow rate of 2.0 mL per minute and (c) a detection wavelength of 220 nm.

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *nifedipine BPCRS*.

In the chromatogram obtained with solution (1) the areas of any peaks corresponding to the nitrophenylpyridine analogue and the nitrosophenylpyridine analogue are not greater than the areas of the corresponding peaks in the chromatograms obtained with solution (2) (1%) and solution (3) (0.5%), respectively.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) take ten capsules and break them beneath the surface of 30 mL of *acetonitrile*. Stir to dissolve the capsule contents. Transfer the resulting solution to a 250 mL graduated flask. Wash the capsule shells with several portions of the mobile phase, transferring the washings to the flask, add sufficient of the mobile phase to produce 250 mL and mix. If necessary, further dilute a portion of the solution with the mobile phase to give a solution containing 0.02% w/v of nifedipine. For solution (2) dissolve 50 mg of *nifedipine BPCRS* in 30 mL of *acetonitrile* and dilute to 250 mL with the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil C18 is suitable), (b) a mixture of 40 volumes of *acetonitrile* and 60 volumes of a 0.03% v/v solution of *orthophosphoric acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 235 nm.

Calculate the content of $C_{17}H_{18}N_2O_6$ in the capsules using the declared content of $C_{17}H_{18}N_2O_6$ in *nifedipine BPCRS*.

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Nifedipine Oral Suspension

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Calcium channel blocker.

DEFINITION

Nifedipine Oral Suspension is a suspension of Nifedipine in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of nifedipine, $C_{17}H_{18}N_2O_6$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the oral suspension containing 1 mg of Nifedipine with sufficient of a solution containing equal volumes of *dichloromethane* and *methanol* to produce 5 mL.

(2) 0.02% w/v of *nifedipine BPCRS* in equal volumes of *dichloromethane* and *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm in an unsaturated tank.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm* and *366 nm*).

MOBILE PHASE

4 volumes of *ethyl acetate* and 6 volumes of *cyclohexane*.

SYSTEM SUITABILITY

The test is not valid unless the principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Impurities A and B

Carry out the method for *liquid chromatography,* Appendix III D, using the following solutions.

(1) Disperse a quantity of the oral suspension containing 5 mg of Nifedipine in 10 mL of *methanol*, shake for 15 minutes, add sufficient *methanol* to produce 20 mL and filter through a 0.45-µm nylon filter.

(2) 0.000125% w/v of *dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate BPCRS* (impurity A) in the mobile phase.

(3) 0.000125% w/v of *dimethyl 2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate BPCRS* (impurity B) in the mobile phase.

(4) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase; mix 1 volume of the resulting solution with 1 volume of solution (2) and 1 volume of solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (LiChrospher RP is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

9 volumes of *acetonitrile*, 36 volumes of *methanol* and 55 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nifedipine (retention time, about 27.3 minutes) are: impurity A, about 0.63; impurity B, about 0.79.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to impurity A and impurity B is at least 1.5;

the *resolution* between the peaks due to impurity B and nifedipine is at least 1.5;

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if there is a peak with a relative retention of about 0.74 with reference to nifedipine (propyl parahydroxybenzoate), the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to propyl parahydroxybenzoate.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (impurity A) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to dimethyl 2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate (impurity B) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a weighed quantity of the oral suspension containing 1 mg of Nifedipine in 9 mL of a mixture containing 1 volume of *acetonitrile* and 4 volumes of *methanol* and shake for 15 minutes. Add sufficient water to produce 20 mL, shake for a further 15 minutes and filter through a 0.45-µm nylon filter.
(2) Dissolve 25 mg of *nifedipine BPCRS* in a mixture containing 4.5 mL of *acetonitrile* and 18 mL of *methanol*. Add sufficient *water* to produce 50 mL and dilute 1 volume to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Impurities A and B may be used.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{17}H_{18}N_2O_6$, weight in volume, using the declared content of $C_{17}H_{18}N_2O_6$ in *nifedipine BPCRS*.

STORAGE

Nifedipine Oral Suspension should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed under Nifedipine.

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Nifedipine Prolonged-release Capsules

General Notices

Prolonged-release Nifedipine Capsules

Nifedipine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Calcium channel blocker.

DEFINITION

Nifedipine Prolonged-release Capsules contain Nifedipine. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Nifedipine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of nifedipine, $C_{17}H_{18}N_2O_6$

95.0 to 105.0% of the stated amount.

Carry out all the following procedures in the dark or under long-wavelength light (greater than 420 nm). Prepare solutions immediately before use and protect them from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 20 mg of Nifedipine with 100 mL of a solution containing equal volumes of *dichloromethane* and *methanol* and filter through a Whatman GF/C filter.

(2) 0.02% w/v of *nifedipine BPCRS* in equal volumes of *dichloromethane* and *methanol*.

(3) Equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

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(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm in an unsaturated tank.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

40 volumes of *ethyl acetate* and 60 volumes of *cyclohexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) appears as a single spot.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered content of the capsules containing 50 mg of Nifedipine in 15 mL of *methanol*, dilute to 25 mL with *methanol* and filter. Dilute 1 volume of the resulting solution with 1 volume of the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of the resulting solution to 5 volumes with the mobile phase.

(3) 0.0005% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate BPCRS* in the mobile phase.

(4) 0.0005% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate BPCRS* in the mobile phase.

(5) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of the resulting solution with 1 volume of solution (3) and 1 volume of solution (4).

(6) Dilute 1 volume of solution (2) to 4 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

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9 volumes of *acetonitrile*, 36 volumes of *methanol* and 55 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5):

the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate and dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate is at least 1.5;

the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate and nifedipine is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to *dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine- 3,5-dicarboxylate* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak corresponding to *dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered mixed contents of 20 capsules containing 50 mg of Nifedipine, add 15 mL of *methanol*, dilute to 50 mL with *methanol* and filter. Dilute 1 volume of the resulting solution to 5 volumes with the mobile phase.
(2) 0.02% w/v *nifedipine BPCRS* in the mobile phase.
(3) 0.0003% w/v of *nifedipine BPCRS*, 0.0002% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate BPCRS* and 0.0002% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in solution (3):

the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate and dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate is at least 1.5;

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the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate and nifedipine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{18}N_2O_6$ in the capsules using the declared content of $C_{17}H_{18}N_2O_6$ in *nifedipine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nifedipine.

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Nifedipine Prolonged-release Tablets

General Notices

Prolonged-release Nifedipine Tablets

Nifedipine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Calcium channel blocker.

DEFINITION

Nifedipine Prolonged-release Tablets contain Nifedipine. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Nifedipine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nifedipine, $C_{17}H_{18}N_2O_6$

95.0 to 105.0% of the stated amount.

Carry out all the following procedures in the dark or under long-wavelength light (greater than 420 nm). Prepare solutions immediately before use and protect them from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Nifedipine with 100 mL of a solution containing equal volumes of *dichloromethane* and *methanol* and filter (Whatman GF/C is suitable).

(2) 0.02% w/v of *nifedipine BPCRS* in equal volumes of *dichloromethane* and *methanol*.

(3) Equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

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(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm in an unsaturated tank.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

40 volumes of *ethyl acetate* and 60 volumes of *cyclohexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) appears as a single spot.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Nifedipine in 15 mL of *methanol*, dilute to 25 mL with *methanol* and filter. Dilute 1 volume of the resulting solution with 1 volume of the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of the resulting solution to 5 volumes with the mobile phase.

(3) 0.0005% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate BPCRS* in the mobile phase.

(4) 0.0005% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate BPCRS* in the mobile phase.

(5) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of the resulting solution with 1 volume of solution (3) and 1 volume of solution (4).

(6) Dilute 1 volume of solution (2) to 4 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

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9 volumes of *acetonitrile*, 36 volumes of *methanol* and 55 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (5):

the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate and dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate is at least 1.5;

the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate and nifedipine is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak corresponding to dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D.

(1) Scratch the film coating on 10 whole tablets, add 450 mL of *methanol*, mix with the aid of ultrasound until completely disintegrated, add sufficient *methanol* to produce 500 mL and filter. Dilute a volume of the resulting filtrate with sufficient mobile phase to produce a solution containing 0.02% w/v of Nifedipine.
(2) 0.02% w/v of *nifedipine BPCRS* in the mobile phase.
(3) 0.0003% w/v of *nifedipine BPCRS*, 0.0002% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate BPCRS* and 0.0002% w/v of *dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3):

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the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrophenyl)pyridine- 3,5-dicarboxylate and dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate is at least 1.5;

the *resolution factor* between the peaks due to dimethyl-2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate and nifedipine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{18}N_2O_6$ in the tablets using the declared content of $C_{17}H_{18}N_2O_6$in *nifedipine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nifedipine.

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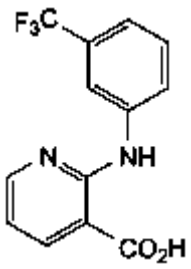
Niflumic Acid

General Notices

(Ph. Eur. monograph 2115)



$C_{13}H_9F_3N_2O_2$ 282.2 *4394-00-7*

Ph Eur

DEFINITION

2-[[3-(Trifluoromethyl)phenyl]amino]pyridine-3-carboxylic acid.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent) and in methanol.

mp

About 204 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *niflumic acid CRS*.

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TESTS

Impurity C

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.50 g of the substance to be examined in 5 mL of *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 25 mg of *3-trifluoromethylaniline R* (impurity C) in 20 mL of *methanol R* and dilute to 100 mL with the same solvent. Dilute 1.0 mL of this solution to 100 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetic acid R*, *ethyl acetate R*, *toluene R* (5:25:90 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air, until the solvents have evaporated.

Detection Spray with *4-dimethylaminocinnamaldehyde solution R* and heat at 60 °C for 10 min.

Limit:

— *impurity C*: any spot due to impurity C is not more intense than the principal spot in the chromatogram obtained with the reference solution (50 ppm).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in 10 mL of *acetonitrile R* and dilute to 20.0 mL with *water R*.

Reference solution Dissolve 5.0 mg of *niflumic acid impurity A CRS*, 5.0 mg of *niflumic acid impurity B CRS* and 6.0 mg of *niflumic acid impurity E CRS* in 20 mL of *acetonitrile R*, add 5.0 mL of the test solution and dilute to 50.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase *phosphoric acid R*, *acetonitrile R*, *water R* (2.5:500:500 *V/V/V*).

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 267 nm.

Injection 10 µL.

Run time 4 times the retention time of niflumic acid.

Relative retention With reference to niflumic acid (retention time = about 5.5 min): impurity A = about 0.25; impurity B = about 0.57; impurity E = about 0.64.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurities B and E.

Limits:

— *impurity B*: not more than 4 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.4 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to niflumic acid in the chromatogram obtained with the reference solution (0.10 per cent);

— *sum of impurities other than B*: not more than twice the area of the peak due to niflumic acid in the chromatogram obtained with the reference solution (0.2 per cent);

— *disregard limit*: 0.5 times the area of the peak due to niflumic acid in the chromatogram obtained with the reference solution (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.5 g in a mixture of 1 mL of *nitric acid R* and 10 mL of *methanol R*, and dilute to 20 mL with *water R*. To 10 mL of this solution add 5 mL of *water R*.

Phosphates (2.4.11)

Maximum 100 ppm.

Dilute 1.0 mL of the test solution prepared as described in general chapter 2.4.8 (method C) to 100 mL with *water R*.

Loss on drying (2.2.32)

Maximum 0.3 per cent, determined on 2.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

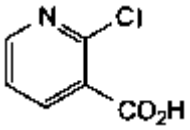
Dissolve 0.200 g in a mixture of 10 mL of *water R* and 40 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.22 mg of $C_{13}H_9F_3N_2O_2$.

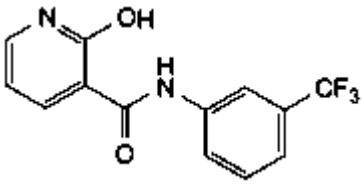
IMPURITIES

Specified impurities A, B, C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E, F.

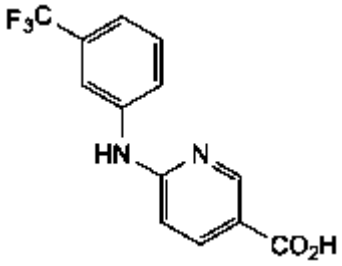


A. 2-chloropyridine-3-carboxylic acid,



B. 2-hydroxy-*N*-[3-(trifluoromethyl)phenyl]pyridine-3-carboxamide,

C. 3-(trifluoromethyl)aniline,



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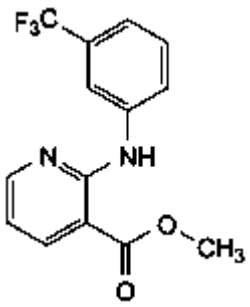
E. 6-[[3-(trifluoromethyl)phenyl]amino]pyridine-3-carboxylic acid,



F. methyl 2-[[3-(trifluoromethyl)phenyl]amino]pyridine-3-carboxylate.

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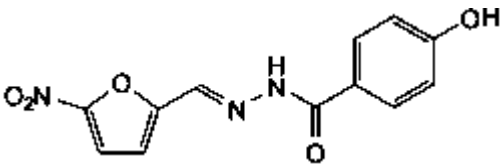
Nifuroxazide

General Notices

(Ph. Eur. monograph 1999)



$C_{12}H_9N_3O_5$ 275.2 *965-52-6*

Action and use

Antibacterial.

Ph Eur

DEFINITION

(*E*)-4-Hydroxy-*N*′-[(5-nitrofuran-2-yl)methylidene]benzohydrazide.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Bright yellow, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *nifuroxazide CRS*.

TESTS

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Specific absorbance (2.2.25)

940 to 1000 at the absorption maximum at 367 nm.

Protected from light, dissolve 10.0 mg in 10 mL of *ethylene glycol monomethyl ether R* and dilute to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 100.0 mL with *methanol R*.

Impurity A

Maximum 0.05 per cent.

Test solution (a) Dissolve 1.0 g of the substance to be examined in *dimethyl sulfoxide R* and dilute to 10.0 mL with the same solvent.

Test solution (b) To 5.5 mL of test solution (a) add 50.0 mL of *water R* while stirring. Allow to stand for 15 min and filter.

Reference solution To 0.5 mL of test solution (a) add 5.0 mL of a 50 mg/L solution of *4-hydroxybenzohydrazide R* (impurity A) in *dimethyl sulfoxide R*. Add 50.0 mL of *water R* while stirring. Allow to stand for 15 min and filter.

Add 0.5 mL of *phosphomolybdotungstic reagent R* and 10.0 mL of *sodium carbonate solution R* separately to 10.0 mL of test solution (b) and to 10.0 mL of the reference solution. Allow to stand for 1 h. Examine the 2 solutions at 750 nm. The absorbance (2.2.25) of the solution obtained with test solution (b) is not greater than that obtained with the reference solution.

Related substances

Liquid chromatography (2.2.29). *Use amber volumetric flasks, unless otherwise specified.*

Solvent mixture *acetonitrile R*, *water R* (40:60 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture, using sonication for not more than 5 min, and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) In order to prepare impurity E *in situ*, dissolve 5 mg of the substance to be examined in the solvent mixture in a colourless volumetric flask, using sonication for 5 min, and dilute to 50 mL with the solvent mixture. Allow to stand in ambient light for 1 h.

Reference solution (c) Dissolve 5.0 mg of *methyl parahydroxybenzoate CRS* (impurity B) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 10 °C.

Mobile phase:

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— *mobile phase A*: *tetrahydrofuran R*, *water R* (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	67	33
10 - 30	67 → 43	33 → 57

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 50 µL.

Relative retention With reference to nifuroxazide (retention time = about 8 min): impurity A (keto-enol tautomers) = about 0.36 and 0.39; impurity E = about 0.9; impurity B = about 1.2; impurity C = about 2.6; impurity D = about 3.4.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity E and nifuroxazide.

Limits:

— *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities B, C, D*: for each impurity, not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent), and not more than 1 such peak has an area greater than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peaks due to impurity A.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g, with heating if necessary, in 30 mL of *dimethylformamide R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

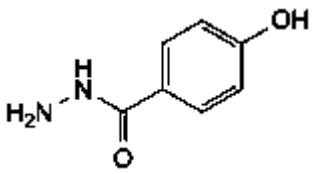
1 mL of *0.1 M sodium hydroxide* is equivalent to 27.52 mg of $C_{12}H_9N_3O_5$.

STORAGE

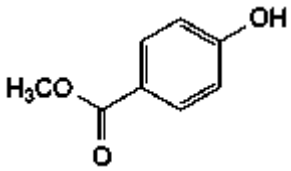
Protected from light.

IMPURITIES

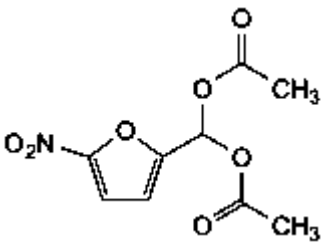
Specified impurities *A, B, C, D, E.*



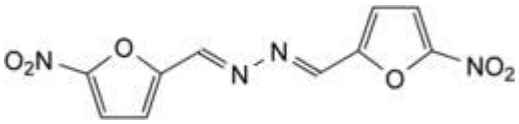
A. 4-hydroxybenzohydrazide (*p*-hydroxybenzohydrazide),



B. methyl 4-hydroxybenzoate (methyl parahydroxybenzoate),



C. (5-nitrofuran-2-yl)methylidene diacetate,



D. (*E,E*)-*N,N*′-bis[(5-nitrofuran-2-yl)methylidene]hydrazine (5-nitrofurfural azine),

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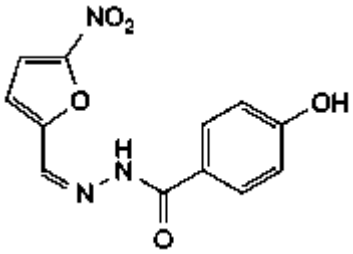

E. (*Z*)-4-hydroxy-*N*′-[(5-nitrofuran-2-yl)methylidene]benzohydrazide.

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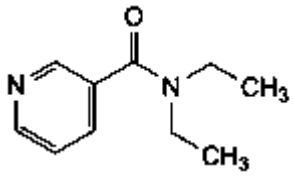
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Nikethamide

General Notices

(Ph. Eur. monograph 0233)



$C_{10}H_{14}N_2O$ 178.2 *59-26-7*

Action and use

Central nervous system stimulant.

Ph Eur

DEFINITION

Nikethamide contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of *N,N*-diethylpyridine-3-carboxamide, calculated with reference to the anhydrous substance.

CHARACTERS

An oily liquid or a crystalline mass, colourless or slightly yellowish, miscible with water and with ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Dissolve 0.15 g in *0.01 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 1.0 mL of this solution to 100.0 mL with *0.01 M hydrochloric acid*. Examined between 230 nm and 350 nm (*2.2.25*) in a 2 cm cell, the solution shows a single absorption maximum, at 263 nm. The specific absorbance at the maximum is about 285.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *nikethamide CRS*.

C. Heat 0.1 g with 1 mL of *dilute sodium hydroxide solution R*. Diethylamine is evolved progressively and is recognisable by its characteristic odour and by its turning *red litmus paper R* blue.

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D. Dilute 1 mL of solution S (see Tests) to 250 mL with *water R*. To 2 mL of this solution add 2 mL of *cyanogen bromide solution R*. Add 3 mL of a 25 g/L solution of *aniline R* and shake. A yellow colour develops.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Appearance

The substance to be examined, in liquid form or liquefied by slight heating, is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 6.0 to 7.8.

Refractive index (*2.2.6*)

1.524 to 1.526.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 0.4 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 40 mg of *ethylnicotinamide CRS* in *methanol R* and dilute to 100 mL with the same solvent.

Reference solution (b) Dilute 1 mL of reference solution (a) to 10 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 25 volumes of *propanol R* and 75 volumes of *chloroform R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. In the chromatogram obtained with the test solution, any spot corresponding to ethylnicotinamide is not more intense than the spot in the chromatogram obtained with reference solution (a) (1.0 per cent) and any spot, apart from the principal spot and the spot corresponding to ethylnicotinamide, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.1 per cent).

Water (*2.5.12*)

Not more than 0.3 per cent, determined on 2.00 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.150 g in a mixture of 5 mL of *acetic anhydride R* and 20 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 17.82 mg of $C_{10}H_{14}N_2O$.

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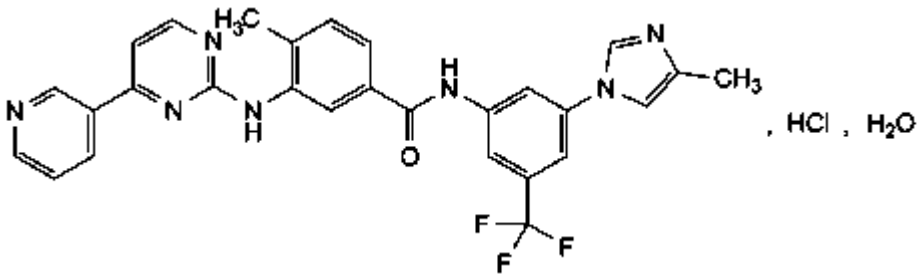
Nilotinib Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 2993)



$C_{28}H_{23}ClF_3N_7O,H_2O$ 584.0 *923288-90-8*

Action and use

Tyrosine kinase (BCR-ABL) inhibitor; treatment of chronic myeloid leukaemia.

Ph Eur

DEFINITION

4-Methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide hydrochloride monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellowish or slightly greenish-yellow, hygroscopic, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol, very slightly soluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *nilotinib hydrochloride monohydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (b) of chlorides (2.3.1).

C. Water (see Tests).

TESTS

Impurity A

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Solvent mixture *dimethyl sulfoxide R*, *water R* (20:80 *V/V*).

Test solution Dissolve 0.300 g of the substance to be examined in 2 mL of *dimethyl sulfoxide R*, add 7 mL of *water R*, allow to equilibrate at room temperature without shaking to avoid foam formation, and then dilute to 10.0 mL with *water R*. Shake well, allow the substance to be examined to precipitate for about 2 h in the dark and filter the supernatant through a 0.45 µm filter.

Reference solution (a) Dissolve 7.5 mg of *nilotinib impurity A CRS* in *dimethyl sulfoxide R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *dimethyl sulfoxide R*. Dilute 2.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 7.5 mg of *nilotinib impurity B CRS* and 7.5 mg of *nilotinib impurity C CRS* in *dimethyl sulfoxide R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *dimethyl sulfoxide R*. Dilute 2.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (c) Dilute 2.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *encapsulated polar-embedded octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1.36 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: mobile phase A, *acetonitrile R1* (20:80 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 10	85 → 80	15 → 20
10 - 12	80 → 75	20 → 25
12 - 18	75 → 10	25 → 90
18 - 19	10	90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 207 nm.

Injection 20 µL of the test solution and reference solution (a).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to nilotinib (retention time = about 17 min): impurity A = about 0.3.

System suitability:

— *repeatability*: maximum relative standard deviation of 5.0 per cent determined on 6 injections of reference solution (a).

Calculation of content:

— for impurity A, use the concentration of impurity A in reference solution (a).

Limit:

— *impurity A*: maximum 3 ppm.

Impurities B and C

Liquid chromatography (2.2.29) as described in the test for impurity A with the following modifications.

Detection Spectrophotometer at 225 nm.

Injection Test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to nilotinib (retention time = about 17 min): impurity C = about 0.2; impurity B = about 0.6.

System suitability:

— signal-to-noise ratio: minimum 10 for the peaks due to impurities B and C in the chromatogram obtained with reference solution (c);

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— *repeatability*: maximum relative standard deviation of 5.0 per cent for the areas of the peaks due to impurities B and C, determined on 6 injections of reference solution (b).

Calculation of contents:

— for impurities B and C, use the concentration of the corresponding impurity in reference solution (b).

Limits:

— *impurities B, C*: for each impurity, maximum 2 ppm.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Solvent mixture anhydrous ethanol R, water R (50:50 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of nilotinib hydrochloride monohydrate CRS in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of nilotinib for system suitability CRS (containing impurities E, F and G) in the solvent mixture and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1.36 g/L solution of potassium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R;

— *mobile phase B*: mobile phase A, acetonitrile for chromatography R (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 16	90 → 10	10 → 90

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
16 - 17	10	90

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *nilotinib for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities E, F and G.

Relative retention With reference to nilotinib (retention time = about 12 min): impurity E = about 1.03; impurity F = about 1.07; impurity G = about 1.09.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities F and G;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to nilotinib.

Calculation of percentage contents:

— for each impurity, use the concentration of nilotinib hydrochloride monohydrate in reference solution (b).

Limits:

— *impurity F*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.40 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

3.0 per cent to 5.0 per cent, determined on 0.150 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

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Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{28}H_{23}ClF_3N_7O$ taking into account the assigned content of *nilotinib hydrochloride monohydrate CRS*.

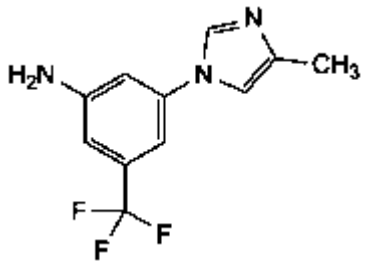
STORAGE

In an airtight container.

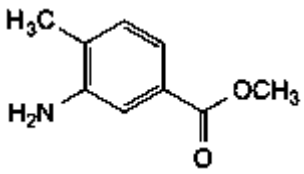
IMPURITIES

Specified impurities *A, B, C, F.*

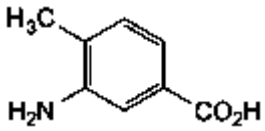
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, G, H.*



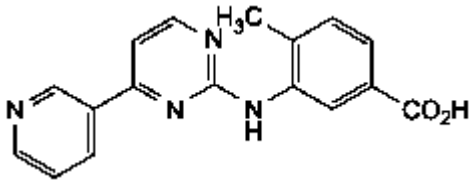
A. 3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)aniline,



B. methyl 3-amino-4-methylbenzoate,



C. 3-amino-4-methylbenzoic acid,



D. 4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzoic acid,

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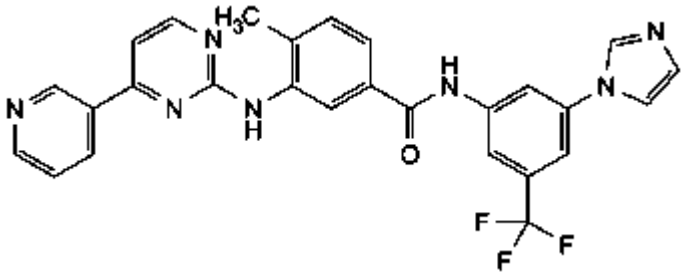
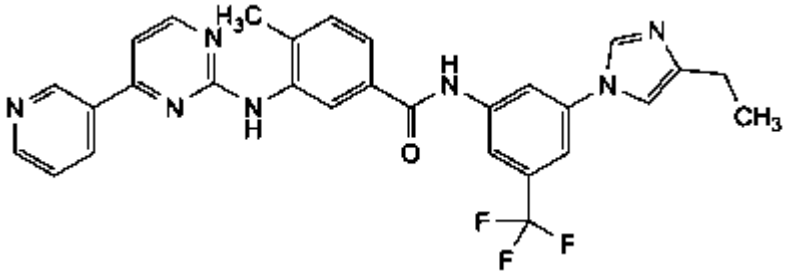
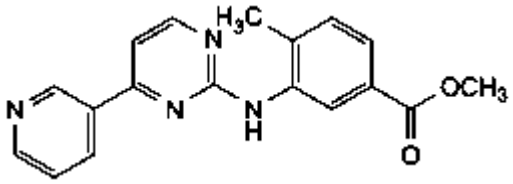


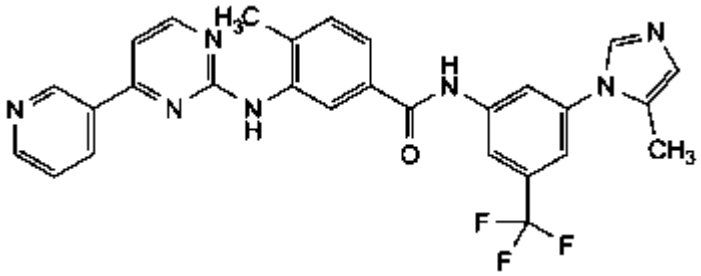
E. *N*-[3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide,



F. *N*-[3-(4-ethyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide,



G. methyl 4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzoate,



H. 4-methyl-*N*-[3-(5-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide.

Ph Eur

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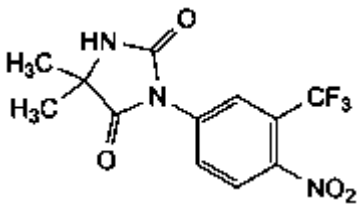
Nilutamide

General Notices

(Ph. Eur. monograph 2256)



$C_{12}H_{10}F_3N_3O_4$ 317.2 *63612-50-0*

Action and use

Cytotoxic.

Ph Eur

DEFINITION

5,5-Dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]imidazolidine-2,4-dione.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, freely soluble in acetone, soluble in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *nilutamide CRS*.

TESTS

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TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture acetonitrile for chromatography R, water R (35:65 *V/V*).

Test solution Dissolve 0.10 g of the substance to be examined in the solvent mixture and dilute to 100 mL with the solvent mixture.

Reference solution (a) Dilute 20.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of the substance to be examined and 2 mg of nilutamide impurity B CRS in the solvent mixture and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: 2.0 g/L solution of potassium dihydrogen phosphate R adjusted to pH 7.5 with 1 M sodium hydroxide;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	55	45
8 - 30	55 → 30	45 → 70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to nilutamide (retention time = about 5.3 min): impurity B = about 0.9.

System suitability Reference solution (b):

— resolution: minimum 3.0 between the peaks due to impurity B and nilutamide.

Limits:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

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— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29). *The solutions are stable for 24 h at room temperature and in daylight.*

Solvent mixture acetonitrile for chromatography R, water R (35:65 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution Dissolve 50.0 mg of nilutamide CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 40 volumes of acetonitrile R and 60 volumes of a 2.0 g/L solution of potassium dihydrogen phosphate R adjusted to pH 7.5 with 1 M sodium hydroxide.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 267 nm.

Injection 20 µL.

Retention time About 9 min.

Calculate the percentage content of $C_{12}H_{10}F_3N_3O_4$ from the declared content of nilutamide CRS.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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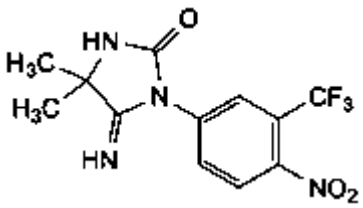
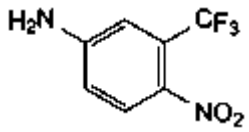
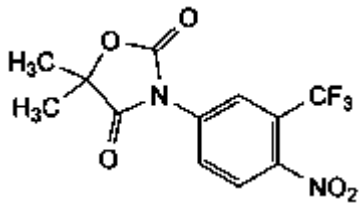
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



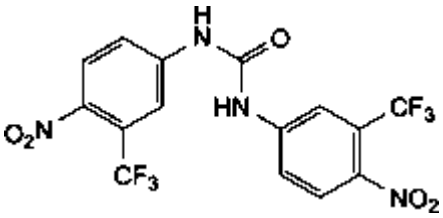
A. 5-imino-4,4-dimethyl-1-[4-nitro-3-(trifluoromethyl)phenyl]imidazolidin-2-one,



B. 4-nitro-3-(trifluoromethyl)aniline (nifeline),



C. 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]oxazolidine-2,4-dione,



D. 1,3-bis[4-nitro-3-(trifluoromethyl)phenyl]urea.

Ph Eur

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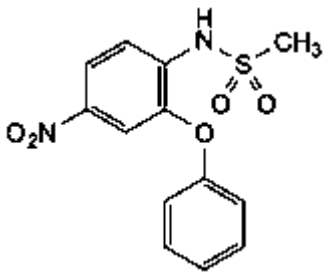
Nimesulide

General Notices

(Ph. Eur. monograph 1548)



$C_{13}H_{12}N_2O_5S$ 308.3 *51803-78-2*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

N-(4-Nitro-2-phenoxyphenyl)methanesulfonamide.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Yellowish, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, slightly soluble in anhydrous ethanol.

mp

About 149 °C.

It shows polymorphism (*5.9*).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison nimesulide CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Absorbance (2.2.25)

Maximum 0.50 at 450 nm.

Dissolve 1.0 g in acetone R and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in 8 mL of acetonitrile R and dilute to 20.0 mL with water R.

Reference solution (a) Dissolve 5 mg of 2-phenoxyaniline R (impurity C) in 10 mL of acetonitrile R and dilute to 25.0 mL with water R. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase. Mix 1.0 mL of this solution with the contents of a vial of nimesulide impurity D CRS previously dissolved in 1.0 mL of acetonitrile R.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 4 mg of nimesulide for peak identification CRS (containing impurities A, B, E and F) in 4.0 mL of acetonitrile R and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 35 volumes of acetonitrile R and 65 volumes of a 1.15 g/L solution of ammonium dihydrogen phosphate R previously adjusted to pH 7.0 with ammonia R.

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

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Run time 7 times the retention time of nimesulide.

Identification of impurities Use the chromatogram supplied with *nimesulide for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, E and F; use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

Relative retention With reference to nimesulide (retention time = about 5 min): impurity A = about 0.3; impurity B = about 2.4; impurity C = about 3.2; impurity D = about 3.7; impurity E = about 4.2; impurity F = about 6.1.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities C and D.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.7; impurity E = 1.4;

— *impurity E*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities A, B, C, D, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.240 g in 30 mL of previously neutralised *acetone R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 30.83 mg of $C_{13}H_{12}N_2O_5S$.

IMPURITIES

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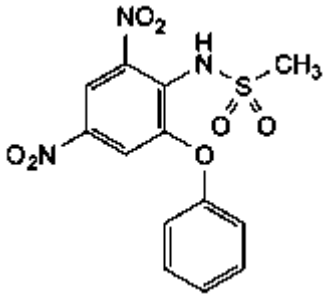
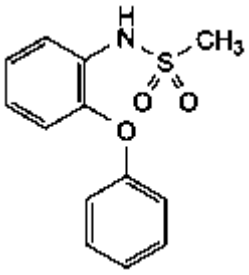
Specified impurities A, B, C, D, E, F.

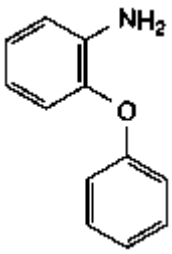
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) G.



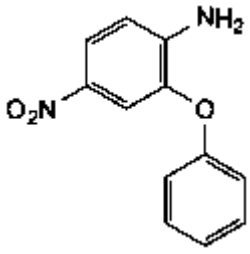
A. *N*-(2,4-dinitro-6-phenoxyphenyl)methanesulfonamide,



B. *N*-(2-phenoxyphenyl)methanesulfonamide,



C. 2-phenoxyaniline,



D. 4-nitro-2-phenoxyaniline,

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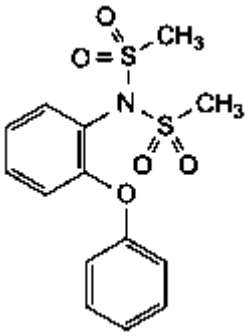
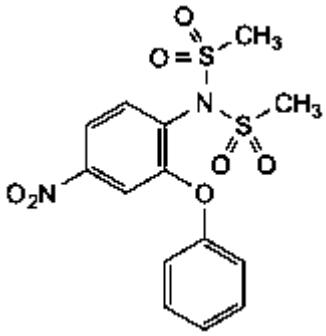
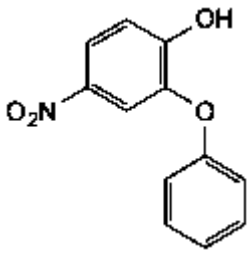


E. *N*,*N*-bis(methylsulfonyl)-2-phenoxyaniline,



F. *N*,*N*-bis(methylsulfonyl)-4-nitro-2-phenoxyaniline,



G. 4-nitro-2-phenoxyphenol.

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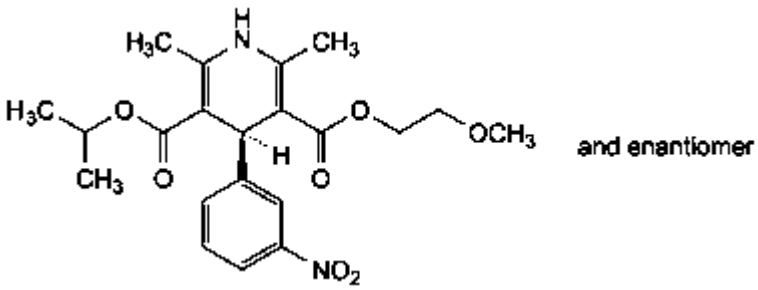
Nimodipine

General Notices

(Ph. Eur. monograph 1245)



and enantiomer

$C_{21}H_{26}N_2O_7$ 418.4 *66085-59-4*

Action and use

Calcium channel blocker.

Preparations

Nimodipine Infusion

Nimodipine Tablets

Ph Eur

DEFINITION

2-Methoxyethyl 1-methylethyl (4*RS*)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Light yellow or yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethyl acetate, sparingly soluble in anhydrous ethanol.

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It shows polymorphism (*5.9*).

Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative.

IDENTIFICATION

A. Optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *nimodipine CRS*.

If the spectra obtained in the solid state show differences, record new spectra using 20 g/L solutions in *methylene chloride R* and a 0.2 mm cell.

TESTS

Prepare solutions immediately before use either protected from light or under long-wavelength light (> 420 nm).

Solution S

Dissolve 1.0 g in *acetone R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40 mg of the substance to be examined in 2.5 mL of *tetrahydrofuran R* and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of *nimodipine for peak identification CRS* (containing impurity C) in 0.25 mL of *tetrahydrofuran R* and dilute to 2.5 mL with the mobile phase.

Reference solution (c) Dilute 0.5 mL of the test solution to 25.0 mL with the mobile phase. Mix 0.5 mL of this solution with 0.5 mL of *nimodipine impurity A CRS* and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

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— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *methanol R*, *tetrahydrofuran R*, *water R* (20:20:60 *V/V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Run time 4.5 times the retention time of nimodipine.

Identification of impurities Use the chromatogram supplied with *nimodipine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to nimodipine (retention time = about 7 min): impurity C = about 0.5; impurity A = about 0.9.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to nimodipine.

Limits:

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities* : for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Prepare solutions immediately before use either protected from light or under long-wavelength light (> 420 nm).

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Dissolve with gentle heating 0.180 g in a mixture of 25 mL of *2-methyl-2-propanol R* and 25 mL of *perchloric acid solution R*. Add 0.1 mL of *ferroin R*. Titrate with *0.1 M cerium sulfate*. Titrate slowly towards the end of the titration. Carry out a blank titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 20.92 mg of $C_{21}H_{26}N_2O_7$.

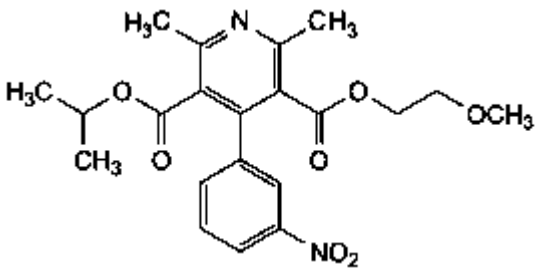
STORAGE

Protected from light.

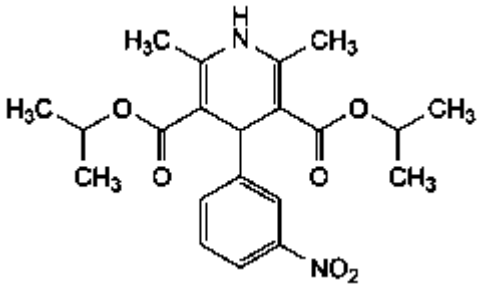
IMPURITIES

Specified impurities C.

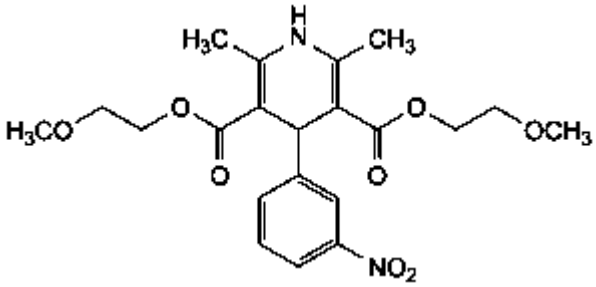
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



A. 2-methoxyethyl 1-methylethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate,



B. bis(1-methylethyl) 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate,



C. bis(2-methoxyethyl) 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

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Nimodipine Infusion

General Notices

Nimodipine Intravenous Infusion

Action and use

Calcium channel blocker.

DEFINITION

Nimodipine Infusion is a sterile solution containing Nimodipine in a suitable aqueous alcoholic solvent. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of nimodipine, $C_{21}H_{26}N_2O_7$

95.0 to 105.0% of the stated amount.

Carry out the following procedures protected from light or under long-wavelength light (greater than 420 nm). Prepare the solutions immediately before use and protect them from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a volume of the infusion containing 4 mg of Nimodipine with 4 mL of *dichloromethane* and use the dichloromethane layer.

(2) 0.1% w/v solution of *nimodipine BPCRS* in *dichloromethane*.

(3) A mixture of equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck HPTLC silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution as bands.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Spray the plate with a freshly prepared 0.1% w/v solution of *2,6-dichloroquinonechlorimide* in *ethanol* and heat at 110° for about 3 minutes.

MOBILE PHASE

40 volumes of *ethyl acetate* and 60 volumes of *cyclohexane*.

CONFIRMATION

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The bands due to nimodipine are brownish-green to bluish-green.

The principal band in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

The principal band in the chromatogram obtained with solution (3) appears as a single compact band.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.5, Appendix V L.

Bacterial endotoxins

The endotoxin limit concentration is 5.0 IU per mL, Appendix XIV C.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the infusion, if necessary, with *absolute ethanol*, to contain 0.02% w/v of Nimodipine.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 2 volumes of this solution to 10 volumes with the mobile phase.
(3) 0.0001% w/v of *nimodipine impurity A BPCRS* in *absolute ethanol*.
(4) 0.0001% w/v each of *nimodipine BPCRS* and *nimodipine impurity A BPCRS* in *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP-18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 235 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

12 volumes of *acetonitrile*, 24 volumes of *tetrahydrofuran* and 64 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to nimodipine and nimodipine impurity A is at least 1.5 and the *symmetry factor* of the peak due to nimodipine is not more than 2.0.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to nimodipine impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* other than any peak corresponding to impurity A is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the infusion, if necessary, with *absolute ethanol*, to produce a solution containing 0.02% w/v of Nimodipine.
(2) 0.02% w/v of *nimodipine BPCRS* in *absolute ethanol*.
(3) 0.0001% w/v each of *nimodipine BPCRS* and *nimodipine impurity A BPCRS* in *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 1.3 and the *symmetry factor* of the peak due to nimodipine is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{26}N_2O_7$ in the infusion using the declared content of $C_{21}H_{26}N_2O_7$ in *nimodipine BPCRS*.

STORAGE

Nimodipine Infusion should be protected from light. It should not be allowed to come into contact with polyvinyl chloride (PVC).

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nimodipine.

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Nimodipine Tablets

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Nimodipine Tablets contain Nimodipine. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nimodipine, $C_{21}H_{26}N_2O_7$

95.0 to 105.0% of the stated amount.

Carry out the following procedures protected from light or under long-wavelength light (greater than 420 nm). Prepare solutions immediately before use and protect them from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 60 mg of Nimodipine with 10 mL of *ethyl acetate* for 15 minutes, centrifuge and use the supernatant liquid.

(2) 0.6% w/v solution of *nimodipine BPCRS* in *ethyl acetate*.

(3) A mixture of equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck HPTLC silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*. Spray the plate with a freshly prepared 0.1% w/v solution of *2,6-dichloroquinonechlorimide* in *ethanol* and heat at 110° for about 3 minutes.

MOBILE PHASE

40 volumes of *ethyl acetate* and 60 volumes of *cyclohexane*.

CONFIRMATION

The spot due to nimodipine is greyish-violet.

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

The principal spot in the chromatogram obtained with solution (3) appears as a single, compact spot.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of acetate buffer pH 4.5 prepared as described below containing 0.3% w/v of *sodium dodecyl sulfate* at a temperature of 37°, as the medium.

Prepare the buffer solution by dissolving 0.299 g of *sodium acetate* in 50 mL of *water*, add 0.174 g of *glacial acetic acid* and dilute to 100 mL with *water*.

PROCEDURE

(1) After 30 minutes withdraw a 10 mL sample of the medium and filter. Measure the *absorbance* of the filtrate, suitably diluted with the dissolution medium if necessary, at the maximum at 340 nm, Appendix II B using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *nimodipine BPCRS* using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of nimodipine, $C_{21}H_{26}N_2O_7$, in the medium from the absorbances obtained and using the declared content of $C_{21}H_{26}N_2O_7$ in *nimodipine BPCRS*.

LIMITS

The amount of nimodipine released is not less than 85% of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of *methanol* to a quantity of the powdered tablets containing 60 mg of Nimodipine, mix with the aid of ultrasound for 5 minutes, add sufficient *methanol* to produce 100 mL, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 2 volumes of this solution to 10 volumes with the mobile phase.

(3) 0.0003% w/v of *nimodipine impurity A BPCRS* in the mobile phase.

(4) 0.0002% w/v each of *nimodipine BPCRS* and *nimodipine impurity A BPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP-18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

13 volumes of *acetonitrile*, 26 volumes of *tetrahydrofuran* and 60 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to nimodipine and nimodipine impurity A is at least 1.5 and the *symmetry factor* of the peak due to nimodipine is not more than 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to nimodipine impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* other than any peak corresponding to impurity A is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of *methanol* to a quantity of the powdered tablets containing 60 mg of Nimodipine, mix with the aid of ultrasound for 5 minutes, add sufficient *methanol* to produce 100 mL, centrifuge and use the supernatant liquid.

(2) 0.06% w/v of *nimodipine BPCRS* in *methanol*.

(3) 0.0002% w/v of *nimodipine BPCRS* and 0.0002% w/v of *nimodipine impurity A BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to nimodipine and nimodipine impurity A is at least 1.5, and the *symmetry factor* of the peak due to nimodipine is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{26}N_2O_7$ in the tablets using the declared content of $C_{21}H_{26}N_2O_7$ in *nimodipine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nimodipine.

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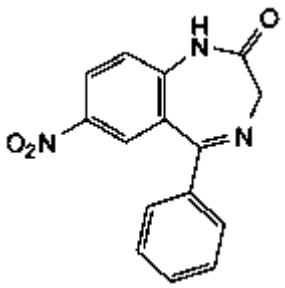
Nitrazepam

General Notices

(Ph. Eur. monograph 0415)



$C_{15}H_{11}N_3O_3$ 281.3 *146-22-5*

Action and use

Benzodiazepine.

Preparations

Nitrazepam Oral Suspension

Nitrazepam Tablets

Ph Eur

DEFINITION

7-Nitro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellow, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison nitrazepam CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 50 mg of the substance to be examined in acetonitrile R and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with acetonitrile R. Dilute 1.0 mL of this solution to 10.0 mL with acetonitrile R.

Reference solution (b) Dissolve 2 mg of clonazepam CRS in acetonitrile R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 7.8 g/L solution of sodium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	65	35
3 - 10	65 → 50	35 → 50
10 - 20	50	50

Flow rate 1 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 10 µL.

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Relative retention With reference to nitrazepam (retention time = about 9 min): clonazepam = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to clonazepam and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to nitrazepam.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 25 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 28.13 mg of $C_{15}H_{11}N_3O_3$.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D.*

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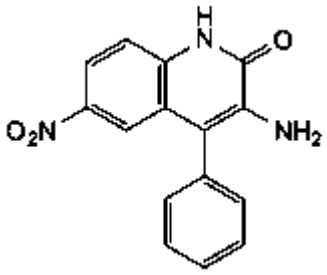
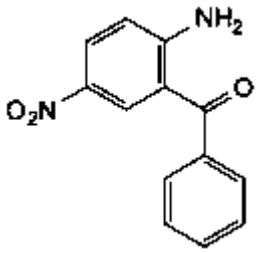
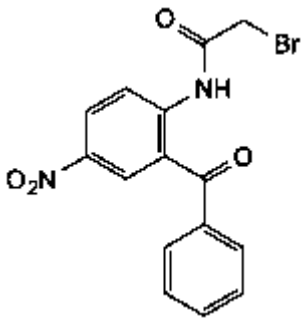


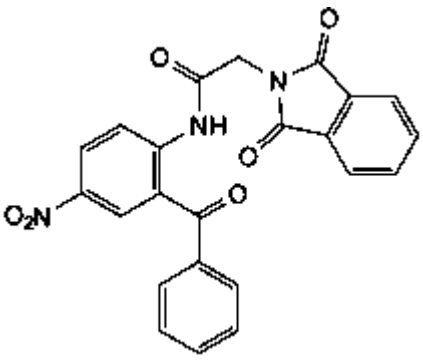
A. 3-amino-6-nitro-4-phenylquinolin-2(1*H*)-one,



B. (2-amino-5-nitrophenyl)phenylmethanone,



C. 2-bromo-*N*-[4-nitro-2-(phenylcarbonyl)phenyl]acetamide,



D. 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-*N*-[4-nitro-2-(phenylcarbonyl)phenyl]acetamide.

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Nitrazepam Oral Suspension

General Notices

Action and use

Benzodiazepine.

DEFINITION

Nitrazepam Oral Suspension is a suspension of Nitrazepam in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of nitrazepam, $C_{15}H_{11}N_3O_3$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the oral suspension containing 2.5 mg of Nitrazepam with 10 mL of *acetonitrile*, centrifuge and use the supernatant liquid.

(2) 0.025% w/v of *nitrazepam BPCRS in methanol*.

(3) 0.025% w/v each of *nitrazepam BPCRS* and *diazepam BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *dilute potassium iodobismuthate solution* and examine in daylight.

MOBILE PHASE

5 volumes of *concentrated ammonia*, 10 volumes of *methanol* and 85 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Carry out the following tests protected from light.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the oral suspension containing 5 mg of Nitrazepam with 60 mL of *acetonitrile*, add sufficient *acetonitrile* to produce 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.

(3) 0.01% w/v of *nitrazepam BPCRS* and 0.0002% w/v of *clonazepam BPCRS* in *acetonitrile*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Licrospher RP8 is suitable) and a stainless steel guard column (4 mm × 2 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Phenomenex C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05M *sodium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*.

Mobile phase B 20 volumes of mobile phase A and 80 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to nitrazepam (retention time about 9 minutes) are: impurity A, about 1.3 and impurity B, about 1.6.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0→3	55	45	isocratic
3→10	55→37	45→63	linear gradient
10→20	37	63	isocratic
20→22	37→55	63→45	linear gradient
22→30	55	45	re-equilibration

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nitrazepam and clonazepam is at least 1.3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.8 times the area of the principal peak in the chromatogram obtained with solution (2) (1.8%);

the area of any peak corresponding to impurity B is not greater than 3.2 times the area of the principal peak in the chromatogram obtained with solution (2) (3.2%);

the area of any other *secondary peak* is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (6%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add a weighed quantity of the oral suspension containing 12.5 mg of Nitrazepam to 25 mL of *water*, extract with three 50-mL quantities of *chloroform*, filtering each extract through phase-separating paper and add sufficient *chloroform* to produce 200 mL.
(2) 0.00625% w/v of *nitrazepam BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Lichrosorb or Partisil is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

10 volumes of *absolute ethanol* and 90 volumes of *n-hexane*.

Under the prescribed conditions the retention time of the peak due to nitrazepam is about 8 minutes.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{11}N_3O_3$, weight in volume, using the declared content of $C_{15}H_{11}N_3O_3$ in *nitrazepam BPCRS*.

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STORAGE

Nitrazepam Oral Suspension should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nitrazepam.

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Nitrazepam Tablets

General Notices

Action and use

Benzodiazepine.

DEFINITION

Nitrazepam Tablets contain Nitrazepam.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of Nitrazepam, $C_{15}H_{11}N_3O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 30 mg of Nitrazepam with 10 mL of *acetone*, filter and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of nitrazepam (*RS 482*).

TESTS

Carry out the following tests protected from light.

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 280 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *nitrazepam BPCRS* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of nitrazepam, $C_{15}H_{11}N_3O_3$, in the medium from the absorbances obtained and using the declared content of $C_{15}H_{11}N_3O_3$ in *nitrazepam BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 25 mg of Nitrazepam with 10 mL of *acetonitrile*, add sufficient *acetonitrile* to produce 20 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.

(3) 0.1% w/v of *nitrazepam BPCRS* and 0.002% w/v of *clonazepam BPCRS* in *acetonitrile*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05M *sodium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*.

Mobile phase B 20 volumes of mobile phase A and 80 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions the approximate retention time of nitrazepam is about 9 minutes. The retention times relative to nitrazepam are clonazepam, about 1.1; impurity A, about 1.34; impurity B, about 1.58.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0→3	55	45	isocratic
3→10	55→37	45→63	linear gradient
10→20	37	63	isocratic
20→22	37→55	63→45	linear gradient
22→30	55	45	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nitrazepam and clonazepam is at least 1.3.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of nitrazepam, comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse one tablet with 30 mL of *acetonitrile* with the aid of ultrasound, add sufficient *acetonitrile* to produce 50 mL and filter. Dilute the filtrate, if necessary, to produce a solution containing 0.01% w/v of Nitrazepam.
(2) 0.01% w/v of *nitrazepam BPCRS* in *acetonitrile*.
(3) 0.01% w/v of *nitrazepam BPCRS* and 0.002% w/v of *clonazepam BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 270 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.05M *sodium dihydrogen orthophosphate*, previously adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nitrazepam and clonazepam is at least 1.3.

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DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}N_3O_3$ in each tablet using the declared content of $C_{15}H_{11}N_3O_3$ in *nitrazepam BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Nitrazepam

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Nitrazepam

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 5 mg of Nitrazepam with 30 mL of *acetonitrile*, add sufficient *acetonitrile* to produce 50 mL and filter.

(2) 0.01% w/v of *nitrazepam BPCRS* in *acetonitrile*.

(3) 0.01% w/v of *nitrazepam BPCRS* and 0.002% w/v of *clonazepam BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nitrazepam and clonazepam is at least 1.3.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}N_3O_3$ in the tablets using the declared content of $C_{15}H_{11}N_3O_3$ in *nitrazepam BPCRS*.

STORAGE

Nitrazepam Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Nitrazepam.

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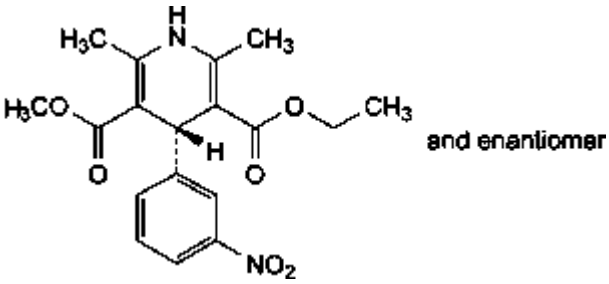
Nitrendipine

General Notices

(Ph. Eur. monograph 1246)



and enantiomer

$C_{18}H_{20}N_2O_6$ 360.4 *39562-70-4*

Action and use

Calcium channel blocker.

Ph Eur

DEFINITION

Ethyl methyl (4*RS*)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethyl acetate, sparingly soluble in anhydrous ethanol and in methanol.

It shows polymorphism (*5.9*).

Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative.

Prepare solutions immediately before use either protected from light or under long-wavelength light (> 420 nm).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison nitrendipine CRS.

If the spectra obtained in the solid state show differences, record new spectra using 20 g/L solutions in methylene chloride R and a 0.2 mm cell.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in 2.5 mL of tetrahydrofuran R and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 15.0 mg of nitrendipine impurity A CRS in 2.5 mL of tetrahydrofuran R and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c) Dilute 0.5 mL of the test solution to 20.0 mL with the mobile phase.

Reference solution (d) Mix 1.0 mL of reference solution (b) and 1.0 mL of reference solution (c), then dilute to 25.0 mL with the mobile phase.

Reference solution (e) Dissolve 2 mg of nitrendipine for peak identification CRS (containing impurities B and C) in 0.5 mL of tetrahydrofuran R and dilute to 1.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: irregular octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase acetonitrile R, tetrahydrofuran R, water R (14:22:64 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL of the test solution and reference solutions (a), (d) and (e).

Run time 5 times the retention time of nitrendipine.

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Identification of impurities Use the chromatogram supplied with *nitrendipine for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities B and C; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention With reference to nitrendipine (retention time = about 9 min): impurity B = about 0.7; impurity A = about 0.8; impurity C = about 1.4.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to impurity A and nitrendipine.

Limits:

— *impurities B, C*: for each impurity, not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 0.7 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.160 g with gentle heating if necessary in a mixture of 25 mL of *2-methyl-2-propanol R* and 25 mL of *perchloric acid solution R*. Titrate with *0.1 M cerium sulfate*, using 0.1 mL of *ferroin R* as indicator. Titrate slowly towards the end of the titration. Carry out a blank titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 18.02 mg of $C_{18}H_{20}N_2O_6$.

STORAGE

Protected from light.

IMPURITIES

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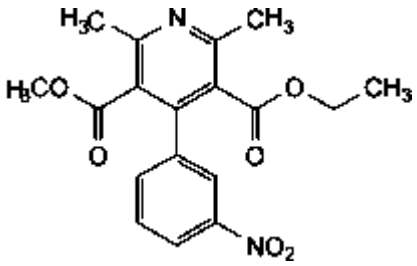
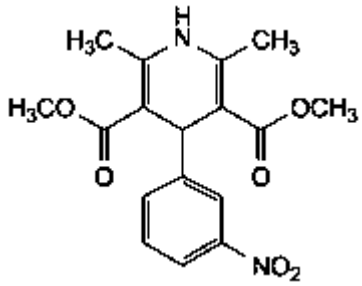
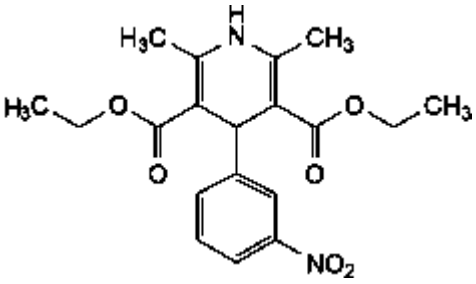
Specified impurities *A, B, C.*



A. ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate,



B. dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate,



C. diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

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Nitric Acid

General Notices

(Ph. Eur. monograph 1549)

HNO_3 63.0 *7697-37-2*

Ph Eur

DEFINITION

Content

68.0 per cent *m/m* to 70.0 per cent *m/m*.

CHARACTERS

Appearance

Clear, colourless or almost colourless liquid.

Solubility

Miscible with water.

Relative density

About 1.41.

IDENTIFICATION

A. Dilute 1 mL to 100 mL with *water R*. The solution is strongly acid (*2.2.4*).

B. 0.2 mL of the solution obtained in identification test A gives the reaction of nitrates (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dilute 2 mL to 10 mL with *water R*.

Chlorides (*2.4.4*)

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Maximum 0.5 ppm.

To 5 g add 10 mL of *water R* and 0.3 mL of *silver nitrate solution R2* and allow to stand for 2 min protected from light. Any opalescence is not more intense than that of a standard prepared at the same time in the same manner using 13 mL of *water R*, 0.5 mL of *nitric acid R*, 0.5 mL of *chloride standard solution (5 ppm Cl) R* and 0.3 mL of *silver nitrate solution R2*.

Sulfates (*2.4.13*)

Maximum 10 ppm.

To 15 g add 0.2 g of *sodium carbonate R*. After carbon dioxide has evolved, evaporate to dryness. Dissolve the residue in 15 mL of *distilled water R*.

Iron (*2.4.9*)

Maximum 10 ppm.

Dissolve the residue obtained in the test for sulfated ash in 1 mL of *dilute hydrochloric acid R* and dilute to 20 mL with *water R*. Dilute 1 mL of this solution to 10 mL with *water R*.

Sulfated ash

Maximum 0.01 per cent.

Carefully evaporate 20.00 g to dryness. Moisten the residue with a few drops of *sulfuric acid R* and ignite to dull red.

ASSAY

To 0.750 g add 50 mL of *water R* and titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 63.0 mg of HNO_3.

STORAGE

Protected from light.

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Nitric Oxide

General Notices

(Ph. Eur. monograph 1550)

NO 30.01 *10102-43-9*

Ph Eur

DEFINITION

Content

Minimum 99.0 per cent *V/V* of NO.

This monograph applies to nitric oxide for medicinal use.

CHARACTERS

Appearance

Colourless gas which turns brown when exposed to air.

Solubility

At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 21 volumes of water.

PRODUCTION

Carbon dioxide

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas Mixture containing 3000 ppm *V/V* of *carbon dioxide R1* in *nitrogen R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 3.5 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R*;

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— *temperature*: 50 °C.

Carrier gas helium for chromatography R.

Flow rate 15 mL/min.

Detection Thermal conductivity.

Injection Loop injector.

System suitability:

— the chromatograms obtained show a clear separation of carbon dioxide from nitric oxide.

Limit:

— carbon dioxide: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (3000 ppm *V/V*).

Nitrogen

Gas chromatography (2.2.28).

Gas to be examined The substance to be examined.

Reference gas Mixture containing 3000 ppm *V/V* of nitrogen R in helium for chromatography R.

Column:

— *material*: stainless steel;

— *size*: *l* = 3.5 m, Ø = 2 mm;

— *stationary phase*: molecular sieve for chromatography R (0.5 nm);

— *temperature*: 50 °C.

Carrier gas helium for chromatography R.

Flow rate 15 mL/min.

Detection Thermal conductivity.

Injection Loop injector.

System suitability:

— the chromatograms obtained show a clear separation of nitrogen from nitric oxide.

Limit:

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— *nitrogen*: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (3000 ppm *V/V*).

Nitrogen dioxide

Maximum 400 ppm *V/V*.

Ultraviolet absorption spectrophotometry analyser.

Gas to be examined The substance to be examined.

Reference gas (a) *nitrogen R1*.

Reference gas (b) Mixture containing 400 ppm *V/V* of *nitrogen dioxide R* in *nitrogen R*.

Apparatus:

— an ultraviolet-visible light source (analytical wavelength about 400 nm);

— a sample gas cell through which the feed gas flows;

— a closed reference gas cell containing *nitrogen R1* in parallel with the sample gas cell;

— a rotating chopper which feeds light alternately through the reference gas cell and the sample gas cell;

— a semiconductor detector which generates a frequency modulated output whose amplitude is a measure of the difference of absorption of the sample gas and the reference gas.

Analysis:

— set the zero of the instrument using reference gas (a) through the sample gas cell at a flow rate of 1 L/min;

— adjust the span while feeding reference gas (b) through the sample gas cell at a flow rate of 1 L/min;

— feed the gas to be examined through the sample gas cell at a flow rate of 1 L/min, read the value from the instrument output and calculate, if necessary, the concentration of nitrogen dioxide.

Nitrous oxide

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas Mixture containing 3000 ppm *V/V* of *nitrous oxide R* in *nitrogen R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 3.5 m, Ø = 2 mm;

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— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R*;

— *temperature*: 50 °C.

Carrier gas *helium for chromatography R*.

Flow rate 15 mL/min.

Detection Thermal conductivity.

Injection Loop injector.

System suitability:

— the chromatograms obtained show a clear separation of nitrous oxide from nitric oxide.

Limit:

— *nitrous oxide*: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (3000 ppm *V/V*).

Water (*2.5.28*)

Maximum 100 ppm *V/V*.

Assay

Determine the content of nitric oxide by difference using the mass balance equation after determining the sum of the impurities described under Production.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of nitric oxide*.

STORAGE

Compressed at a pressure not exceeding 2.5 MPa (25 bar) measured at 15 °C, in suitable containers complying with the legal regulations.

IMPURITIES

Specified impurities *A, B, C, D, E.*

A. CO_2: carbon dioxide,

B. N_2: nitrogen,

C. NO_2: nitrogen dioxide,

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D. N_2O: nitrous oxide,

E. H_2O: water.

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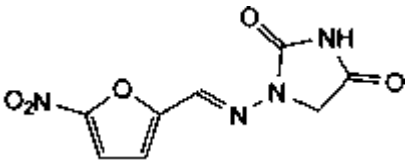
Nitrofurantoin

General Notices

(Ph. Eur. monograph 0101)



$C_8H_6N_4O_5$ 238.2 *67-20-9*

Action and use

Antibacterial.

Preparations

Nitrofurantoin Oral Suspension

Nitrofurantoin Tablets

Ph Eur

DEFINITION

Nitrofurantoin contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 1-[[(5-nitrofuran-2-yl)methylene]amino]imidazolidine-2,4-dione, calculated with reference to the dried substance.

CHARACTERS

A yellow, crystalline powder or yellow crystals, very slightly soluble in water and in ethanol (96 per cent), soluble in dimethylformamide.

IDENTIFICATION

A. *Carry out the test protected from bright light*. Use the solution prepared for the assay. Examined between 220 nm and 400 nm (*2.2.25*), the solution shows two absorption maxima, at 266 nm and 367 nm. The ratio of the absorbance at the maximum at 367 nm to that at the maximum at 266 nm is 1.36 to 1.42.

B. Dissolve about 10 mg in 10 mL of *dimethylformamide R*. To 1 mL of the solution add 0.1 mL of 0.5 M alcoholic potassium hydroxide. A brown colour develops.

TESTS

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Related substances

Examine by thin-layer chromatography (2.2.27), using *silica gel HF_{254} R* as the coating substance.

Test solution Dissolve 0.25 g of the substance to be examined in a minimum of *dimethylformamide R* and dilute to 10 mL with *acetone R*.

Reference solution Dilute 1 mL of the test solution to 100 mL with *acetone R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *methanol R* and 90 volumes of *nitromethane R*. Allow the plate to dry in air and heat at 100 °C to 105 °C for 5 min. Examine in ultraviolet light at 254 nm. Spray with *phenylhydrazine hydrochloride solution R*. Heat the plate at 100 °C to 105 °C for a further 10 min. When examined in ultraviolet light and after spraying, any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (1.0 per cent).

Loss on drying (2.2.32)

Not more than 1.0 per cent, determined on 1.00 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the assay protected from bright light Dissolve 0.120 g in 50 mL of *dimethylformamide R* and dilute to 1000.0 mL with *water R*. Dilute 5.0 mL of the solution to 100.0 mL with a solution containing 18 g/L of *sodium acetate R* and 0.14 per cent *V/V* of *glacial acetic acid R*. Measure the absorbance (2.2.25) at the absorption maximum at 367 nm, using the sodium acetate solution described above as compensation liquid.

Calculate the content of $C_8H_6N_4O_5$, taking the specific absorbance to be 765.

STORAGE

Store protected from light, at a temperature below 25 °C.

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Nitrofurantoin Oral Suspension

General Notices

Action and use

Antibacterial.

DEFINITION

Nitrofurantoin Oral Suspension is a suspension of Nitrofurantoin in a suitable flavoured vehicle.

Nitrofurantoin Oral Suspension should not be diluted.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of nitrofurantoin, $C_8H_6N_4O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 300 to 400 nm, of the final solution obtained in the Assay exhibits a maximum at 367 nm.

B. Dissolve 5 mg of the residue obtained by centrifuging a quantity of the oral suspension containing 50 mg of Nitrofurantoin in 5 mL of 0.1M *sodium hydroxide*. A deep yellow solution is produced, which changes to deep orange-red.

ASSAY

Carry out the following procedure in subdued light. To a weighed quantity containing 30 mg of Nitrofurantoin add, in successive small volumes, 50 mL of *dimethylformamide*, stirring well between each addition. Continue stirring until the sample is completely dissolved and dilute to 500 mL with an aqueous solution containing 1.8% w/v of *sodium acetate* and 0.14% v/v of *glacial acetic acid*. Dilute 10 mL of this solution to 100 mL with the sodium acetate-acetic acid solution and measure the *absorbance* of the resulting solution at the maximum at 367 nm, Appendix II B, using in the reference cell a 1% v/v solution of *dimethylformamide* in the sodium acetate-acetic acid solution. Calculate the content of $C_8H_6N_4O_5$ taking 765 as the value of A(1%, 1 cm) at the maximum at 367 nm. Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_8H_6N_4O_5$, weight in volume.

STORAGE

Nitrofurantoin Oral Suspension should be protected from light.

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Nitrofurantoin Tablets

General Notices

Action and use

Antibacterial.

DEFINITION

Nitrofurantoin Tablets contain Nitrofurantoin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nitrofurantoin, $C_8H_6N_4O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

The *light absorption*, Appendix II B, in the range 220 to 400 nm of the final solution obtained in the Assay exhibits two maxima, at 266 nm and 367 nm.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* HF_{254} as the coating substance and a mixture of 10 volumes of *methanol* and 90 volumes of *nitromethane* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.1 g of Nitrofurantoin with 10 mL of a mixture of 1 volume of *dimethylformamide* and 9 volumes of *acetone* and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *acetone*. After removal of the plate, allow it to dry in air, heat at 100° to 105° for 5 minutes and examine under *ultraviolet light (254 nm)*. Spray the plate with *phenylhydrazine hydrochloride solution* and heat it at 100° to 105° for a further 10 minutes. By each method of visualisation, any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the following procedure in subdued light. Weigh and powder 20 tablets. To a quantity of the powder containing 0.12 g of Nitrofurantoin add 50 mL of *dimethylformamide*, shake for 5 minutes, add sufficient *water* to produce 1000 mL and mix. Dilute 5 mL to 100 mL with a solution containing 1.8% w/v of *sodium acetate* and 0.14% v/v of *glacial acetic acid* and filter. Measure the *absorbance* of the filtrate at the maximum at 367 nm, Appendix II B, using the sodium acetate-acetic acid solution in the reference cell. Calculate the content of $C_8H_6N_4O_5$ taking 765 as the value of A(1%, 1 cm) at 367 nm.

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STORAGE

Nitrofurantoin Tablets should be protected from light.

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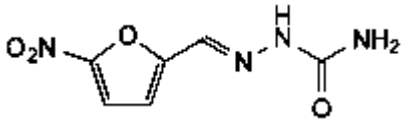
Nitrofurazone

General Notices

(Nitrofural, Ph. Eur. monograph 1135)



$C_6H_6N_4O_4$ 198.1 *59-87-0*

Action and use

Antibacterial; topical antiprotozoal.

Ph Eur

DEFINITION

2-[(5-Nitrofuran-2-yl)methylene]diazanecarboxamide.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow or brownish-yellow, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25). *Carry out the test protected from bright light.*

Test solution Use the solution prepared for the assay.

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Spectral range 220-400 nm.

Absorption maxima At 260 nm and 375 nm.

Absorbance ratio A_{375}/A_{260} = 1.15 to 1.30.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *nitrofural CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *nitrofural CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *methanol R*, *nitromethane R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with *phenylhydrazine hydrochloride solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 1 mg in 1 mL of *dimethylformamide R* and add 0.1 mL of *alcoholic potassium hydroxide solution R*. A violet-red colour is produced.

TESTS

pH (2.2.3)

5.0 to 7.0.

To 1.0 g add 100 mL of *carbon dioxide-free water R*. Shake and filter.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

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Reference solution (a) Dissolve 10.0 mg of *nitrofural impurity B CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of the substance to be examined and 10 mg of *nitrofurantoin R* in the mobile phase and dilute to 100 mL with the mobile phase. Dilute 5 mL of the solution to 100 mL with the mobile phase.

Reference solution (c) Dissolve, using sonication, the contents of a vial of *nitrofural for peak identification A CRS* (containing impurity A) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *water for chromatography R* (40:60 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 310 nm.

Injection 20 µL.

Run time 10 times the retention time of nitrofural.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B; use the chromatogram supplied with *nitrofural for peak identification A CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to nitrofural (retention time = about 4 min): nitrofurantoin = about 1.2; impurity B = about 4.0; impurity A = about 7.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to nitrofural and nitrofurantoin.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

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Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the assay protected from bright light.

Dissolve 60.0 mg in 20 mL of *dimethylformamide R* and dilute to 500.0 mL with *water R*. Dilute 5.0 mL of the solution to 100.0 mL with *water R*. Prepare a reference solution in the same manner using 60.0 mg of *nitrofural CRS*. Measure the absorbances (*2.2.25*) of the 2 solutions at the absorption maximum at 375 nm.

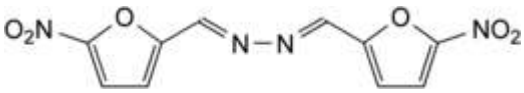
Calculate the content of $C_6H_6N_4O_4$ from the absorbances measured and the concentrations of the solutions.

STORAGE

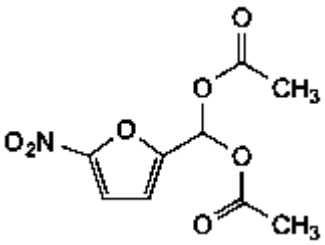
Protected from light.

IMPURITIES

Specified impurities *A, B.*



A. 1,2-bis[(5-nitrofuran-2-yl)methylidene]diazane,



B. (5-nitrofuran-2-yl)methylene diacetate.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Nitrogen

General Notices

(Ph. Eur. monograph 1247)

Nitrogen should be kept in approved metal cylinders, the shoulders of which are painted black and the remainder grey. The cylinder should carry a label stating 'Nitrogen'.

N_2 28.01 *7727-37-9*

Ph Eur

DEFINITION

Content

Minimum 99.5 per cent *V/V* of N_2.

This monograph applies to nitrogen for medicinal use.

CHARACTERS

Appearance

Colourless, odourless gas.

Solubility

At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 62 volumes of water and about 10 volumes of ethanol (96 per cent).

PRODUCTION

Carbon dioxide

Maximum 300 ppm *V/V*, determined using an infrared analyser (*2.5.24*).

Gas to be examined The substance to be examined. It must be filtered to avoid stray light phenomena.

Reference gas (a) *Nitrogen R1*.

Reference gas (b) Mixture containing 300 ppm *V/V* of *carbon dioxide R1* in *nitrogen R1*.

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Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon dioxide in the gas to be examined.

Carbon monoxide

Maximum 5 ppm *V/V*, determined using an infrared analyser (*2.5.25*).

Gas to be examined The substance to be examined. It must be filtered to avoid stray light phenomena.

Reference gas (a) *Nitrogen R1*.

Reference gas (b) Mixture containing 5 ppm *V/V* of *carbon monoxide R* in *nitrogen R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

Oxygen

Maximum 50 ppm *V/V*, determined using an oxygen analyser with a detector scale ranging from 0-100 ppm *V/V* and equipped with an electrochemical cell.

The gas to be examined passes through a detection cell containing an aqueous solution of an electrolyte, generally potassium hydroxide. The presence of oxygen in the gas to be examined produces variation in the electric signal recorded at the outlet of the cell that is proportional to the oxygen content.

Calibrate the analyser according to the instructions of the manufacturer. Pass the gas to be examined through the analyser using a suitable pressure regulator and airtight metal tubes and operating at the prescribed flow-rates until constant readings are obtained.

Water (*2.5.28*)

Maximum 67 ppm *V/V*.

Assay

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas (a) Ambient air.

Reference gas (b) *Nitrogen R1*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *molecular sieve for chromatography R* (0.5 nm).

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Carrier gas *helium for chromatography R*.

Flow rate 40 mL/min.

Temperature:

— *column*: 50 °C;

— *detector*: at a constant temperature between 50 °C and 200 °C.

Detection Thermal conductivity.

Injection 1 mL loop injector.

System suitability Reference gas (a):

— *resolution*: minimum 1.5 between the peaks due to oxygen and nitrogen.

The requirement for the symmetry factor (see general chapter *2.2.46*) does not apply.

Calculate the content of N_2 in the gas to be examined.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Examine the chromatograms obtained in the assay (see Production).

Results The principal peak in the chromatogram obtained with the substance to be examined is similar in retention time to the principal peak in the chromatogram obtained with reference gas (b).

B. In a 250 mL conical flask replace the air by the substance to be examined. Place a burning or glowing splinter of wood in the flask. The splinter is extinguished.

C. In a suitable test tube, place 0.1 g of *magnesium R* in turnings. Close the tube with a two-hole stopper fitted with a glass tube reaching about 1 cm above the turnings. Pass the substance to be examined through the glass tube for 1 min without heating, then for 15 min while heating the test tube to a red glow. After cooling, add 5 mL of *dilute sodium hydroxide solution R*. The evolving vapours change the colour of moistened *red litmus paper R* blue.

TESTS

Carbon dioxide (*2.1.6*)

Maximum 300 ppm *V/V*, determined using a carbon dioxide detector tube.

Carbon monoxide (*2.1.6*)

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Maximum 5 ppm *V/V*, determined using a carbon monoxide detector tube.

Water vapour (2.1.6)

Maximum 67 ppm *V/V*, determined using a water vapour detector tube.

STORAGE

As a compressed gas or a liquid in appropriate containers complying with the legal regulations.

IMPURITIES

Specified impurities *A, B, C, D.*

A. CO_2: carbon dioxide,

B. CO: carbon monoxide,

C. O_2: oxygen,

D. H_2O: water.

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Nitrous Oxide

General Notices

(Ph. Eur. monograph 0416)

Nitrous oxide should be kept in approved metal cylinders which are painted blue and carry a label stating 'Nitrous Oxide'. In addition, 'Nitrous Oxide' or the symbol 'N2O' should be stencilled in paint on the shoulder of the cylinder.

N_2O 44.01 *10024-97-2*

Action and use

General anaesthetic; analgesic.

Ph Eur

DEFINITION

Content

Minimum 98.0 per cent *V/V* of N_2O in the gaseous phase, when sampled at 15 °C.

This monograph applies to nitrous oxide for medicinal use.

CHARACTERS

Appearance

Colourless gas.

Solubility

At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 1.5 volumes of water.

PRODUCTION

Nitrous oxide is produced from ammonium nitrate by thermic decomposition.

Examine the gaseous phase.

If the test is performed on a cylinder, keep the cylinder at room temperature for at least 6 h before carrying out the tests. Keep the cylinder in the vertical position with the outlet valve uppermost.

Carbon dioxide

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Gas chromatography (2.2.28).

Gas to be examined The substance to be examined.

Reference gas A mixture containing 300 ppm *V/V* of carbon dioxide R1 in nitrous oxide R.

Column:

— *material*: stainless steel;

— *size*: *l* = 3.5 m, Ø = 2 mm;

— *stationary phase*: ethylvinylbenzene-divinylbenzene copolymer R.

Carrier gas helium for chromatography R.

Flow rate 15 mL/min.

Temperature:

— *column*: 40 °C;

— *detector*: 90 °C.

Detection Thermal conductivity.

Injection Loop injector.

Adjust the injected volumes and operating conditions so that the height of the peak due to carbon dioxide in the chromatogram obtained with the reference gas is at least 35 per cent of the full scale of the recorder. The test is not valid unless the chromatograms obtained show a clear separation of carbon dioxide from nitrous oxide.

Limit:

— carbon dioxide: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (300 ppm *V/V*).

Carbon monoxide

Gas chromatography (2.2.28). *When the test is carried out on a cylinder, use the first portion of gas to be withdrawn.*

Gas to be examined The substance to be examined.

Reference gas A mixture containing 5 ppm *V/V* of carbon monoxide R in nitrous oxide R.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 4 mm;

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— *stationary phase*: suitable molecular sieve for chromatography (0.5 nm).

Carrier gas helium for chromatography R.

Flow rate 60 mL/min.

Temperature:

— *column*: 50 °C;

— *injection port and detector*: 130 °C.

Detection Flame ionisation with methaniser.

Injection Loop injector.

Adjust the injected volumes and the operating conditions so that the height of the peak due to carbon monoxide in the chromatogram obtained with the reference gas is at least 35 per cent of the full scale of the recorder.

Limit:

— carbon monoxide: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (5 ppm *V/V*).

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V* in total in the gaseous and liquid phases, determined using a chemiluminescence analyser (2.5.26).

Gas to be examined The substance to be examined.

Reference gas (a) Nitrous oxide R.

Reference gas (b) A mixture containing 2 ppm *V/V* of nitrogen monoxide R in nitrogen R1.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of nitrogen monoxide and nitrogen dioxide, separately examining the samples collected from the gaseous phase and the liquid phase of the gas to be examined.

Multiply the result obtained by the quenching correction factor in order to correct the quenching effect on the analyser response caused by the nitrous oxide matrix effect.

The quenching correction factor is determined by applying a known reference mixture of nitrogen monoxide in nitrous oxide and comparing the actual content with the content indicated by the analyser which has been calibrated with an NO/N_2 reference mixture.

$$\text{Quenching correction factor} = \frac{\text{actual nitrogen monoxide content}}{\text{indicated nitrogen monoxide content}}$$

Water

Maximum 67 ppm *V/V*, determined using an electrolytic hygrometer (2.5.28).

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Assay

Infrared analyser (2.5.35).

Gas to be examined The substance to be examined. It must be filtered to avoid stray light phenomena.

Reference gas (a) Nitrous oxide R.

Reference gas (b) A mixture containing 5.0 per cent *V/V* of nitrogen R1 and 95.0 per cent *V/V* of nitrous oxide R.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of nitrous oxide in the gas to be examined.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. It complies with the limits of the assay.
B. Place a glowing splinter of wood in the substance to be examined. The splinter bursts into flame.
C. Introduce the substance to be examined into alkaline pyrogallol solution R. A brown colour does not develop.

TESTS

Examine the gaseous phase.

If the test is performed on a cylinder, keep the cylinder of the substance to be examined at room temperature for at least 6 h before carrying out the tests. Keep the cylinder in the vertical position with the outlet valve uppermost.

Carbon dioxide

Maximum 300 ppm *V/V*, determined using a carbon dioxide detector tube (2.1.6).

Carbon monoxide

Maximum 5 ppm *V/V*, determined using a carbon monoxide detector tube (2.1.6). *When the test is carried out on a cylinder, use the first portion of the gas to be withdrawn.*

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V*, determined using a nitrogen monoxide and nitrogen dioxide detector tube (2.1.6).

Water vapour

Maximum 67 ppm *V/V*, determined using a water vapour detector tube (2.1.6).

STORAGE

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Store liquefied under pressure in suitable containers complying with the legal regulations. The taps and valves are not greased or oiled.

IMPURITIES

Specified impurities *A, B, C, D, E.*

A. CO_2: carbon dioxide,

B. CO: carbon monoxide,

C. NO: nitrogen monoxide,

D. NO_2: nitrogen dioxide,

E. H_2O: water.

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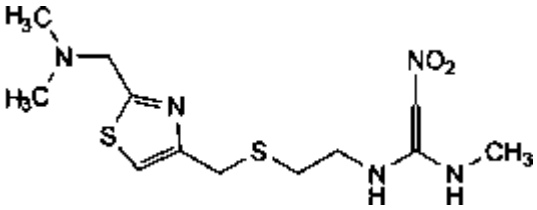
Nizatidine

General Notices

(Ph. Eur. monograph 1453)



$C_{12}H_{21}N_5O_2S_2$ 331.5 *76963-41-2*

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer.

Preparation

Nizatidine Infusion

Ph Eur

DEFINITION

(*EZ*)-*N*-[2-[[[2-[(Dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-*N*′-methyl-2-nitroethene-1,1-diamine.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Almost white or slightly brownish, crystalline powder.

Solubility

Sparingly soluble in water, soluble in methanol.

IDENTIFICATION

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First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 131 °C to 134 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.10 g in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *methanol R*.

Spectral range 220-350 nm.

Absorption maxima At 242 nm and 325 nm.

Absorbance ratio A_{325}/A_{242} = 2.2 to 2.5.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *nizatidine CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *nizatidine CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 50 mg of *nizatidine CRS* and 50 mg of *ranitidine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *concentrated ammonia R1*, *2-propanol R*, *ethyl acetate R* (4:8:30:50 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots are clearly visible. Examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

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Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Dissolve 0.2 g in a 10 g/L solution of *hydrochloric acid R* and dilute to 20 mL with the same solution.

pH (2.2.3)

8.5 to 10.0.

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase B, mobile phase A (15:85 *V/V*).

Test solution (a) Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 15.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 15.0 mg of *nizatidine CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of the substance to be examined and 0.5 mg of *nizatidine impurity F CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *2-(dimethylamino)thioacetamide hydrochloride R* (impurity H hydrochloride) in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 20.0 mL with the solvent mixture. Use 1.0 mL of this solution to dissolve 5 mg of *nizatidine for system suitability CRS* (containing impurities A, B, C, D, G, J and K).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 5.9 g of *ammonium acetate R* in 760 mL of *water R*, add 1 mL of *diethylamine R*, and adjust to pH 7.5 with *acetic acid R*;

— *mobile phase B*: *methanol R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	85	15
3 - 20	85 → 50	15 → 50
20 - 45	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram supplied with *nizatidine for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, G, H, J and K; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity F.

Relative retention With reference to nizatidine (retention time = about 18 min): impurity A = about 0.19; impurity K = about 0.21; impurity H = about 0.5; impurity B = about 0.6; impurity C = about 0.66; impurity J = about 0.7; impurity D = about 0.75; impurity F = about 1.03; impurity G = about 1.5.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to nizatidine and impurity F in the chromatogram obtained with reference solution (c); minimum 1.5 between the peaks due to impurities A and K in the chromatogram obtained with reference solution (d).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.7; impurity D = 2.3; impurity H = 0.5;

— *impurities A, B, C, D, F, G, H, J, K*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (35:65 *V/V*).

Injection Test solution (b) and reference solution (b).

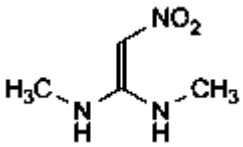
Retention time Nizatidine = 9 min.

Calculate the percentage content of $C_{12}H_{21}N_5O_2S_2$ taking into account the assigned content of *nizatidine CRS*.

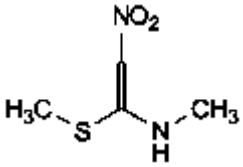
IMPURITIES

Specified impurities *A, B, C, D, F, G, H, J, K.*

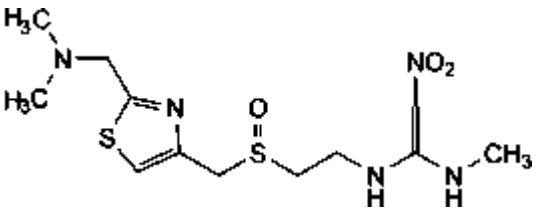
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, I.*



A. *N,N′*-dimethyl-2-nitroethene-1,1-diamine,



B. (*EZ*)-*N*-methyl-1-(methylsulfanyl)-2-nitroethen-1-amine,



C. (*EZ*)-*N*-[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfinyl]ethyl]-*N′*-methyl-2-nitroethene-1,1-diamine,

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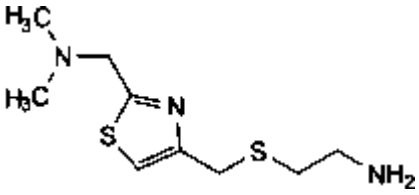
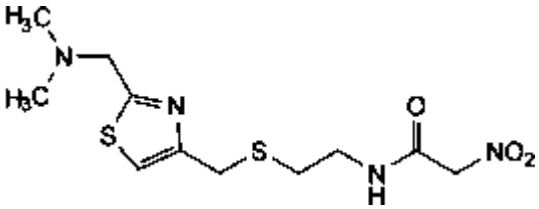
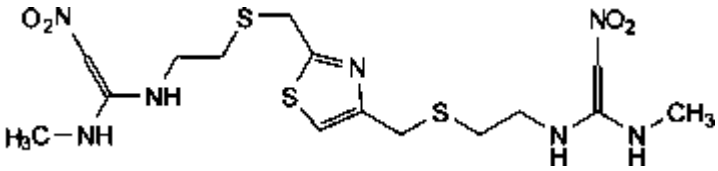


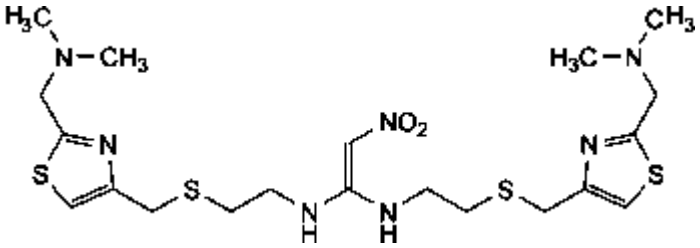
D. 2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethanamine,



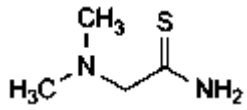
E. *N*-[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-2-nitroacetamide,



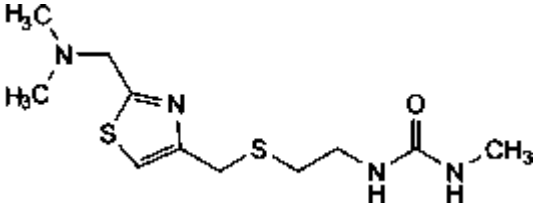
F. (*EZ*)-*N*-methyl-*N*′-[2-[[[4-[[[2-[[(*EZ*)-1-(methylamino)-2-nitroethenyl]amino]ethyl]sulfanyl]methyl]thiazol-2-yl]methyl]sulfanyl]ethyl]-2-nitroethene-1,1-diamine,



G. *N*,*N*′-bis[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-2-nitroethene-1,1-diamine,



H. 2-(dimethylamino)thioacetamide,



I. *N*-[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-*N*′-methylurea,

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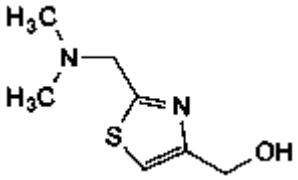
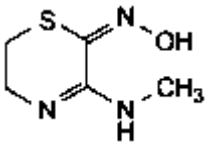


J. [2-[(dimethylamino)methyl]thiazol-4-yl]methanol,



K. 3-(methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-one oxime.

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Nizatidine Infusion

General Notices

Nizatidine Intravenous Infusion

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer.

DEFINITION

Nizatidine Infusion is a sterile solution containing Nizatidine. It is prepared by diluting Nizatidine Sterile Concentrate with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations.

NIZATIDINE STERILE CONCENTRATE

DEFINITION

Nizatidine Sterile Concentrate is a sterile solution of Nizatidine in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of nizatidine, $C_{12}H_{21}N_5O_2S_2$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless to yellow solution that darkens on storage.

IDENTIFICATION

Shake a volume of the concentrate containing 50 mg of Nizatidine with 10 mL of *dichloromethane* for 5 minutes. Filter the *dichloromethane* layer through *anhydrous sodium sulfate* and evaporate the filtrate to dryness on a rotary evaporator at 40°. Cool the residue in a refrigerator for 15 hours and, if necessary, induce crystallisation by scratching the wall of the container with a glass rod. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of nizatidine (*RS 410*).

TESTS

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Acidity or alkalinity

pH of the concentrate diluted with *water* to contain 1.0% w/v of Nizatidine, 6.0 to 8.0, Appendix V L.

Colour of solution

Dilute the concentrate with *water* to produce a solution containing 1.0% w/v of Nizatidine. The *absorbance* of the solution at 410 nm, Appendix II B, is not more than 0.40 determined using water in the reference cell.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the concentrate with mobile phase A to produce a solution containing 0.5% w/v of Nizatidine.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) 0.005% w/v of *nizatidine EPCRS* and 0.005% w/v of *nizatidine impurity F EPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelco LC-18-DB and Kromasil C18 are suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

Mobile phase A Dissolve 5.9 g of *ammonium acetate* in 760 mL of *water*, add 1 mL of *diethylamine* and adjust the pH to 7.5 with 6M *acetic acid* (solution A). Prepare a mixture of 24 volumes of *methanol* and 76 volumes of solution A.

Mobile phase B 50 volumes of *methanol* and 50 volumes of solution A.

Time (minutes)	Mobile phase A % v/v	Mobile phase B % v/v
0 – 3	100	0
3 – 20	100 → 0	0 → 100
20 – 45	0	100

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the retention time of Nizatidine is between 10 and 20 minutes and the *symmetry factor* of the peak due to Nizatidine is not greater than 2.0.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peak due to Nizatidine (first peak) and Nizatidine impurity F (second peak) is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak with a relative retention time of about 0.7 (impurity E) is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of any other *secondary peak* is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of all the *secondary peaks* is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the concentrate with mobile phase A to produce a solution containing 0.03% w/v of Nizatidine.
(2) 0.03% w/v solution of *nizatidine EPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to Nizatidine is not greater than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{12}H_{21}N_5O_2S_2$ in the concentrate using the declared content of $C_{12}H_{21}N_5O_2S_2$ in *nizatidine EPCRS*.

STORAGE

Nizatidine Sterile Concentrate should be protected from light.

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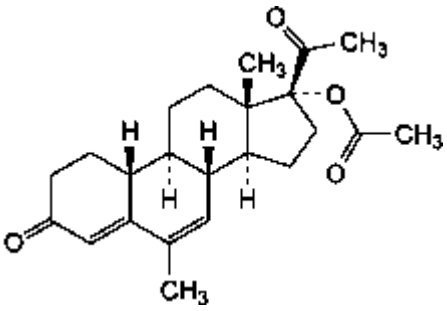
Nomegestrol Acetate

General Notices

(Ph. Eur. monograph 1551)



$C_{23}H_{30}O_4$ 370.5 *58652-20-3*

Action and use

Progestogen.

Ph Eur

DEFINITION

6-Methyl-3,20-dioxo-19-norpregna-4,6-dien-17-yl acetate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

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Comparison *nomegestrol acetate for ID and assay CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 1.0 g in *methylene chloride R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-64.0 to -60.0 (dried substance).

Dissolve 0.500 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 25.0 mg of *nomegestrol acetate for ID and assay CRS* in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 25.0 mg of *nomegestrol acetate impurity A CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 0.25 mL of the solution to 25.0 mL with reference solution (a).

Reference solution (d) Dissolve the contents of a vial of *nomegestrol acetate impurity B CRS* in 1 mL of *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, *methanol R1*, *water for chromatography R* (24:38:38 *V/V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 245 nm and at 290 nm.

Injection 10 µL of the test solution and reference solutions (b), (c), (d).

Run time 1.5 times the retention time of nomegestrol acetate.

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Identification of impurities Use the chromatogram obtained with reference solution (c) at 245 nm to identify the peak due to impurity A; use the chromatogram obtained with reference solution (d) at 290 nm to identify the peak due to impurity B.

Relative retention With reference to nomegestrol acetate (retention time = about 17 min): impurity B = about 0.6; impurity A = about 1.1.

System suitability Reference solution (c) at 245 nm:

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to nomegestrol acetate.

Calculation of percentage contents:

— for each impurity at 245 nm, use the concentration of impurity A in reference solution (c);

— for each impurity at 290 nm, use the concentration of nomegestrol acetate in reference solution (b).

Limits:

— *impurity A at 245 nm*: maximum 0.2 per cent;

— *impurity B at 290 nm*: maximum 0.15 per cent;

— *unspecified impurities at 245 nm and at 290 nm*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than A at 245 nm and 290 nm*: maximum 0.3 per cent;

— *reporting threshold at 245 nm and at 290 nm*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications:

Detection Spectrophotometer at 290 nm.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{23}H_{30}O_4$ taking into account the assigned content of *nomegestrol acetate for ID and assay CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B.*

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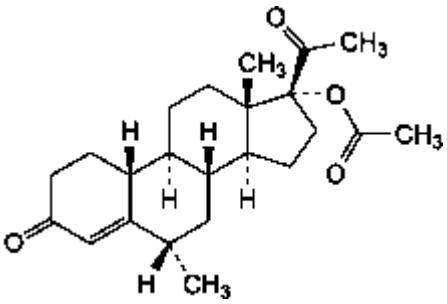
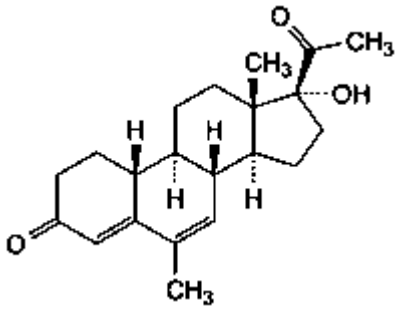


A. 6α-methyl-3,20-dioxo-19-norpregn-4-en-17-yl acetate,



B. 17-hydroxy-6-methyl-19-norpregna-4,6-diene-3,20-dione (nomegestrol).

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Nonoxinol 9

General Notices

(Ph. Eur. monograph 1454)

Action and use

Spermatocide.

Ph Eur

DEFINITION

α-(4-Nonylphenyl)-ω-hydroxynona(oxyethylene).

Mixture consisting mainly of monononylphenyl ethers of macrogols corresponding to the formula: $C_9H_{19}C_6H_4$-$[OCH_2$-$CH_2]_n$-OH where the average value of *n* is 9. It may contain free macrogols.

CHARACTERS

Appearance

Clear, colourless or light yellow, viscous liquid.

Solubility

Miscible with water, with ethanol (96 per cent) and with vegetable oils.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *nonoxinol 9 CRS*.

Preparation Film between *sodium chloride R* plates.

B. Cloud point (see Tests).

TESTS

Acidity or alkalinity

Boil 1.0 g with 20 mL of *carbon dioxide-free water R* for 1 min, with constant stirring. Cool and filter. To 10 mL of the filtrate, add 0.05 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the

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colour of the indicator.

Hydroxyl value (*2.5.3, Method A*)

84 to 94.

Cloud point

52 °C to 58 °C.

Dissolve 1.0 g in 99 g of *water R*. Transfer about 30 mL of this solution into a test-tube, heat on a water-bath and stir continuously until the solution becomes cloudy. Remove the test-tube from the water-bath (ensuring that the temperature does not increase to more than 2 °C) and continue to stir. The cloud point is the temperature at which the solution becomes sufficiently clear that the entire thermometer bulb is plainly seen.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 2.00 g.

Total ash (*2.4.16*)

Maximum 0.4 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

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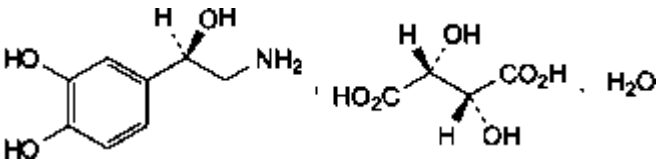
Noradrenaline Acid Tartrate / Norepinephrine Acid Tartrate

General Notices

(Noradrenaline Tartrate, Ph. Eur. monograph 0285)



$C_{12}H_{17}NO_9,H_2O$ 337.3 *108341-18-0*

Action and use

Alpha-adrenoceptor agonist.

Preparation

Noradrenaline Injection/Norepinephrine Injection

Ph Eur

DEFINITION

(1*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate monohydrate.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 2 g in 20 mL of a 5 g/L solution of *sodium metabisulfite R* and make alkaline by addition of *ammonia R*. Keep in iced water for 1 h and filter. Reserve the filtrate for identification test C. Wash the precipitate with 3 quantities, each of 2 mL, of *water R*, then with 5 mL of

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ethanol (96 per cent) R and finally with 5 mL of methylene chloride R and dry *in vacuo* for 3 h. The specific optical rotation (2.2.7) of the precipitate (noradrenaline base) is -48 to -44, determined using a 20.0 g/L solution in 0.5 M hydrochloric acid.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs of noradrenaline base prepared as described in identification test A.

Comparison Use noradrenaline base prepared as described in identification test A from a suitable amount of noradrenaline tartrate CRS.

C. 0.2 mL of the filtrate obtained in identification test A gives reaction (b) of tartrates (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

Dissolve 0.2 g in water R and dilute to 10 mL with the same solvent. Examine the solution immediately.

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from air. Remove oxygen from the mobile phases with nitrogen R immediately before use. Fill up the flasks.*

Test solution Dissolve 0.20 g of the substance to be examined in mobile phase A and dilute to 50 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 10 mg of the substance to be examined in 5 mL of 0.1 M hydrochloric acid. To 1 mL of this solution add 0.1 mL of strong hydrogen peroxide solution R and expose to UV light at 254 nm for 90 min. Dilute to 10 mL with mobile phase A. The degradation of noradrenaline produces 2 peaks, one with a relative retention of about 1.2 (unidentified compound) and the other with a relative retention of about 1.5 (impurity B). Use this solution to identify the peak due to impurity B.

Reference solution (c) Dissolve 7.5 mg of noradrenaline impurity D CRS and 5 mg of noradrenaline impurity E CRS in mobile phase A and dilute to 100 mL with mobile phase A.

Reference solution (d) Dissolve 5 mg of noradrenaline impurity F CRS in mobile phase A and dilute to 10 mL with mobile phase A. To 1 mL of this solution, add 1 mL of reference solution (c) and dilute to 20 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped monolithic octadecylsilyl silica gel for chromatography R;

— *temperature*: 25 °C.

Mobile phase:

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— *mobile phase A*: dissolve 0.50 g of *sodium heptanesulfonate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; adjust to pH 2.2 with *phosphoric acid R*;

— *mobile phase B*: dissolve 0.25 g of *sodium heptanesulfonate R* in *water for chromatography R* and dilute to 500 mL with the same solvent; add 500 mL of *acetonitrile for chromatography R* and adjust the apparent pH to 2.4 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 2.0	98	2	1.5
2.0 - 17.0	98 → 70	2 → 30	1.5
17.0 - 24.0	70 → 50	30 → 50	1.5
24.0 - 24.1	50 → 0	50 → 100	1.5 → 4.0
24.1 - 28.0	0	100	4.0
28.0 - 28.1	0 → 98	100 → 2	4.0
28.1 - 30.0	98	2	4.0 → 1.5

Detection Spectrophotometer at 280 nm, except for impurity F: spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (d).

Relative retention With reference to noradrenaline (retention time = about 3 min): impurity B = about 1.5; impurity D = about 2.8; impurity E = about 3.0; impurity F = about 6.9.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurities D and E.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.3; impurity E = 0.3; impurity F = 1.5;

— *impurity F at 254 nm*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurities B, D, E at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of the impurities at 280 nm and impurity F at 254 nm*: maximum 0.3 per cent;

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— *disregard limit at 280 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

4.5 per cent to 5.8 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*, heating gently if necessary. Titrate with *0.1 M perchloric acid* using 0.1 mL of *crystal violet solution R* as indicator, until a bluish-green colour is obtained.

1 mL of *0.1 M perchloric acid* is equivalent to 31.93 mg of $C_{12}H_{17}NO_9$.

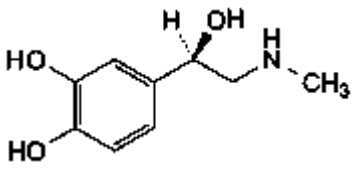
STORAGE

In an airtight container or preferably in a sealed tube under vacuum or under an inert gas, protected from light.

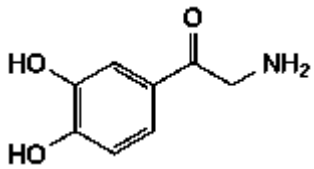
IMPURITIES

Specified impurities *B, D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, G.*



A. 4-[(1*R*)-1-hydroxy-2-(methylamino)ethyl]benzene-1,2-diol (adrenaline),



B. 2-amino-1-(3,4-dihydroxyphenyl)ethanone (noradrenalone),

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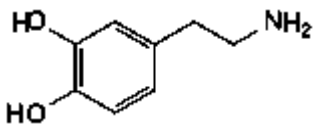
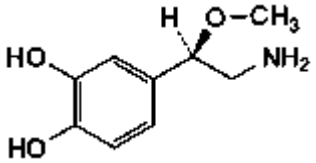
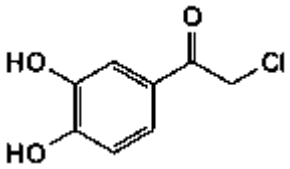


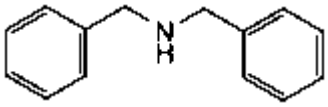
C. 4-(2-aminoethyl)benzene-1,2-diol (dopamine),



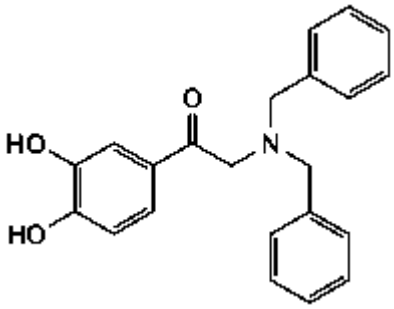
D. 4[(1*R*)-2-amino-1-methoxyethyl]benzene-1,2-diol (noradrenaline methyl ether),



E. 2-chloro-1-(3,4-dihydroxyphenyl)ethanone,



F. *N*-benzyl-1-phenylmethanamine,



G. 2-(dibenzylamino)-1-(3,4-dihydroxyphenyl)ethanone.

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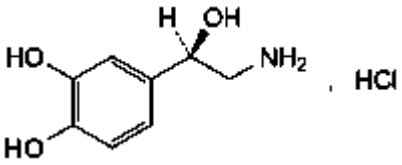
Noradrenaline Hydrochloride / Norepinephrine Hydrochloride

General Notices

(Noradrenaline Hydrochloride, Ph. Eur. monograph 0732)



$C_8H_{12}ClNO_3$ 205.6 *329-56-6*

Action and use

Alpha-adrenoceptor agonist.

Ph Eur

DEFINITION

(1*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol hydrochloride.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or brownish-white, crystalline powder.

Solubility

Very soluble in water, slightly soluble in ethanol (96 per cent).

It becomes coloured on exposure to air and light.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

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Preparation Discs of noradrenaline base prepared as follows. Dissolve 2 g in 20 mL of a 5 g/L solution of *sodium metabisulfite R* and make alkaline by addition of *ammonia R*. Keep in iced water for 1 h and filter. Wash the precipitate with 3 quantities, each of 2 mL, of *water R*, then with 5 mL of *ethanol (96 per cent) R* and finally with 5 mL of *methylene chloride R* and dry *in vacuo* for 3 h.

Comparison Use noradrenaline base prepared as above from a suitable amount of *noradrenaline tartrate CRS*.

C. 0.2 mL of solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than a mixture of 0.2 mL of blue primary solution, 0.4 mL of yellow primary solution, 0.4 mL of red primary solution and 9 mL of a 13.7 per cent *V/V* solution of *dilute hydrochloric acid R* (*2.2.2, Method II*).

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Examine the solution immediately.

pH (*2.2.3*)

3.5 to 4.5 for solution S.

Specific optical rotation (*2.2.7*)

-37 to -41 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*). *Protect the solutions from air. Remove oxygen from the mobile phases with nitrogen R immediately before use. Fill up the flasks.*

Test solution Dissolve 0.125 g of the substance to be examined in mobile phase A and dilute to 50 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 10 mg of the substance to be examined in 5 mL of *0.1 M hydrochloric acid*. To 1 mL of this solution add 0.1 mL of *strong hydrogen peroxide solution R* and expose to UV light at 254 nm for 90 min. Dilute to 10 mL with mobile phase A. The degradation of noradrenaline produces 2 peaks, one with a relative retention of about 1.2 (unidentified compound) and the other with a relative retention of about 1.5 (impurity B). Use this solution to identify the peak due to impurity B.

Reference solution (c) Dissolve 7.5 mg of *noradrenaline impurity D CRS* and 5 mg of *noradrenaline impurity E CRS* in mobile phase A and dilute to 100 mL with mobile phase A.

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Reference solution (d) Dissolve 5 mg of *noradrenaline impurity F CRS* in mobile phase A and dilute to 10 mL with mobile phase A. To 1 mL of this solution, add 1 mL of reference solution (c) and dilute to 20 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped monolithic octadecylsilyl silica gel for chromatography R;

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.50 g of *sodium heptanesulfonate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; adjust to pH 2.2 with *phosphoric acid R*;

— *mobile phase B*: dissolve 0.25 g of *sodium heptanesulfonate R* in *water for chromatography R* and dilute to 500 mL with the same solvent; add 500 mL of *acetonitrile for chromatography R* and adjust the apparent pH to 2.4 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 2.0	98	2	1.5
2.0 - 17.0	98 → 70	2 → 30	1.5
17.0 - 24.0	70 → 50	30 → 50	1.5
24.0 - 24.1	50 → 0	50 → 100	1.5 → 4.0
24.1 - 28.0	0	100	4.0
28.0 - 28.1	0 → 98	100 → 2	4.0
28.1 - 30.0	98	2	4.0 → 1.5

Detection Spectrophotometer at 280 nm, except for impurity F: spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (d).

Relative retention With reference to noradrenaline (retention time = about 3 min): impurity B = about 1.5; impurity D = about 2.8; impurity E = about 3.0; impurity F = about 6.9.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurities D and E.

Limits:

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— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.3; impurity E = 0.3; impurity F = 1.5;

— *impurity D at 280 nm*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity F at 254 nm*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurities B, E at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities at 280 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than D at 280 nm*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of the impurities at 280 nm and impurity F at 254 nm*: maximum 0.7 per cent;

— *disregard limit at 280 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.180 g in 50 mL of *acetic anhydride R* and add 10 mL of *anhydrous formic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 20.56 mg of $C_8H_{12}ClNO_3$.

STORAGE

In an airtight container, or preferably in a sealed tube under vacuum or under an inert gas, protected from light.

IMPURITIES

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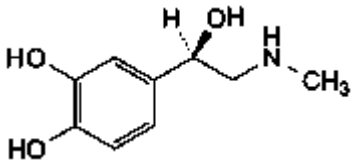
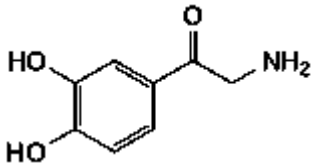
Specified impurities B, D, E, F.

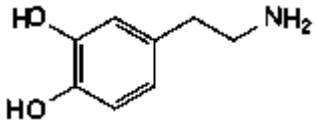
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, G.



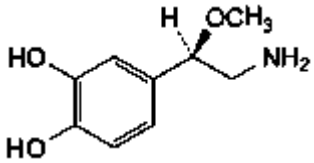
A. 4-[(1*R*)-1-hydroxy-2-(methylamino)ethyl]benzene-1,2-diol (adrenaline),



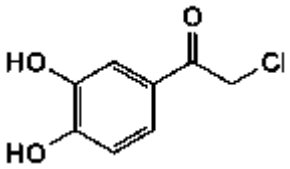
B. 2-amino-1-(3,4-dihydroxyphenyl)ethanone (noradrenalone),



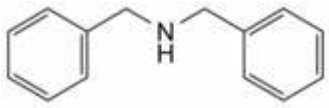
C. 4-(2-aminoethyl)benzene-1,2-diol (dopamine),



D. 4-[(1*R*)-2-amino-1-methoxyethyl]benzene-1,2-diol (noradrenaline methyl ether),



E. 2-chloro-1-(3,4-dihydroxyphenyl)ethanone,



F. *N*-benzyl-1-phenylmethanamine,

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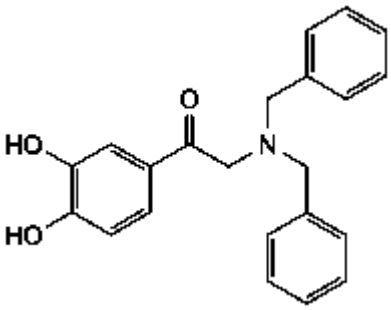

G. 2-(dibenzylamino)-1-(3,4-dihydroxyphenyl)ethanone.

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Noradrenaline Injection / Norepinephrine Injection

General Notices

Action and use

Alpha-adrenoceptor agonist.

DEFINITION

Noradrenaline Injection is a sterile solution of Noradrenaline Acid Tartrate. It is either supplied as a ready-to-use solution or prepared immediately before use by diluting Noradrenaline Sterile Concentrate with Sodium Chloride and Glucose Intravenous Infusion or with Glucose Intravenous Infusion (5.0% w/v) in accordance with the manufacturer's instructions.

The injection complies with the requirements stated under Parenteral Preparations.

When supplied as a ready-to-use solution, the injection complies with the following requirements.

Content of noradrenaline acid tartrate, $C_8H_{11}NO_3,C_4H_6O_6,H_2O$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless liquid.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. Mix a volume of the solution containing 1 mg of Noradrenaline Acid Tartrate with 10 mL of *phthalate buffer pH 3.6*, add 1 mL of 0.05M *iodine*, allow to stand for 5 minutes and add 2 mL of 0.1M *sodium thiosulfate*; not more than a very faint red colour is produced. Repeat the test using *phosphate buffer pH 6.6*; a strong reddish violet colour is produced.

TESTS

Acidity

pH, 3.0 to 4.6, Appendix V L.

Adrenaline

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Use the injection diluted, if necessary, to contain 0.020% w/v of Noradrenaline Acid Tartrate.

(2) 0.0002% w/v of *adrenaline acid tartrate BPCRS* in the mobile phase.

(3) 0.0002% w/v of *adrenaline acid tartrate BPCRS* and 0.0002% w/v of *noradrenaline acid tartrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution containing 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* in a mixture of 950 mL of *water* and 50 mL of *methanol* and adjusting the pH to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to adrenaline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection with the mobile phase, if necessary, to produce a solution containing 0.02% w/v of Noradrenaline Acid Tartrate.

(2) 0.02% w/v of *noradrenaline acid tartrate BPCRS* in the mobile phase.

(3) 0.02% w/v of *noradrenaline acid tartrate BPCRS* and 0.02% w/v of *adrenaline acid tartrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the test for Adrenaline may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}NO_3,C_4H_6O_6,H_2O$ in the injection using the declared content of $C_8H_{11}NO_3,C_4H_6O_6,H_2O$ in *noradrenaline acid tartrate BPCRS*.

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STORAGE

The ready-to-use solution should be protected from light. If the solution is brown, it should be discarded.

NORADRENALINE STERILE CONCENTRATE/NOREPINEPHINE STERILE CONCENTRATE

DEFINITION

Noradrenaline Sterile Concentrate is a sterile, isotonic solution containing Noradrenaline Acid Tartrate in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of noradrenaline acid tartrate, $C_8H_{11}NO_3,C_4H_6O_6,H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. Mix a volume containing 1 mg of Noradrenaline Acid Tartrate with 10 mL of *phthalate buffer pH 3.6*, add 1 mL of 0.05M *iodine*, allow to stand for 5 minutes and add 2 mL of 0.1M *sodium thiosulfate*; not more than a very faint red colour is produced. Repeat the test using *phosphate buffer pH 6.6*; a strong reddish violet colour is produced.

TESTS

Acidity

pH, 3.0 to 4.6, Appendix V L.

Noradrenalone

Dilute the concentrate with 0.01M *hydrochloric acid* to produce a solution containing 0.1% w/v of Noradrenaline Acid Tartrate. The *absorbance* of the solution measured at 310 nm, Appendix II B, is not greater than 0.17 (0.12%).

Adrenaline

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the concentrate being examined diluted, if necessary, to contain 0.2% w/v of Noradrenaline Acid Tartrate.

(2) 0.002% w/v of *adrenaline acid tartrate BPCRS* in the mobile phase.

(3) 0.002% w/v of *adrenaline acid tartrate BPCRS* and 0.002% w/v of *noradrenaline acid tartrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution containing 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* in a mixture of 50 mL of *methanol* and 950 mL of *water* and adjusting the pH to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to adrenaline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute one volume of the concentrate being examined with the mobile phase to produce a solution containing 0.02% w/v of Noradrenaline Acid Tartrate.

(2) 0.02% w/v of *noradrenaline acid tartrate BPCRS* in the mobile phase.

(3) 0.02% w/v of *adrenaline acid tartrate BPCRS* and 0.02% w/v of *noradrenaline acid tartrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the test for Adrenaline may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}NO_3,C_4H_6O_6,H_2O$ in the concentrate using the declared content of $C_8H_{11}NO_3,C_4H_6O_6,H_2O$ of *noradrenaline acid tartrate BPCRS*.

STORAGE

Noradrenaline Sterile Concentrate should be protected from light. If the solution is brown it should be discarded.

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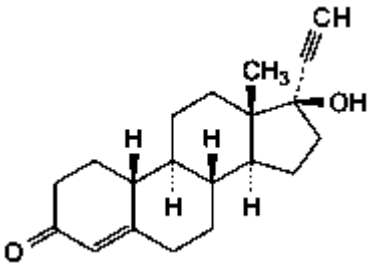
Norethisterone

General Notices

(Ph. Eur. monograph 0234)



$C_{20}H_{26}O_2$ 298.4 *68-22-4*

Action and use

Progestogen.

Preparations

Norethisterone Tablets

Estradiol and Norethisterone Tablets

Ph Eur

DEFINITION

17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, sparingly soluble in acetone and in anhydrous ethanol.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison norethisterone CRS.

TESTS

Specific optical rotation (2.2.7)

-32.0 to -37.0 (dried substance).

Dissolve 0.250 g in acetone R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in a mixture of 40 volumes of water R and 60 volumes of acetonitrile R1 and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 5 mg of norethisterone for system suitability CRS (containing impurities A, B, C, D, E, F, G and H) in a mixture of 40 volumes of water R and 60 volumes of acetonitrile R1 and dilute to 2.0 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of 40 volumes of water R and 60 volumes of acetonitrile R1. Dilute 1.0 mL of this solution to 10.0 mL with a mixture of 40 volumes of water R and 60 volumes of acetonitrile R1.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: spherical end-capped octylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: water R;

— *mobile phase B*: acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	63	37
20 - 25	63 → 20	37 → 80
25 - 35	20	80

Flow rate 1.0 mL/min.

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Detection Variable wavelength spectrophotometer capable of operating at 254 nm and at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) and the chromatogram supplied with *norethisterone for system suitability CRS* to identify the peaks due to the impurities A, B, C, D, E, F, G and H.

Relative retention at 254 nm With reference to norethisterone (retention time = about 10 min): impurity H = about 0.3; impurity A = about 0.8; impurity B = about 0.9; impurity G = about 1.5; impurity C (at 210 nm) = about 1.6; impurity D (at 210 nm) = about 1.7; impurity E = about 2.3; impurity F = about 2.4.

System suitability Reference solution (a) at 254 nm:

— *resolution*: baseline separation between the peaks due to impurity B and norethisterone;

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Limits Spectrophotometer at 254 nm:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.5; impurity E = 0.7; impurity F = 1.4; impurity H = 1.7;

— *impurities E, G, H*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities A, B, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Limits Spectrophotometer at 210 nm:

— *impurities C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

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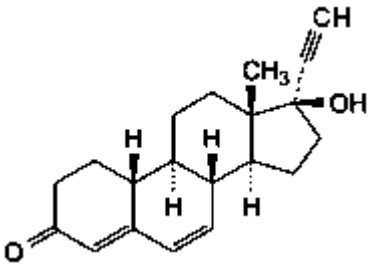
Dissolve 0.200 g in 40 mL of *tetrahydrofuran R*. Add 10 mL of a 100 g/L solution of *silver nitrate R* and titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Rinse the electrode with *acetone R* after each titration.

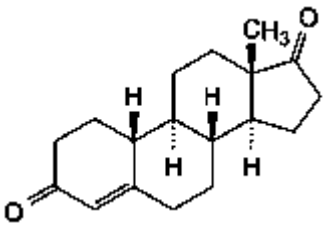
1 mL of *0.1 M sodium hydroxide* is equivalent to 29.84 mg of $C_{20}H_{26}O_2$.

IMPURITIES

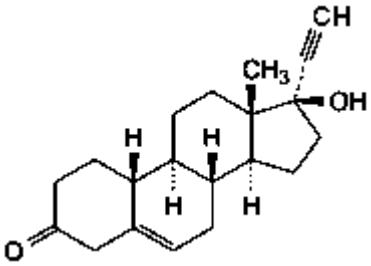
Specified impurities *A, B, C, D, E, F, G, H.*



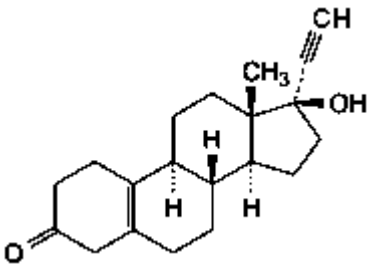
A. 17-hydroxy-19-nor-17α-pregna-4,6-dien-20-yn-3-one,



B. estr-4-ene-3,17-dione (norandrostenedione),



C. 17-hydroxy-19-nor-17α-pregn-5-en-20-yn-3-one,



D. 17-hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one,

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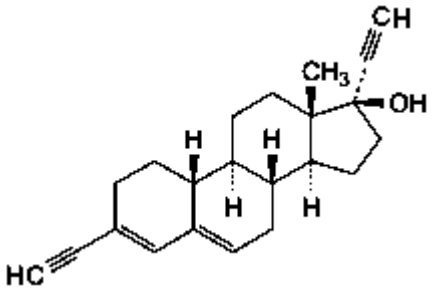
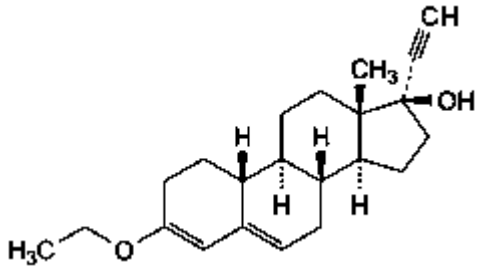
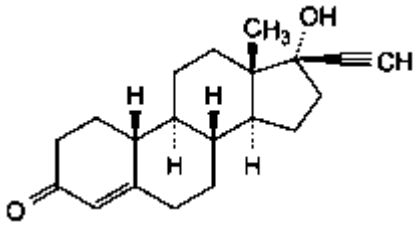


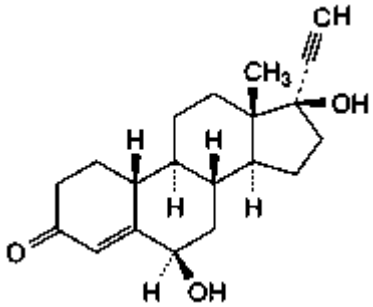
E. 3-ethynyl-19-nor-17α-pregna-3,5-dien-20-yn-17-ol,



F. 3-ethoxy-19-nor-17α-pregna-3,5-dien-20-yn-17-ol,



G. 17-hydroxy-19-norpregn-4-en-20-yn-3-one (17-*epi*-norethisterone),



H. 6β,17-dihydroxy-19-nor-17α-pregn-4-en-20-yn-3-one (6β-hydroxynorethisterone).

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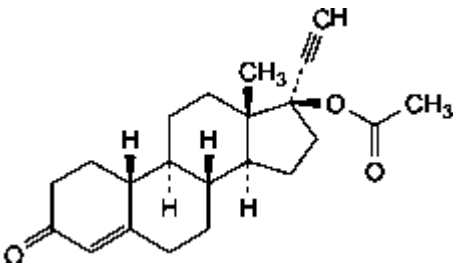
Norethisterone Acetate

General Notices

(Ph. Eur. monograph 0850)



$C_{22}H_{28}O_3$ 340.5 *51-98-9*

Action and use

Progestogen.

Preparation

Estradiol and Norethisterone Acetate Tablets

Ph Eur

DEFINITION

3-Oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *norethisterone acetate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Specific optical rotation (2.2.7)

-35 to -30 (dried substance).

Dissolve 0.500 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve the contents of a vial of *norethisterone acetate for system suitability CRS* (containing impurities B, C, D, E, F, G and H) in 1.0 mL of mobile phase A.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 25.0 mg of *norethisterone acetate CRS* in mobile phase A and dilute to 10.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*, *acetonitrile R1* (40:60 *V/V*);

— *mobile phase B*: *water for chromatography R*, *acetonitrile R1* (10:90 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 17	100	0
17 - 20	100 → 0	0 → 100
20 - 39	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm and, for impurities B and C, at 210 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatograms supplied with *norethisterone acetate for system suitability CRS* and the chromatograms obtained with reference solution (a) to identify the peaks due to impurities B, C, D + G, E, F and H.

Relative retention With reference to norethisterone acetate (retention time = about 12 min): impurity F = about 0.4; impurities D and G = about 0.6; impurity E = about 0.8; impurity C = about 1.5; impurity B = about 1.6; impurity H = about 2.8.

System suitability Reference solution (a) at 210 nm:

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.3; impurity F = 1.7;

— for each impurity, use the concentration of norethisterone acetate in reference solution (b).

Limits:

— *impurities B, C at 210 nm*: for each impurity, maximum 0.3 per cent;

— *impurities F, H*: for each impurity, maximum 0.3 per cent;

— *impurity E*: maximum 0.2 per cent;

— *sum of impurities D and G*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

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Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

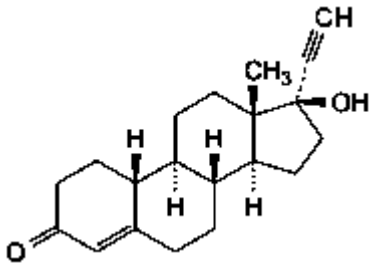
Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{22}H_{28}O_3$ taking into account the assigned content of *norethisterone acetate CRS*.

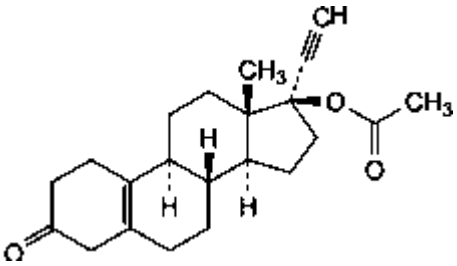
IMPURITIES

Specified impurities *B, C, D, E, F, G, H.*

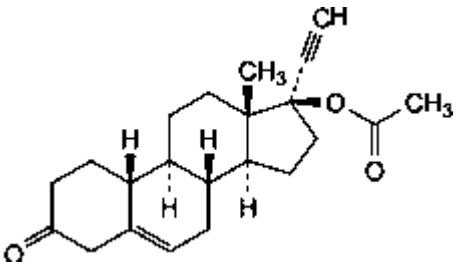
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, I, J.*



A. 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one (norethisterone),



B. 3-oxo-19-nor-17α-pregn-5(10)-en-20-yn-17-yl acetate,



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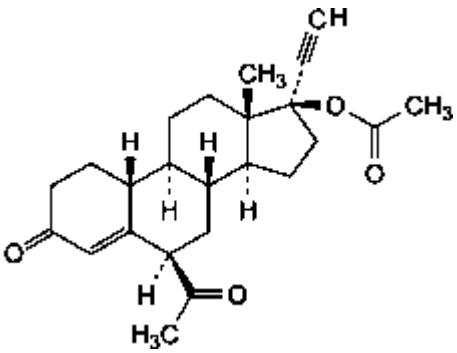
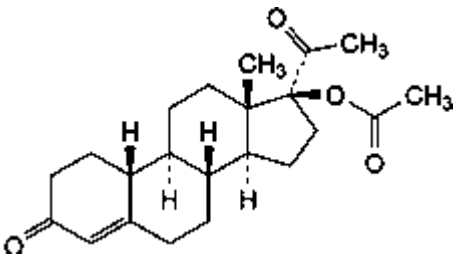
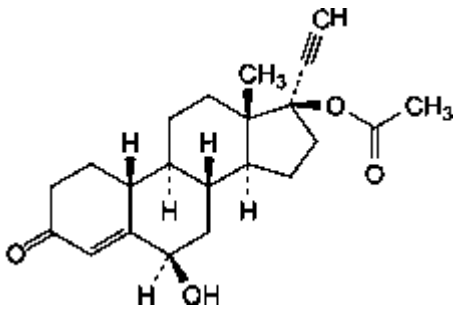
C. 3-oxo-19-nor-17α-pregn-5-en-20-yn-17-yl acetate,



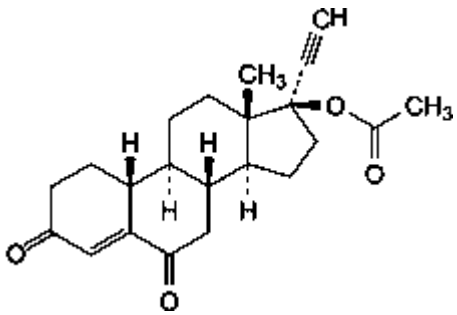
D. 6β-acetyl-3-oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate,



E. 3,20-dioxo-19-nor-17α-pregn-4-en-17-yl acetate,



F. 6β-hydroxy-3-oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate,



G. 3,6-dioxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate,

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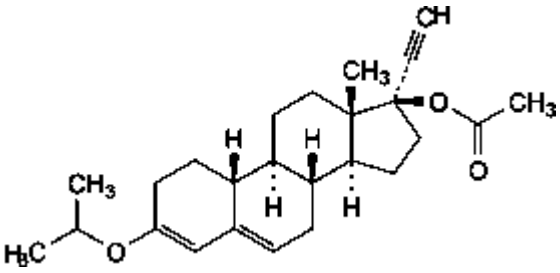
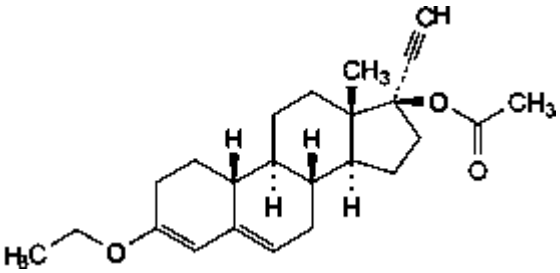
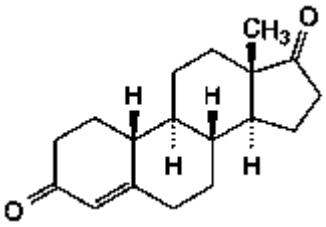


H. 3-(propan-2-yloxy)-19-nor-17α-pregna-3,5-dien-20-yn-17-yl acetate,



I. 3-ethoxy-19-nor-17α-pregna-3,5-dien-20-yn-17-yl acetate,



J. estr-4-ene-3,17-dione (norandrostenedione).

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Norethisterone Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Norethisterone Tablets contain Norethisterone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of norethisterone, $C_{20}H_{26}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Crush one tablet in sufficient *ethanol* (*96%*) to produce a final solution containing approximately 0.035% w/v of Norethisterone, warm to 50° for 10 minutes, mix with the aid of ultrasound, allow to cool and centrifuge to obtain a clear supernatant liquid.
(2) 0.035% w/v of *norethisterone BPCRS* in *ethanol* (*96%*).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 10 cm.
(e) After removal of the plate, dry in air, spray with a mixture of 30 volumes of *methanol* and 70 volumes of *sulfuric acid* and examine under *ultraviolet light* (*365 nm*).

MOBILE PHASE

20 volumes of *ethyl acetate* and 80 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

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Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Norethisterone comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse one tablet in 2 mL of *water* with the aid of ultrasound for 15 minutes, add sufficient *methanol* to produce 5 mL, centrifuge for 10 minutes and use the clear supernatant liquid.
(2) 0.007% w/v of *norethisterone BPCRS* in *methanol* (*60%*).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

28 volumes of *water* and 72 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{26}O_2$ in each tablet using the declared content of $C_{20}H_{26}O_2$ in *norethisterone BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Norethisterone

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Norethisterone

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 5 mg of Norethisterone in 10 mL of *water* with the aid of ultrasound for 15 minutes, add sufficient *methanol* to produce 25 mL, centrifuge for 10 minutes and use the supernatant liquid.
(2) 0.02% w/v of *norethisterone BPCRS* in *methanol* (60%).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{26}O_2$ in the tablets using the declared content of $C_{20}H_{26}O_2$ in *norethisterone BPCRS*.

STORAGE

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Norethisterone Tablets should be protected from light.

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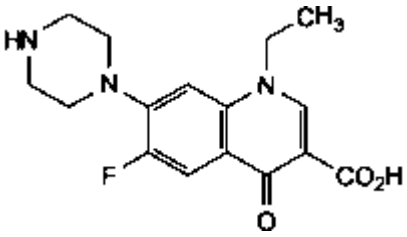
Norfloxacin

General Notices

(Ph. Eur. monograph 1248)



$C_{16}H_{18}FN_3O_3$ 319.3 *70458-96-7*

Action and use

Fluoroquinolone antibacterial.

Preparation

Norfloxacin Tablets

Ph Eur

DEFINITION

1-Ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow, hygroscopic, photosensitive, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in acetone and in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *norfloxacin CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness in a water-bath at 45 °C, dry in an oven at 105 °C for about 1 h and record new spectra using the residues.

TESTS

Appearance of solution

Dissolve 0.5 g in a previously filtered 4 g/L solution of *sodium hydroxide R* in *methanol R* and dilute to 50 mL with the same solution. The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, *Method II*).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* adjusted to pH 2.0 with *phosphoric acid R* (5:95 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 25 mL of the solvent mixture using sonication, and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 4 mg of *norfloxacin for system suitability CRS* (containing impurities A, E and H) in 5 mL of the solvent mixture using sonication, and dilute to 10 mL with the solvent mixture.

Reference solution (c) Dissolve 4 mg of *norfloxacin for peak identification CRS* (containing impurity K) in 5 mL of the solvent mixture using sonication, and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped amidohexadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: *water for chromatography R* adjusted to pH 2.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 7	95 → 93	5 → 7
7 - 10	93 → 87	7 → 13
10 - 15	87 → 47	13 → 53
15 - 20	47 → 10	53 → 90

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *norfloxacin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, E and H; use the chromatogram supplied with *norfloxacin for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity K.

Relative retention With reference to norfloxacin (retention time = about 11 min): impurity K = about 0.6; impurity E = about 0.97; impurity A = about 1.5; impurity H = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities A and H;

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to norfloxacin.

Limits:

— *impurities E, K*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.700 g. Use as the solvent a mixture of 10 mL of *anhydrous methanol R* and 20 mL of *formamide R*.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.240 g in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 31.93 mg of $C_{16}H_{18}FN_3O_3$.

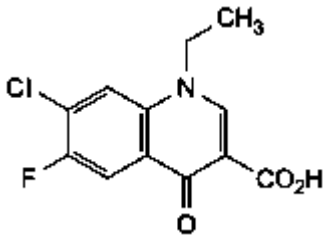
STORAGE

In an airtight container, protected from light.

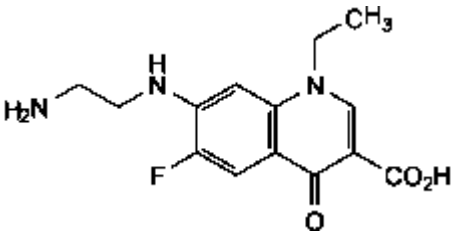
IMPURITIES

Specified impurities E, K.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, F, G, H, I, J.



A. 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



B. 7-[(2-aminoethyl)amino]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

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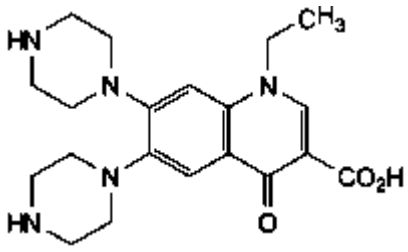
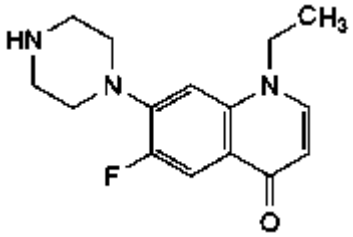
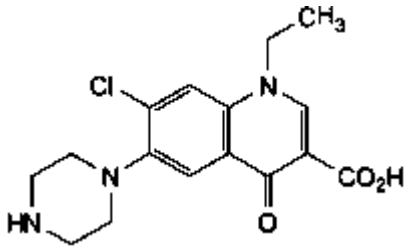


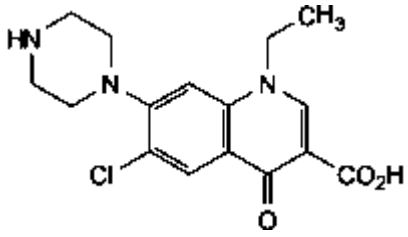
C. 1-ethyl-4-oxo-6,7-di(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,



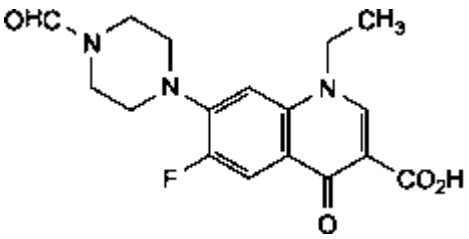
D. 1-ethyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one,



E. 7-chloro-1-ethyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,



F. 6-chloro-1-ethyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,



G. 1-ethyl-6-fluoro-7-(4-formylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

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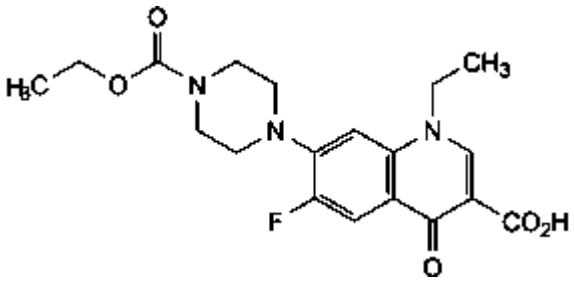
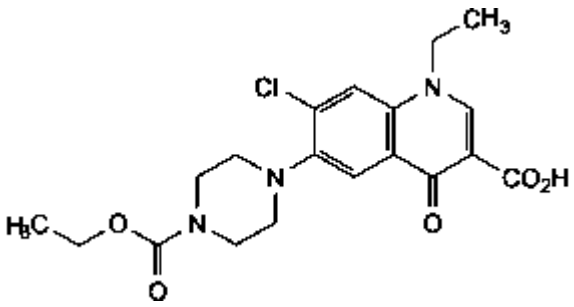
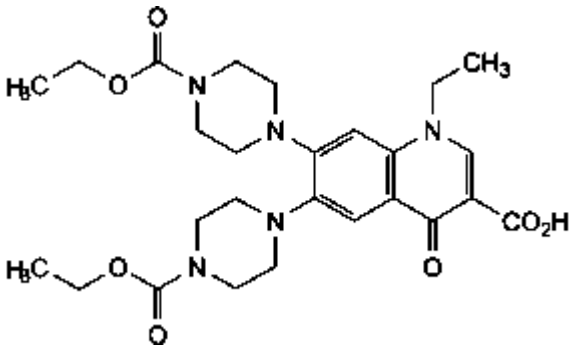


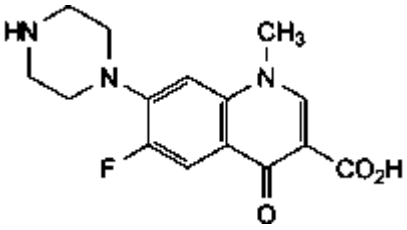
H. 7-[4-(ethoxycarbonyl)piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



I. 7-chloro-6-[4-(ethoxycarbonyl)piperazin-1-yl]-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



J. 6,7-bis[4-(ethoxycarbonyl)piperazin-1-yl]-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,



K. 6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

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Norfloxacin Tablets

General Notices

Action and use

Fluoroquinolone antibacterial.

DEFINITION

Norfloxacin Tablets contain Norfloxacin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of norfloxacin, $C_{16}H_{18}FN_3O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions, protected from light.

(1) Add 2 mL of *water* to a quantity of whole tablets containing 0.4 g of Norfloxacin and disperse with the aid of ultrasound. Add 100 mL of a solution containing 50 volumes of *dichloromethane* and 50 volumes of a solution prepared by adding 9 mL of *hydrochloric acid* to 1000 mL of *methanol*. Mix with the aid of ultrasound until a uniform suspension is produced, add sufficient of the same solvent mixture to produce 200 mL and centrifuge 25 mL of the final solution.

(2) Dissolve, with the aid of ultrasound, 50 mg of *norfloxacin BPCRS* in 15 mL of a solution containing 50 volumes of *dichloromethane* and 50 volumes of a solution prepared by adding 9 mL of *hydrochloric acid* to 1000 mL of *methanol*; add sufficient of the same solvent mixture to produce 25 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* GF_{254} precoated plate (Analtech plates are suitable) which has been previously washed with *methanol* and allowed to dry in air.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light* (*254 nm* and *365 nm*).

MOBILE PHASE

8 volumes of *water*, 14 volumes of *diethylamine*, 20 volumes of *toluene*, 40 volumes of *dichloromethane* and 40 volumes of *methanol*.

CONFIRMATION

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By each method of visualisation, the principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1. Carry out the procedure protected from light.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 750 mL of an acetate buffer solution prepared in the following manner, at a temperature of 37°, as the medium. Add 14.3 mL of *glacial acetic acid* to 4500 mL of *water* and mix. Add slowly, with stirring, 2.5 mL of a 50% w/v solution of *sodium hydroxide* and add sufficient *water* to produce 5000 mL. If necessary, adjust the pH to 4.0 with *glacial acetic acid* or a 50% w/v solution of *sodium hydroxide*.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium, filter and dilute the filtrate with sufficient of the dissolution medium to give a solution expected to contain about 0.0016% w/v of Norfloxacin. Measure the *absorbance* of this solution, Appendix II B, at 313 nm using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0016% w/v solution of *norfloxacin BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of norfloxacin, $C_{16}H_{18}FN_3O_3$, in the medium from the *absorbances* obtained and using the declared content of $C_{16}H_{18}FN_3O_3$ in *norfloxacin BPCRS*.

LIMITS

The amount of norfloxacin released is not less than 80% of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, in 5 volumes of *acetonitrile* and 95 volumes of *water* previously adjusted to pH 2.0 with *orthophosphoric acid*.

(1) Disperse a quantity of powdered tablets containing 0.2 g of Norfloxacin in 250 mL, sonicate and dilute to 500 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Further dilute 1 volume of this solution to 10 volumes.

(3) 0.04% w/v of *norfloxacin for system suitability EPCRS*.

(4) 0.04% w/v of *norfloxacin for peak identification EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped amidohexadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-ABZ is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A *water* adjusted to pH 2.0 with *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	95	5	isocratic
5-7	95→93	5→7	linear gradient
7-10	93→87	7→13	linear gradient
10-15	87→47	13→53	linear gradient
15-20	47→10	53→90	linear gradient
20-22	10	90	isocratic
22-23	10→95	90→5	linear gradient
23-26	95	5	re-equilibration

Use the chromatogram supplied with *norfloxacin for system suitability EPCRS* and the chromatogram obtained with reference solution (3) to identify the peaks due to impurities A, E and H. Use the chromatogram supplied with *norfloxacin for peak identification EPCRS* and the chromatogram obtained with reference solution (4) to identify the peak due to impurity K.

When the chromatograms are recorded under the prescribed conditions the retentions relative to norfloxacin (retention time, about 11 minutes) are: Impurity K, about 0.6; Impurity E, about 0.97; impurity A, about 1.5; impurity H, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity A and impurity H is at least 3.0;

the *peak-to-valley ratio* is at least 5.0, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to norfloxacin.

LIMITS

In the chromatogram obtained with solution (1):

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the areas of any peaks corresponding to impurities E or K are not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) Add 80 mL of the mobile phase to a quantity of the powdered tablets containing 0.1 g of Norfloxacin and mix with the aid of ultrasound for at least 5 minutes. Add sufficient of the mobile phase to produce 200 mL, mix and dilute 10 volumes of this solution to 25 volumes with the mobile phase.
(2) 0.02% w/v of *norfloxacin BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Waters µBondapak C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 275 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

150 volumes of *acetonitrile* and 850 volumes of 0.1% v/v *orthophosphoric acid*.

Precondition the column using 0.01M *anhydrous sodium dihydrogen orthophosphate*, adjusted to pH 4.0 with *orthophosphoric acid*, at a flow rate of 0.5 mL per minute for 8 hours. Equilibrate the column with the mobile phase for about 30 minutes before starting the chromatography.

When the chromatograms are recorded under the prescribed conditions, the retention time of norfloxacin is about 5 minutes.

SYSTEM SUITABILITY

The Assay is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is less than 2.0.

Inject solution (2) six times. The Assay is not valid unless the relative standard deviation of the area of the principal peak is at most 2.0%.

DETERMINATION OF CONTENT

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Calculate the content of $C_{16}H_{18}FN_3O_3$ in the tablets using the declared content of $C_{16}H_{18}FN_3O_3$ in *norfloxacin BPCRS*.

STORAGE

Norfloxacin Tablets should be protected from light and moisture.

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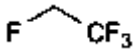
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Norflurane

General Notices

(Ph. Eur. monograph 2257)



$C_2H_2F_4$ 102.0 *811-97-2*

Action and use

General anaesthetic.

Ph Eur

DEFINITION

1,1,1,2-Tetrafluoroethane (HFC 134a).

CHARACTERS

Appearance

Clear, colourless gas, liquid under pressure.

Solubility

At 20 °C and at a pressure of 101 kPa, slightly soluble in water, freely soluble in ethanol (96 per cent).

Relative density

About 1.23 at 20 °C, for the gas in the liquid phase.

bp

About -26 °C.

It is a hygroscopic, non-flammable gas.

IDENTIFICATION

Carry out either test A or test B.

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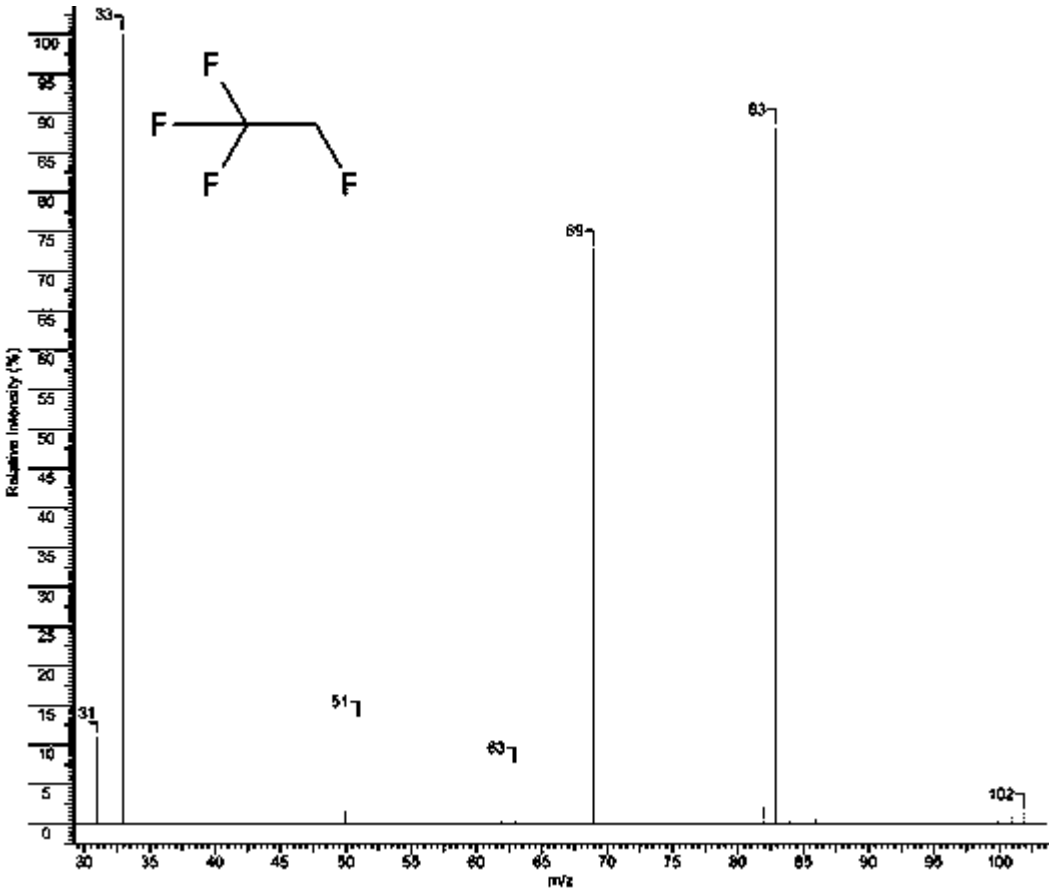
A. Infrared absorption spectrophotometry (2.2.24). *Carry out the test at atmospheric pressure.*

Preparation Dilute the gas to be examined in *nitrogen R* (approximately 20:80 *V/V* depending on the sensitivity of the spectrophotometer).

Comparison *Ph. Eur. reference spectrum of norflurane*.

B. Mass spectrometry (2.2.43).

Results The mass spectrum obtained with the gas to be examined is similar to the mass spectrum of norflurane shown in Figure 2257.-1.



m/z	RI (%)	ion	*m/z*	RI (%)	ion
31	11.1	$[CF]^+$	82	2.1	$[CF_2\text{-}CHF]^{+\cdot}$
33	100.0	$[CH_2F]^+$	83	88.2	$[CF_2\text{-}CH_2F]^+$
50	1.5	$[CF_2]^{+\cdot}$	100	0.3	$[CF_3\text{-}CF]^{+\cdot}$
51	13.2	$[CHF_2]^+$	101	0.9	$[CF_3\text{-}CHF]^+$
63	7.4	$[CF{=}CHF]^+$	102	1.5	$[CF_3\text{-}CH_2F]^{+\cdot}$
69	72.9	$[CF_3]^+$			

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Figure 2257.-1. – *Mass spectrum of norflurane*

TESTS

Acidity

Maximum 0.1 ppm, expressed as HCl.

Transfer 200 mL of deionised *water R* previously neutralised to *bromocresol purple solution R* to a glass washing bottle fitted with a distribution tube with a sintered-glass disc. Pass 750 g of the gas to be examined through the water, at a rate of about 60 L/h. Titrate with *0.02 M sodium hydroxide* using *bromocresol purple solution R* as indicator until the colour changes from yellow to bluish-violet. Carry out a blank titration using deionised *water R*.

1 mL of *0.02 M sodium hydroxide* is equivalent to 0.729 mg of HCl.

Non-volatile matter

Maximum 50 ppm.

Carry out the test using a glass double-wall vessel (see Figure 2257.-2).

Dry the removable part in an oven at 105 ± 2 °C for 30 min. Allow to cool in a desiccator and weigh to the nearest 0.1 mg. Connect it to the vessel.

Weigh the gas cylinder to the nearest 1 g. Fill the vessel with about 500 mL of liquefied gas and weigh the gas cylinder again. Determine the mass of the sample by weight difference. Using a suitable heating device such as a water-bath, heat the removable part such that the sample evaporates in about 2 h. Dry the removable part in an oven at 105 ± 2 °C for 30 min. Allow to cool in a desiccator and weigh to the nearest 0.1 mg. Determine the mass of the residue by weight difference.

Calculate the content of non-volatile matter in the gas using the following expression:

$$\frac{10^3 \times m}{M}$$

m	=	mass of residue, in milligrams;
M	=	mass of sample, in grams.

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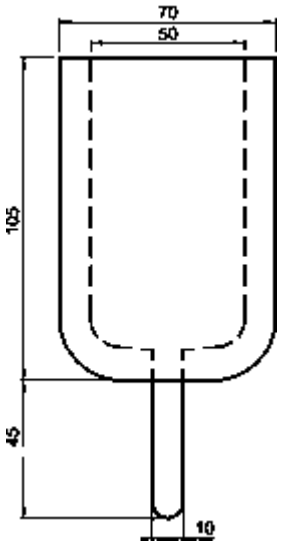

Figure 2257.-2. – *Glass double-wall vessel*

Dimensions in millimetres

Non-condensable gases

Maximum 1.5 per cent *V/V*.

Gas chromatography (*2.2.28*).

Gas to be examined The sample is taken from the vapour phase maintaining the cylinder in an upright position. Evacuate the gas loop using a multiway tap and fill cautiously with the gas to be examined.

Reference gases Mixtures of ambient air in *helium for chromatography R* covering a concentration range of 0.5 per cent to 2.0 per cent.

Column:

— *material*: stainless steel;

— *size*: *l* = 5 m, Ø = 2 mm;

— *stationary phase*: *oxypropionitrilsilyl silica gel for chromatography R* (150-180 µm).

Carrier gas *helium for chromatography R*.

Flow rate 21 mL/min.

Temperature:

— *column*: 80 °C;

— *injection port*: 150 °C;

— *detector*: 180 °C.

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Detection Thermal conductivity.

Injection 150 µL loop injector.

Run time 10 min.

Relative retention With reference to norflurane (retention time = about 4 min): non-condensable gases = about 0.4.

Determine the concentration (*V/V*) of non-condensable gases in the gas to be examined using the calibration curve obtained with the reference gases.

Related substances

Gas chromatography (2.2.28), equipped with a gas valve sampling system and a cryogenic unit, coupled with mass spectrometry (2.2.43).

Gas to be examined Connect the cylinder to the gas valve sampling system and sample from the liquid phase. Then evacuate the loop including the transfer line using a multiway tap and a vacuum pump. Open the valves of the cylinder and fill the loop cautiously with the gas to be examined.

Reference gas (a) Prepare a mixture in *helium for chromatography R* of the impurities expected in the gas to be examined (see Table 2257.-1) at a concentration of 2-6 ppm each, always including impurity G.

Reference gas (b) Prepare a mixture of FC 1318my/c (impurity S) and FC 1318my/t (impurity T) in *helium for chromatography R* at a combined concentration of approximately 20 ppm.

Reference gas (c) Prepare a mixture of CFC 114 (impurity L) and HCC 40 (impurity W) in *helium for chromatography R* at a concentration of approximately 1 ppm each.

Reference gas (d) Prepare a 5-fold dilution of reference gas (a) in *helium for chromatography R*.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.18 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.1 mL/min.

Split ratio 1:75.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 2	-25
	2 - 7.2	-25 → -12
	7.2 - 14	-12 → 15
	14 - 18.7	15 → 250
	18.7 - 21.2	250
Injection port		150

Detection Mass spectrometer; the following settings were found to be suitable and are given as examples; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criteria:

— *ionisation mode*: electron impact (70 eV);

— *trap current*: 0.2 mA;

— *mass range*: 30-300 Da;

— *scan rate*: ≤ 0.2 s/scan;

— *temperature*: ion source: 160 °C; transfer line: 200 °C.

Injection 500 µL.

Identification of impurities Use the reconstructed ion chromatogram obtained with reference gas (a) and the information supplied in Table 2257.-1.

System suitability:

— *resolution*: minimum 1.4 between the peaks due to FC 1318my/c (impurity S) and FC 1318my/t (impurity T) in the chromatogram obtained with reference gas (b);

— *signal-to-noise ratio*: minimum 10 each for CFC 114 (impurity L) and HCC 40 (impurity W) in the chromatogram obtained with reference gas (c).

Selectivity – co-elution Several impurities elute with a resolution of less than 1; close inspection of the individual ion traces is necessary to detect and quantify potential co-eluting compounds; the relative retentions of these compounds are indicated in italics in Table 2257.-1.

Before assessing the presence of individual impurities in the reconstructed ion chromatogram, a suitable background subtraction may be necessary. Two potential sources of background have to be taken into account: use of cryo-cooling (liquid carbon dioxide, *m/z* 44) and possible bleeding of the column (siloxanes, several ions at *m/z* greater than 200).

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If a peak is observed at a retention time where co-elution is possible, the identification and quantification are applied to each of the co-eluting compounds.

Calculation of parts per million contents:

— for impurities A, B, C, D, E, F, G, H and I, use the concentration of the corresponding impurity in reference gas (a);

— for the other impurities, use the concentration of impurity G in reference gas (a);

— for the reporting threshold, use the concentration of impurity G in reference gas (d).

Table 2257.-1. – *Norflurane impurities: quantification ions and relative retentions*

Impurity	Code	Structure	M_r	Quantification ion *(m/z)*	Relative retention
P	CFC 13	$CClF_3$	104	69	0.71
QQ	HFC 23	CHF_3	70	51	*0.73*
JJ	HFC 1132a	$CH_2=CF_2$	64	64	*0.73*
N	CFC 115	$CClF_2$-CF_3	154	85	0.77
D	HFC 143a	CH_3-CF_3	84	65/69*	*0.81*
SS	HFC 32	CH_2F_2	52	51/33*	*0.81*
II	HFC 1123	$CHF=CF_2$	82	63	*0.82*
MM	HFC 125	CHF_2-CF_3	120	101	*0.84*
T	FC 1318my/t	CF_3-CF=CF-CF_3	200	131	*0.84*
S	FC 1318my/c	CF_3-CF=CF-CF_3	200	131	0.87
Q	CFC 217ba	CF_3-$CClF$-CF_3	204	85	0.93
KK	HFC 1234yf	$CH_2=CF$-CF_3	114	114	0.96
RR	HFC 245cb	CH_3-CF_2-CF_3	134	65	0.98
Norflurane	**HFC 134a**	**CH_2F-CF_3**	**102**	**83**	**1**
R	FC 115B1	$CBrF_2$-CF_3	198	119	1.03
H	HFC 1225ye/c	$CHF=CF$-CF_3	132	113	*1.10*
E	HFC 152a	CH_3-CHF_2	66	65	*1.11*

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Impurity	Code	Structure	M_r	Quantification ion *(m/z)*	Relative retention
PP	HFC 161	CH_3-CH_2F	48	33/47*	*1.11*
I	HFC 1243zf	CH_2=CH-CF_3	96	96	*1.11*
LL	HFC 1234ze	CHF=CH-CF_3	114	114	1.14
A	CFC 12	CCl_2F_2	120	85	1.17
C	HFC 134	CHF_2-CHF_2	102	51/83*	1.21
NN	HFC 1336mzz/c	CF_3-CH=CH-CF_3	164	95	*1.30*
GG	HCFC 22	$CHClF_2$	86	51	*1.32*
L	CFC 114	$CClF_2$-$CClF_2$	170	85	*1.63*
M	CFC 114a	CCl_2F-CF_3	170	101/103*	*1.64*
W	HCC 40	CH_3Cl	50	52	1.67
G	HCFC 1122	CHCl=CF_2	98	98	1.72
DD	HCFC 124a	CHF_2-$CClF_2$	136	101	1.77
B	HCFC 124	CHClF-CF_3	136	67	1.87
HH	HCFC 31	CH_2ClF	68	68	1.97
Y	HCFC 1122a/c	CHF=CClF	98	98	2.03
O	CFC 12B1	$CBrClF_2$	164	85	2.08
AA	HCFC 1131/t	CHCl=CHF	80	80	2.19
OO	HFC 152	CH_2F-CH_2F	66	33	2.41
FF	HCFC 133a	CH_2Cl-CF_3	118	118	2.47
F	CFC 1112a	CCl_2=CF_2	132	132	2.74
Z	HCFC 1131/c	CHCl=CHF	80	80	2.84
J	CFC 11	CCl_3F	136	101	2.97
CC	HCFC 123a	CHClF-$CClF_2$	152	67	3.15
BB	HCFC 123	$CHCl_2$-CF_3	152	83	*3.18*

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Impurity	Code	Structure	M_r	Quantification ion *(m/z)*	Relative retention
K	CFC 113	$CCl_2F\text{-}CClF_2$	186	151	*3.18*
X	HCFC 1121/t	CHCl=CClF	114	114	3.25
V	HCC 30	CH_2Cl_2	84	49	3.29
EE	HCFC 132b	$CClF_2\text{-}CH_2Cl$	134	99	3.32
U	HCC 1120	$CHCl=CCl_2$	130	95	3.59
* Depending on the actual chromatographic resolution and potentially overlapping compounds, it may be necessary to select a different quantification ion.					

Limits:

Saturated impurities

— *HFC 134 (impurity C)*: maximum 1000 ppm;

— *HFC 152a (impurity E)*: maximum 500 ppm;

— *CFC 12 (impurity A), HCFC 124 (impurity B)*: for each impurity, maximum 100 ppm;

— *HFC 143a (impurity D)*: maximum 50 ppm.

Unsaturated impurities

— *CFC 1112a (impurity F), HCFC 1122 (impurity G), HFC 1225ye/c (impurity H), HFC 1243zf (impurity I)*: for each impurity, maximum 5 ppm.

Other detectable impurities

— *other saturated or unsaturated impurities or unknow impurities*: for each impurity, maximum 5 ppm;

— *sum of other detectable impurities*: maximum 10 ppm.

Total

Maximum 1000 ppm.

Reporting threshold

1 ppm.

Water (*2.5.32*)

Maximum 10 ppm, determined on 30.0 g. *Take care to avoid uptake of water by the gas to be examined during the test.*

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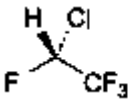
Transfer the gas to be examined in liquid phase from the inverted steel cylinder to an evacuated sample can. To transfer the sample, connect a metal tube with fittings at one end to the cylinder valve, and at the other end to the needle valve on the sample can.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I.*

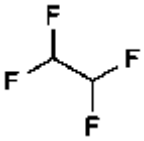
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z, AA, BB, CC, DD, EE, FF, GG, HH, II, JJ, KK, LL, MM, NN, OO, PP, QQ, RR, SS.*

A. dichlorodifluoromethane (CFC 12 [75-71-8]),

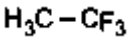


and enantiomer

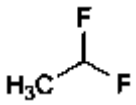
B. (2*RS*)-2-chloro-1,1,1,2-tetrafluoroethane (HCFC 124 [2837-89-0]),



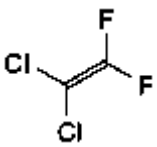
C. 1,1,2,2-tetrafluoroethane (HFC 134 [359-35-3]),



D. 1,1,1-trifluoroethane (HFC 143a [420-46-2]),



E. 1,1-difluoroethane (HFC 152a [75-37-6]),



F. 1,1-dichloro-2,2-difluoroethene (CFC 1112a [79-35-6]),

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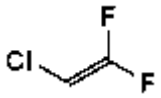
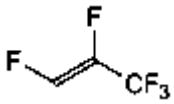


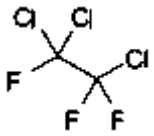
G. 1-chloro-2,2-difluoroethene (HCFC 1122 [359-10-4]),



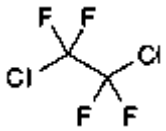
H. (1Z)-1,2,3,3,3-pentafluoroprop-1-ene (HFC 1225ye/c [5528-43-8]),

I. 3,3,3-trifluoroprop-1-ene (HFC 1243zf [677-21-4]),

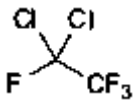
J. trichlorofluoromethane (CFC 11 [75-69-4]),



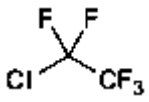
K. 1,1,2-trichloro-1,2,2-trifluoroethane (CFC 113 [76-13-1]),



L. 1,2-dichloro-1,1,2,2-tetrafluoroethane (CFC 114 [76-14-2]),



M. 1,1-dichloro-1,2,2,2-tetrafluoroethane (CFC 114a [374-07-2]),



N. 1-chloro-1,1,2,2,2-pentafluoroethane (CFC 115 [76-15-3]),

O. bromochlorodifluoromethane (CFC 12B1 [353-59-3]),

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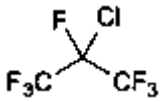
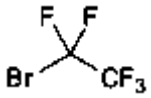
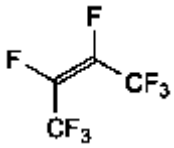
P. chlorotrifluoromethane (CFC 13 [75-72-9]),



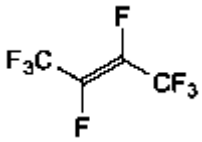
Q. 2-chloro-1,1,1,2,3,3,3-heptafluoropropane (CFC 217ba [76-18-6]),



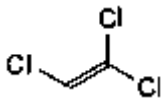
R. 1-bromo-1,1,2,2,2-pentafluoroethane (FC 115B1 [354-55-2]),



S. (2*Z*)-1,1,1,2,3,4,4,4-octafluorobut-2-ene (FC 1318my/c [1516-65-0]),



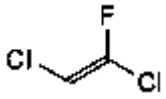
T. (2*E*)-1,1,1,2,3,4,4,4-octafluorobut-2-ene (FC 1318my/t [1516-64-9]),



U. 1,1,2-trichloroethene (trichloroethylene, HCC 1120 [79-01-6]),

V. dichloromethane (methylene chloride, HCC 30 [75-09-2]),

W. chloromethane (methyl chloride, HCC 40 [74-87-3]),



X. (*E*)-1,2-dichloro-1-fluoroethene (HCFC 1121/t),

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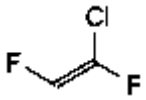
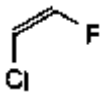
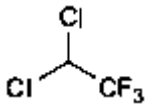


Y. (*Z*)-1-chloro-1,2-difluoroethene (HCFC 1122a/c [359-04-6]),

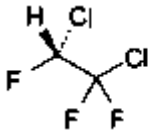


Z. (*Z*)-1-chloro-2-fluoroethene (HCFC 1131/c [2268-31-7]),

AA. (*E*)-1-chloro-2-fluoroethene (HCFC 1131/t [2268-32-8]),

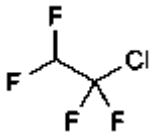


BB. 1,1-dichloro-2,2,2-trifluoroethane (HCFC 123 [306-83-2]),

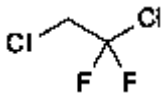


and enantiomer

CC. (2*RS*)-1,2-dichloro-1,1,2-trifluoroethane (HCFC 123a [354-23-4]),



DD. 1-chloro-1,1,2,2-tetrafluoroethane (HCFC 124a [354-25-6]),



EE. 1,2-dichloro-1,1-difluoroethane (HCFC 132b [1649-08-7]),

FF. 2-chloro-1,1,1-trifluoroethane (HCFC 133a [75-88-7]),

GG. chlorodifluoromethane (HCFC 22 [75-45-6]),

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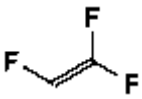
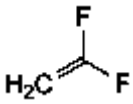
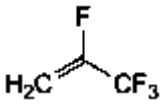
HH. chlorofluoromethane (HCFC 31 [593-70-4]),



II. 1,1,2-trifluoroethene (HFC 1123 [359-11-5]),

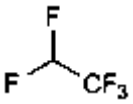


JJ. 1,1-difluoroethene (HFC 1132a [75-38-7]),

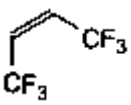


KK. 2,3,3,3-tetrafluoroprop-1-ene (HFC 1234yf [754-12-1]),

LL. (1*E*)-1,3,3,3-tetrafluoroprop-1-ene (HFC 1234ze [1645-83-6]),

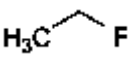


MM. 1,1,1,2,2-pentafluoroethane (HFC 125 [354-33-6]),



NN. (2*Z*)-1,1,1,4,4,4-hexafluorobut-2-ene (HFC 1336mzz/c [692-49-9]),

OO. 1,2-difluoroethane (HFC 152 [624-72-6]),



PP. fluoroethane (HFC 161 [353-36-6]),

QQ. trifluoromethane (HFC 23 [75-46-7]),

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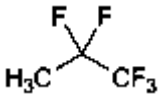

RR. 1,1,1,2,2-pentafluoropropane (HFC 245cb [1814-88-6]),

SS. difluoromethane (HFC 32 [75-10-5]).

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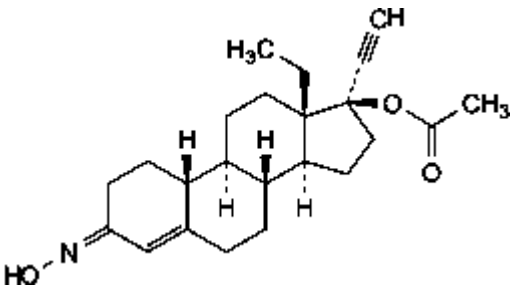
Norgestimate

General Notices

(Ph. Eur. monograph 1732)



$C_{23}H_{31}NO_3$ 369.5 *35189-28-7*

Action and use

Progestogen.

Ph Eur

DEFINITION

(3*EZ*)-13β-Ethyl-3-(hydroxyimino)-18,19-dinor-17α-pregn-4-en-20-yn-17-yl acetate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *norgestimate CRS*.

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TESTS

Specific optical rotation (2.2.7)

+ 42.0 to + 50.0 (dried substance).

Dissolve 0.200 g in *methylene chloride R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *methanol R* (1:4 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of *norgestimate for system suitability CRS* (containing impurity A) in 4 mL of the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, *tetrahydrofuran for chromatography R*, *water R* (18:22:60 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 244 nm.

Injection 25 µL.

Run time Twice the retention time of the (*E*)-isomer of norgestimate.

Identification of impurities Use the chromatogram supplied with *norgestimate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to the (*E*)-isomer of norgestimate (retention time = about 14 min): impurity A = about 0.7; (*Z*)-isomer of norgestimate = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to the (*E*)- and (*Z*)-isomers of norgestimate.

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Limits:

— *correction factor*: for the calculation of content, multiply the peak area of the (*Z*)-isomer of norgestimate by 1.33;

— *impurity A*: not more than twice the sum of the areas of the peaks due to the (*E*)- and (*Z*)-isomers of norgestimate in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the sum of the areas of the peaks due to the (*E*)- and (*Z*)-isomers of norgestimate in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the sum of the areas of the peaks due to the (*E*)- and (*Z*)-isomers of norgestimate in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the sum of the areas of the peaks due to the (*E*)- and (*Z*)-isomers of norgestimate in the chromatogram obtained with reference solution (a) (0.05 per cent).

Ratio of (*E*)- to (*Z*)-isomers

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution.

Calculate the (*E*)- to (*Z*)-isomer ratio by dividing the area of the peak due to the (*E*)-isomer by 1.33 times the area of the peak due to the (*Z*)-isomer. The ratio is 1.27 to 1.78.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.300 g in 40 mL of *tetrahydrofuran R*. Add 10 mL of a 100 g/L solution of *silver nitrate R* and titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Rinse the electrode with *acetone R* after each titration.

If necessary, after several titrations re-equilibrate the electrode in *water R* for 15 min to obtain sharper titration curves.

1 mL of *0.1 M sodium hydroxide* is equivalent to 36.95 mg of $C_{23}H_{31}NO_3$.

IMPURITIES

Specified impurities *A*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D.*

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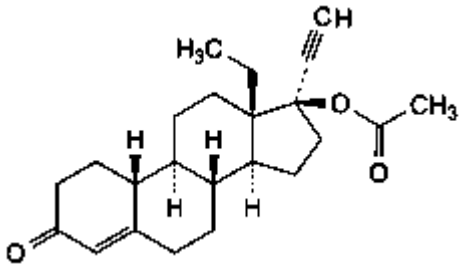
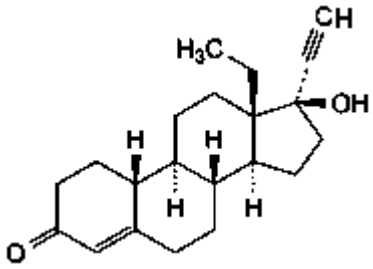
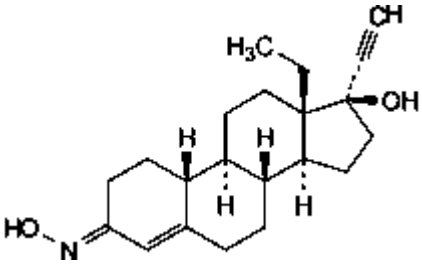


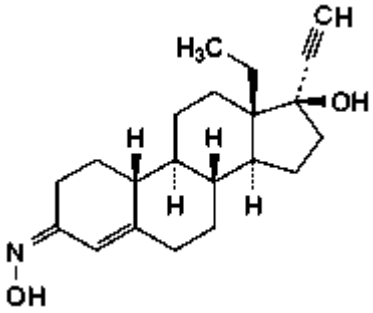
A. 13β-ethyl-3-oxo-18,19-dinor-17α-pregn-4-en-20-yn-17-yl acetate (levonorgestrel acetate),



B. 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (levonorgestrel),



C. (3*E*)-13β-ethyl-3-(hydroxyimino)-18,19-dinor-17α-pregn-4-en-20-yn-17-ol ((*E*)-norelgestromin),



D. (3*Z*)-13β-ethyl-3-(hydroxyimino)-18,19-dinor-17α-pregn-4-en-20-yn-17-ol ((*Z*)-norelgestromin).

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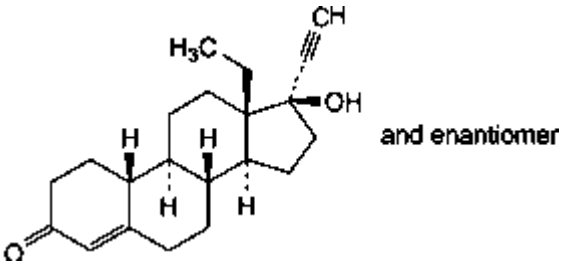
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Norgestrel

General Notices

(Ph. Eur. monograph 0940)



$C_{21}H_{28}O_2$ 312.5 *6533-00-2*

Action and use

Progestogen.

Preparation

Norgestrel Tablets

Ph Eur

DEFINITION

Norgestrel contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of *rac*-13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 0.5 g in *methylene chloride R* and dilute to 10.0 mL with the same solvent. The angle of optical rotation (2.2.7) is + 0.05° to -0.05°.

B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *norgestrel CRS*.

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TESTS

Related substances

Examine by thin-layer chromatography (2.2.27), using *silica gel G R* as the coating substance.

Test solution Dissolve 0.2 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 10 mL with *methylene chloride R*. Dilute 1 mL of this solution to 20 mL with *methylene chloride R*.

Reference solution (b) Dilute 4 mL of reference solution (a) to 10 mL with *methylene chloride R*.

Reference solution (c) Dissolve 5 mg of *norgestrel CRS* and 5 mg of *ethinylestradiol CRS* in *methylene chloride R* and dilute to 50 mL with the same solvent.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 20 volumes of *ethyl acetate R* and 80 volumes of *methylene chloride R*. Allow the plate to dry in air, spray with a 100 g/L solution of *phosphomolybdic acid R* in *alcohol R*, heat at 100-105 °C for 15 min and examine immediately. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the principal spot in the chromatogram obtained with reference solution (a) (0.5 per cent) and at most two such spots are more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated spots.

Loss on drying (2.2.32)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 45 mL of *tetrahydrofuran R*. Add 10 mL of a 100 g/L solution of *silver nitrate R*. After 1 min, titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.25 mg of $C_{21}H_{28}O_2$.

STORAGE

Store protected from light.

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Norgestrel Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Norgestrel Tablets contain Norgestrel. They are coated.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of norgestrel.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of norgestrel, $C_{21}H_{28}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the tablets containing 0.15 mg of Norgestrel add 10 mL of *methanol (80%)*, heat on a water-bath at 60° for 10 minutes, shaking occasionally, allow to cool, dilute with *methanol (80%)* to produce a solution containing 0.00375% w/v of Norgestrel, mix and filter through a membrane with a pore size of 0.45 µm.

(2) 0.004% w/v of *norgestrel BPCRS* in *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 242 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Equal volumes of *methanol* and 1% w/v of *gamma-cyclodextrin* in *water*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to levonorgestrel and dextronorgestrel is at least 1.0.

CONFIRMATION

The two principal peaks in the chromatogram obtained with solution (1) have the same retention times as the peaks due to levonorgestrel and dextronorgestrel in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of a mixture of equal volumes of *methanol (50%)* to a quantity of the powdered tablets containing 0.15 mg of Norgestrel, mix with the aid of ultrasound for 30 minutes, stir vigorously for 15 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (50%)*.

(3) 0.004% w/v each of *ethinylestradiol BPCRS* and *norgestrel BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of norgestrel.

MOBILE PHASE

100 volumes of *methanol*, 240 volumes of *acetonitrile* and 500 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ethinylestradiol and norgestrel is at least 12.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

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Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Norgestrel comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To 1 tablet add 5 mL of the mobile phase, heat on a water bath at 60° for 15 minutes while shaking, disperse with the aid of ultrasound for 5 minutes, centrifuge and use the clear supernatant liquid. Dilute, if necessary, with the mobile phase to produce a solution containing 0.0015% w/v of Norgestrel.

(2) 0.0015% w/v of *norgestrel BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ in each tablet using the declared content of $C_{21}H_{28}O_2$ in *norgestrel BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

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Nortriptyline Capsules

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Nortriptyline Capsules contain Nortriptyline Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of nortriptyline, $C_{19}H_{21}N$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing the equivalent of 5 mg of nortriptyline with 20 mL of *methanol* and filter. To 1 mL of the filtrate add 1 mL of a 2.5% w/v solution of *sodium hydrogen carbonate*, 1 mL of a 2% w/v solution of *sodium periodate* and 1 mL of a 0.3% w/v solution of *potassium permanganate*. Allow to stand for 15 minutes, acidify with 1M *sulfuric acid* and extract with 10 mL of *2,2,4-trimethylpentane*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum only at 265 nm.

B. Triturate a quantity of the contents of the capsules containing the equivalent of 0.1 g of nortriptyline with 10 mL of *chloroform*, filter and evaporate the chloroform. Dissolve 50 mg of the residue in 3 mL of warm *water*, cool and add 0.05 mL of a 2.5% w/v solution of *quinhydrone* in *methanol*. A red colour develops (distinction from amitriptyline).

C. The residue obtained in test B yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Dibenzosuberone

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 3 volumes of *diethylamine*, 15 volumes of *ethyl acetate* and 85 volumes of *cyclohexane* as the mobile phase but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) extract a quantity of the contents of the capsules containing the equivalent of 20 mg of nortriptyline with 5 mL of a mixture of 1 volume of *2M hydrochloric acid* and 9 volumes of *ethanol* (*96%*), centrifuge and use the supernatant liquid. Solution (2) contains 0.0010% w/v of *dibenzosuberone* in *ethanol* (*96%*). After removal of the plate, allow it to dry in air until the solvent has evaporated, spray with *sulfuric acid* containing 4% v/v of *formaldehyde solution* and examine immediately under *ultraviolet light* (*365 nm*). Any spot corresponding to dibenzosuberone in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

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ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using a quantity of the mixed contents of 20 capsules containing the equivalent of 0.1 g of nortriptyline, adding 3 mL of *mercury(II) acetate solution* and using *0.02M perchloric acid VS* as titrant and *crystal violet solution* as indicator. Each mL of *0.02M perchloric acid VS* is equivalent to 5.268 mg of $C_{19}H_{21}N$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of nortriptyline.

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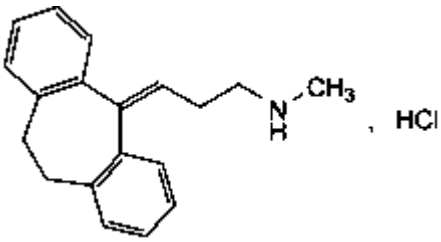
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Nortriptyline Hydrochloride

General Notices

(Ph. Eur. monograph 0941)



$C_{19}H_{22}ClN$ 299.8 *894-71-3*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparations

Nortriptyline Capsules

Nortriptyline Tablets

Ph Eur

DEFINITION

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine hydrochloride.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Sparingly soluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison nortriptyline hydrochloride CRS.

B. Dissolve 20 mg in 2 mL of water R, acidify with 1 drop of dilute sulfuric acid R and add 1 mL of a 6.25 g/L solution of silver sulfate R. Shake and allow to stand. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with 3 quantities, each of 1 mL, of a 0.5 per cent *V/V* solution of sulfuric acid R. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant may not become perfectly clear. Suspend the precipitate in water R and add ammonia R. Shake vigorously for at least 1 min. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, Method II).

Dissolve 0.5 g in water R with gentle heating and dilute to 25 mL with the same solvent.

Acidity or alkalinity

Dissolve 0.2 g with gentle heating in carbon dioxide-free water R and dilute to 10 mL with the same solvent. Add 0.1 mL of methyl red solution R and 0.2 mL of 0.01 M sodium hydroxide. The solution is yellow. Add 0.4 mL of 0.01 M hydrochloric acid. The solution is red.

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of dibenzosuberone CRS (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 20 mg of norcyclobenzaprine CRS (impurity B) in the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 mL of the solution to 10 mL with the mobile phase.

Reference solution (d) Dissolve 10 mg of nortriptyline for system suitability CRS (containing impurity D) in the mobile phase, add 1 mL of reference solution (c) and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: spherical *end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Mix 70 volumes of *methanol R1* and 30 volumes of a solution prepared as follows: mix 3.25 mL of *tetrabutylammonium hydroxide solution (400 g/L) R*, 0.68 g of *potassium dihydrogen phosphate R* and about 900 mL of *water for chromatography R*, then adjust to pH 7.5 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 3 times the retention time of nortriptyline.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram supplied with *nortriptyline for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity D.

Relative retention With reference to nortriptyline (retention time = about 13 min): impurity A = about 0.5; impurity D = about 0.8; impurity B = about 0.9.

System suitability Reference solution (d):

— *resolution*: minimum 1.4 between the peaks due to impurities D and B; minimum 2.0 between the peaks due to impurity B and nortriptyline.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 1.7;

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 30 mL of *ethanol (96 per cent) R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 29.98 mg of $C_{19}H_{22}ClN$.

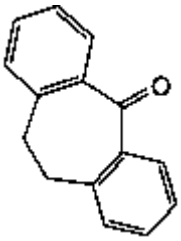
STORAGE

Protected from light.

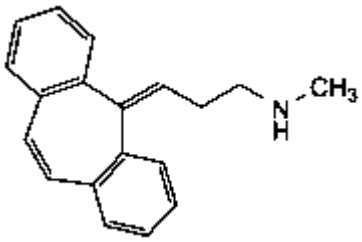
IMPURITIES

Specified impurities A, D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, E, F, G, H, I, J.



A. 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (dibenzosuberone),



B. 3-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (norcyclobenzaprine),

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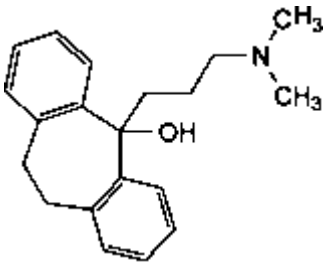
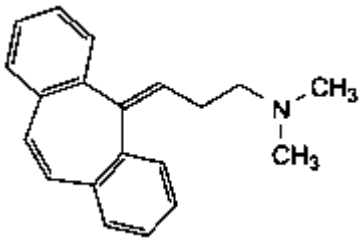
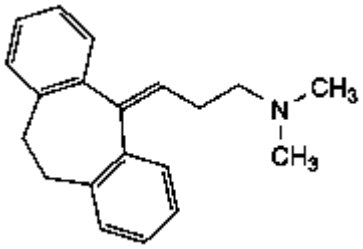


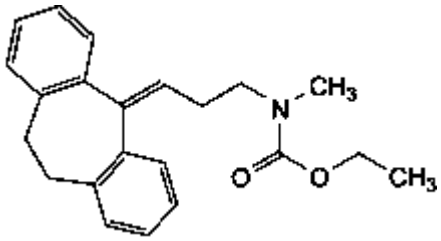
D. 5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol,



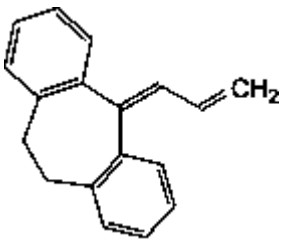
E. 3-(5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)-*N,N*-dimethylpropan-1-amine (cyclobenzaprine),



F. 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine (amitriptyline),



G. ethyl *N*-[3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)propyl]-*N*-methylcarbamate,



H. 5-prop-2-en-1-ylidene-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulene,

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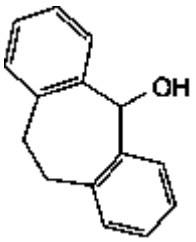
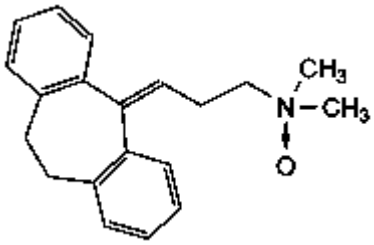


I. 10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ol (dibenzosuberol),



J. [3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)propyl]dimethylamine *N*-oxide (amitriptyline-*N*-oxide).

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Nortriptyline Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Nortriptyline Tablets contain Nortriptyline Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of nortriptyline, $C_{19}H_{21}N$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 5 mg of nortriptyline with 20 mL of *methanol* and filter. To 1 mL of the filtrate add 1 mL of a 2.5% w/v solution of *sodium hydrogen carbonate*, 1 mL of a 2% w/v solution of *sodium periodate* and 1 mL of a 0.3% w/v solution of *potassium permanganate*. Allow to stand for 15 minutes, acidify with 1M *sulfuric acid* and extract with 10 mL of *2,2,4-trimethylpentane*. The *light absorption* of the resulting trimethylpentane solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum only at 265 nm.

B. Triturate a quantity of the powdered tablets containing the equivalent of 0.1 g of nortriptyline with 10 mL of *chloroform*, filter and evaporate the filtrate to a low volume. Add *ether* until a turbidity is produced and allow to stand. Dissolve 50 mg of the precipitate in 3 mL of warm *water*, cool and add 0.05 mL of a 2.5% w/v solution of *quinhydrone* in *methanol*. A red colour develops (distinction from amitriptyline).

C. The precipitate obtained in test B yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Dibenzosuberone

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing the equivalent of 20 mg of nortriptyline with 5 mL of a mixture of 1 volume of 2M *hydrochloric acid* and 9 volumes of *ethanol* (*96%*), centrifuge and use the supernatant liquid.

(2) 0.0010% w/v of *dibenzosuberone* in *ethanol* (*96%*).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

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(c) Apply 5 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry in air until the solvent has evaporated, spray with *sulfuric acid* containing 4% v/v of *formaldehyde solution* and examine immediately under *ultraviolet light* (*365 nm*).

MOBILE PHASE

3 volumes of *diethylamine*, 15 volumes of *ethyl acetate* and 85 volumes of *cyclohexane*.

LIMITS

Any spot corresponding to dibenzosuberone in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of *water* to 20 tablets, shake vigorously until the tablets have completely disintegrated, add 100 mL of *methanol* and shake for 30 minutes. Add sufficient *water* to produce 200 mL, filter and dilute a volume of the filtrate containing the equivalent of 25 mg of nortriptyline to 100 mL with *methanol* (*50%*).

(2) 0.025% w/v solution of *nortriptyline hydrochloride BPCRS* in *methanol* (*50%*).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.56% w/v solution of *sodium hexanesulfonate* in a mixture of equal volumes of *water* and *acetonitrile* adjusted to pH 4.5 with *glacial acetic acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{21}N$ using the declared content of $C_{19}H_{21}N$ in *nortriptyline hydrochloride BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of nortriptyline.

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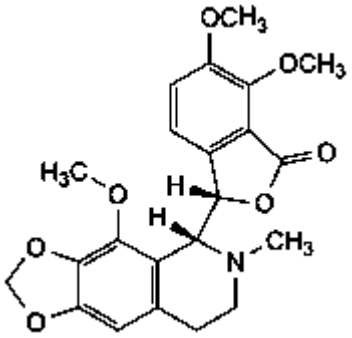
Noscapine

General Notices

(Ph. Eur. monograph 0516)



$C_{22}H_{23}NO_7$ 413.4 *128-62-1*

Action and use

Opioid receptor agonist; cough suppressant.

Ph Eur

DEFINITION

(3*S*)-6,7-Dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]isobenzofuran-1(3*H*)-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, soluble in acetone, slightly soluble in ethanol (96 per cent). It dissolves in strong acids; on dilution of the acid solutions with water, the base may be precipitated.

IDENTIFICATION

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First identification: C, E.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Melting point (2.2.14): 174 °C to 177 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison noscapine CRS.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in acetone R and dilute to 100 mL with the same solvent.

Reference solution Dissolve 25 mg of noscapine CRS in acetone R and dilute to 100 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase concentrated ammonia R, ethanol (96 per cent) R, acetone R, toluene R (1:3:20:20 *V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with dilute potassium iodobismuthate solution R.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

E. To 20 mg add 10 mL of water R and shake. It does not dissolve.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 0.2 g in acetone R and dilute to 10 mL with the same solvent. Examine immediately after dissolution.

Specific optical rotation (2.2.7)

+ 42 to + 48 (dried substance).

Dissolve 0.500 g in 0.1 M hydrochloric acid and dilute to 25.0 mL with the same acid.

Related substances

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Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in 8 mL of methanol R, with the aid of ultrasound, and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 20.0 mL with methanol R. Dilute 1.0 mL of this solution to 10.0 mL with methanol R.

Reference solution (b) Dissolve 5 mg of papaverine hydrochloride R in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 1.5 mg of papaverine hydrochloride R in 10 mL of the test solution and dilute to 25 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: cyanosilyl silica gel for chromatography R (5 µm).

Mobile phase methanol R1, phosphate buffer solution pH 6.0 R1 (350:650 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time 2.5 times the retention time of noscapine.

Relative retention With reference to noscapine (retention time = about 10 min): impurity A = about 1.3.

System suitability Reference solution (c):

— resolution: minimum 2.0 between the peaks due to noscapine and impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *any other impurity*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of impurities other than A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

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Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

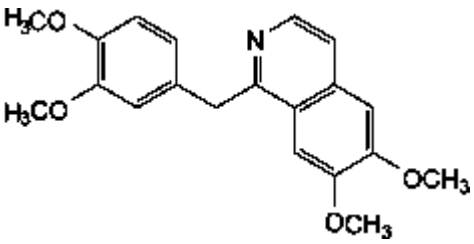
Dissolve 0.350 g in 40 mL of *anhydrous acetic acid R*, warming gently. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 41.34 mg of $C_{22}H_{23}NO_7$.

STORAGE

Protected from light.

IMPURITIES



A. 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (papaverine).

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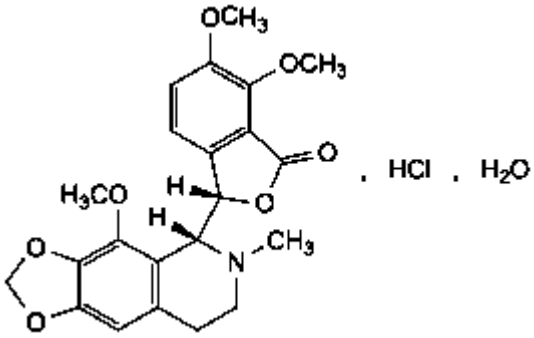
Noscapine Hydrochloride Hydrate

General Notices

Noscapine Hydrochloride

(Ph. Eur. monograph 0515)



$C_{22}H_{24}ClNO_7,H_2O$ 467.9

Action and use

Opioid receptor agonist; cough suppressant.

Ph Eur

DEFINITION

(3*S*)-6,7-Dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]-2-benzofuran-1(3*H*)-one hydrochloride hydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Freely soluble in water and in ethanol (96 per cent). Aqueous solutions are slightly acid; the base may be precipitated when the solutions are allowed to stand.

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mp

About 200 °C, with decomposition.

IDENTIFICATION

First identification: C, E.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Melting point (2.2.14) of the precipitate obtained in identification test E: 174 °C to 177 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Examine the precipitate obtained in identification test E.

Comparison *noscapine CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 100 mL with the same solvent.

Reference solution Dissolve 22 mg of *noscapine CRS* in *acetone R* and dilute to 100 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *ethanol (96 per cent) R*, *acetone R*, *toluene R* (1:3:20:20 *V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *dilute potassium iodobismuthate solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

E. Dissolve about 40 mg in a mixture of 2 mL of *water R* and 3 mL of *ethanol (96 per cent) R* and add 1 mL of *dilute ammonia R2*. Heat until dissolution is complete. Allow to cool, scratching the wall of the tube with a glass rod. Filter. The filtrate gives reaction (a) of chlorides (2.3.1). Wash the precipitate with *water R*, dry at 100-105 °C and reserve for identification tests B and C.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution Y_6 or BY_6 (*2.2.2, Method II*).

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Dissolve 0.5 g in *water R*, add 0.3 mL of *0.1 M hydrochloric acid* and dilute to 25 mL with *water R*.

pH (*2.2.3*)

Minimum 3.0.

Dissolve 0.2 g in 10 mL of *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

+ 38.5 to + 44.0 (dried substance).

Dissolve 0.500 g in *0.01 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40.0 mg of the substance to be examined in *methanol R*, with the aid of ultrasound, and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5.0 mg of *papaverine hydrochloride CRS* (impurity A) in the mobile phase and dilute to 50.0 mL with the mobile phase (solution A). Dilute 1.0 mL of solution A to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 6.0 mL of solution A to 10.0 mL with the test solution.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, *phosphate buffer solution pH 6.0 R1* (35:65 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time 2.5 times the retention time of noscapine.

Relative retention With reference to noscapine (retention time = about 10 min): impurity A = about 1.3.

System suitability Reference solution (c):

— *resolution*: minimum 2 between the peaks due to noscapine and impurity A.

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Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *any other impurity*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of impurities other than A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

2.5 per cent to 6.5 per cent, determined on 0.200 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid over heating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.400 g in a mixture of 3 mL of *anhydrous formic acid R* and 30 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

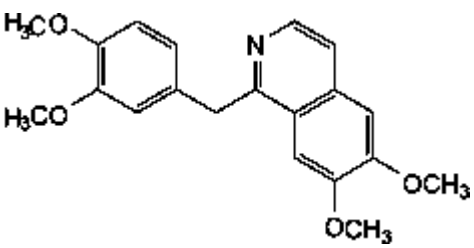
1 mL of *0.1 M perchloric acid* is equivalent to 44.99 mg of $C_{22}H_{24}ClNO_7$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A.*



A. 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline (papaverine).

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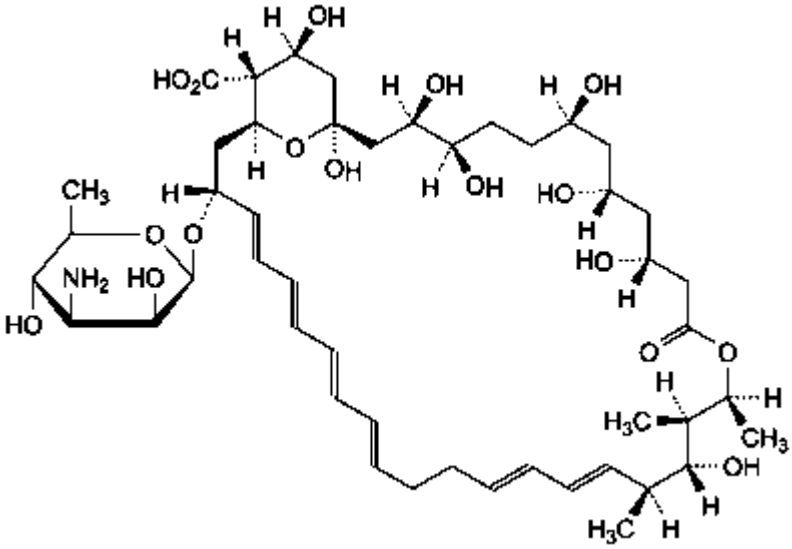
Nystatin

General Notices

(Ph. Eur. monograph 0517)



$C_{47}H_{75}NO_{17}$ 926

Action and use

Antifungal.

Preparations

Nystatin Ointment

Nystatin Oral Suspension

Nystatin Vaginal Tablets

Nystatin Tablets

Ph Eur

DEFINITION

Antifungal substance obtained by fermentation using certain strains of *Streptomyces noursei* as the production micro-organism. It contains mainly tetraenes, the principal component being

(1*S*,3*R*,4*R*,7*R*,9*R*,11*R*,15*S*,16*R*,17*R*,18*S*,19*E*,21*E*,25*E*,27*E*,29*E*,31*E*,33*R*,35*S*,36*R*,37*S*)-33-[(3-amino-3,6-dideoxy-β-D-

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mannopyranosyl)oxy]-1,3,4,7,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,25,27,29,31-hexaene-36-carboxylic acid (nystatin A1).

Content

Minimum 4400 IU/mg (dried substance) and minimum 5000 IU/mg (dried substance) if intended for oral administration.

CHARACTERS

Appearance

Yellow or slightly brownish powder, hygroscopic.

Solubility

Practically insoluble in water, freely soluble in dimethylformamide and in dimethyl sulfoxide, slightly soluble in methanol, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D.

A. Examine the solution prepared in the test for absorbance between 220 nm and 350 nm (*2.2.25*). The solution shows 4 absorption maxima at 230 nm, 291 nm, 305 nm and 319 nm, and a shoulder at 280 nm. The ratios of the absorbances at the absorption maxima at 291 nm and 319 nm to the absorbance at the absorption maximum at 305 nm are 0.61 to 0.73 and 0.83 to 0.96, respectively. The ratio of the absorbance measured at the absorption maximum at 230 nm to that measured at the shoulder at 280 nm is 0.83 to 1.25.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *nystatin CRS*.

C. To about 2 mg add 0.1 mL of *hydrochloric acid R*. A brown colour develops.

D. To about 2 mg add 0.1 mL of *sulfuric acid R*. A brown colour develops that becomes violet on standing.

E. Examine the chromatograms obtained in the test for composition.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Absorbance (*2.2.25*)

Dissolve 0.10 g in a mixture of 5.0 mL of *glacial acetic acid R* and 50 mL of *methanol R* and dilute to 100.0 mL with *methanol R*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Determined at the maximum at 305 nm within 30 min of preparation of the solution, the absorbance is not less than 0.60.

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Composition

Liquid chromatography (2.2.29): use the normalisation procedure. *Carry out the test protected from light.*

Test solution Dissolve 20 mg of the substance to be examined in *dimethyl sulfoxide R* and dilute to 50 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *nystatin CRS* in *dimethyl sulfoxide R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of the substance to be examined in 25 mL of *methanol R* and dilute to 50 mL with *water R*. To 10.0 mL of the solution add 2.0 mL of *dilute hydrochloric acid R*. Allow to stand at room temperature for 1 h.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with *dimethyl sulfoxide R*. Dilute 1.0 mL of this solution to 10.0 mL with *dimethyl sulfoxide R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase: base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, 3.85 g/L solution of *ammonium acetate R* (29:71 *V/V*),

— *mobile phase B*: 3.85 g/L solution of *ammonium acetate R*, *acetonitrile R* (40:60 *V/V*),

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 35	100 → 0	0 → 100
35 - 45	0	100
45 - 50	0 → 100	100 → 0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 305 nm.

Injection 20 µL

Retention time Nystatin A1 = about 14 min.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the 2 principal peaks (retention time = about 13 min and 19 min).

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Composition:

— *nystatin A1*: minimum 85.0 per cent,

— *any other compound*: maximum 4.0 per cent,

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c); disregard any peak with a retention time of less than 2 min.

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa for 3 h.

Sulfated ash (2.4.14)

Maximum 3.5 per cent, determined on 1.0 g.

ASSAY

Carry out the microbiological assay of antibiotics (2.7.2). *Protect the solutions from light throughout the assay.*

Dissolve the substance to be examined and *nystatin CRS* separately in *dimethylformamide R* and dilute with a mixture of 5 volumes of *dimethylformamide R* and 95 volumes of buffer solution pH 6.0.

STORAGE

In an airtight container, protected from light.

LABELLING

The label states where applicable, that the substance is only for cutaneous use.

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Nystatin Ointment

General Notices

Action and use

Antifungal.

DEFINITION

Nystatin Ointment is a dispersion of Nystatin in *microfine powder* in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

IDENTIFICATION

Disperse a quantity containing 25,000 IU in 10 mL of *chloroform*, add 40 mL of *methanol* and shake. Filter and dilute 1 mL of the filtrate to 25 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 250 to 350 nm exhibits three maxima, at 291, 305 and 319 nm. The ratios of the *absorbances* at the maxima at 291 nm and 319 nm to the *absorbance* at the maximum at 305 nm are 0.61 to 0.73 and 0.83 to 0.96, respectively. Use in the reference cell a solution prepared in exactly the same manner but omitting the preparation being examined.

ASSAY

Carry out the following procedure protected from light. Disperse a quantity containing 400,000 IU in 20 mL of *ether* in a stoppered flask, add 70 mL of *dimethylformamide* and shake for 15 minutes. Add 10 mL of *water*, shake vigorously for 2 minutes and filter. Dilute 10 mL of the filtrate to 100 mL with a solution containing 9.56% w/v of *potassium dihydrogen orthophosphate* and 11.5% v/v of 1M *potassium hydroxide* and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU.

LABELLING

The strength is stated as the number of IU (Units) per g.

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Nystatin Oral Suspension

General Notices

Nystatin Oral Drops

Action and use

Antifungal.

DEFINITION

Nystatin Oral Suspension is a suspension of Nystatin in a suitable flavoured vehicle.

Nystatin Oral Suspension should not be diluted.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

IDENTIFICATION

To a quantity containing 300,000 IU add a mixture of 5 mL of *glacial acetic acid* and 50 mL of *methanol* and shake. Add sufficient *methanol* to produce 100 mL, filter and dilute 1 mL of the filtrate to 100 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 250 to 350 nm exhibits three maxima, at 291, 305 and 319 nm. The ratios of the *absorbances* at the maxima at 291 nm and 319 nm to the *absorbance* at the maximum at 305 nm are 0.61 to 0.73 and 0.83 to 0.96, respectively. Use in the reference cell a solution prepared in exactly the same manner but omitting the preparation being examined.

ASSAY

Carry out the following procedure protected from light. Dissolve a quantity containing 200,000 IU in sufficient *dimethylformamide* to produce 50 mL, dilute 10 mL to 200 mL with a solution containing 9.56% w/v of *potassium dihydrogen orthophosphate* and 11.5% v/v of 1M *potassium hydroxide* and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 95.0% and the lower fiducial limit of error is not more than 120.0% of the stated number of IU.

STORAGE

Nystatin Oral Suspension should be protected from light. It should not be allowed to freeze.

LABELLING

The strength is stated as the number of IU (Units) per mL.

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Nystatin Tablets

General Notices

Action and use

Antifungal.

DEFINITION

Nystatin Tablets contain Nystatin. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 300,000 IU with a mixture of 5 mL of *glacial acetic acid* and 50 mL of *methanol*, add sufficient *methanol* to produce 100 mL and filter. Dilute 1 mL of the filtrate to 100 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 250 to 350 nm exhibits three maxima, at 291, 305 and 319 nm. The ratios of the *absorbances* at the maxima at 291 nm and 319 nm to the *absorbance* at the maximum at 305 nm are 0.61 to 0.73 and 0.83 to 0.96, respectively. Use in the reference cell a solution prepared in exactly the same manner but omitting the preparation being examined.

TESTS

Disintegration

Maximum time, 30 minutes, Appendix XII A1, but using a 0.6% v/v solution of *hydrochloric acid* in place of *water*. If the tablets fail to disintegrate, wash them rapidly by immersion in *water* and continue the test using *phosphate buffer pH 6.8*; the tablets then disintegrate within a further 30 minutes.

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, the powdered tablets lose not more than 5.0% of their weight. Use 1 g.

ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 tablets. Shake a quantity of the powder containing 200,000 IU with 50 mL of *dimethylformamide* for 1 hour. Centrifuge, dilute 10 mL of the clear, supernatant liquid to 200 mL with a solution containing 9.56% w/v of *potassium dihydrogen orthophosphate* and 11.5% v/v of 1M *potassium hydroxide* and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated number of IU.

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LABELLING

The quantity of active ingredient is stated as the number of IU (Units).

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Nystatin Vaginal Tablets

General Notices

Nystatin Pessaries

Action and use

Antifungal.

DEFINITION

Nystatin Vaginal Tablets contain Nystatin.

The vaginal tablets comply with the requirements stated under Vaginal Preparations and with the following requirements.

IDENTIFICATION

To a quantity of the powdered vaginal tablets containing 300,000 IU add a mixture of 5 mL of *glacial acetic acid* and 50 mL of *methanol* and shake. Add sufficient *methanol* to produce 100 mL, filter and dilute 1 mL of the filtrate to 100 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 250 to 350 nm exhibits three maxima, at 291, 305 and 319 nm. The ratios of the *absorbances* at the maxima at 291 nm and 319 nm to the *absorbance* at the maximum at 305 nm are 0.61 to 0.73 and 0.83 to 0.96, respectively. Use in the reference cell a solution prepared in exactly the same manner but omitting the preparation being examined.

TESTS

Loss on drying

When dried to constant weight at 105°, the powdered vaginal tablets lose not more than 5.0% of their weight. Use 1 g.

ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 vaginal tablets. Shake a quantity of the powder containing 200,000 IU with 50 mL of *dimethylformamide* for 1 hour. Centrifuge, dilute 10 mL of the clear supernatant liquid to 200 mL with a solution containing 9.56% w/v of *potassium dihydrogen orthophosphate* and 11.5% v/v of 1M *potassium hydroxide* and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 95.0% and the lower fiducial limit of error is not more than 125.0% of the stated number of IU.

LABELLING

The quantity of active ingredient is stated as the number of IU (Units).

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Octanoic Acid

General Notices

(Caprylic Acid, Ph. Eur. monograph 1401)

$C_8H_{16}O_2$ 144.2 *124-07-2*

Action and use

Excipient.

Ph Eur

DEFINITION

Octanoic acid.

Content

99.0 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless or slightly yellowish, oily liquid.

Solubility

Very slightly soluble in water, very soluble in acetone and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Relative density (see Tests).

B. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

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Appearance

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Relative density (*2.2.5*)

0.909 to 0.912.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 0.10 g of the substance to be examined in *ethyl acetate R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.10 g of *caprylic acid CRS* in *ethyl acetate R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *ethyl acetate R*. Dilute 5.0 mL of this solution to 50.0 mL with *ethyl acetate R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 2-nitroterephthalate R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.5 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	100
	1 - 25	100 → 220
	25 - 35	220
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

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System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 5 for the principal peak.

Limits:

— *any impurity*: for each impurity, maximum 0.3 per cent;

— *total*: maximum 0.5 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.7 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.125 g in 25 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

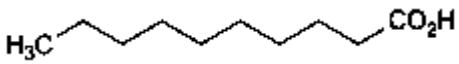
1 mL of *0.1 M sodium hydroxide* is equivalent to 14.42 mg of $C_8H_{16}O_2$.

IMPURITIES

A. hexanoic acid,

B. heptanoic acid,

C. nonanoic acid,



D. decanoic acid,

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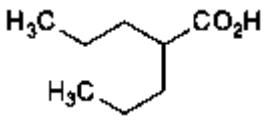
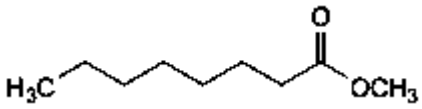
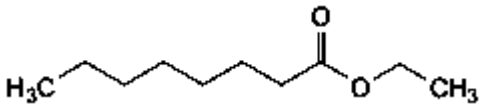


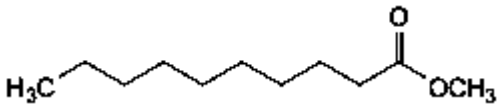
E. 2-propylpentanoic acid (valproic acid),



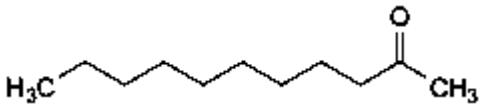
F. methyl octanoate,



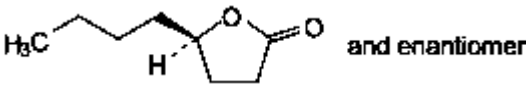
G. ethyl octanoate,



H. methyl decanoate,



I. undecan-2-one,



J. 5-butyltetrahydrofuran-2-one (γ-hydroxyoctanoic acid lactone).

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Octoxinol 10

General Notices

(Ph. Eur. monograph 1553)

Action and use

Excipient.

Ph Eur

DEFINITION

α-[4-(1,1,3,3-Tetramethylbutyl)phenyl]-ω-hydroxydeca(oxyethylene).

Mixture consisting mainly of mono-octylphenyl ethers of macrogols corresponding to the formula $C_8H_{17}C_6H_4$-$[OCH_2$-$CH_2]_n$-OH where the average value of *n* is 10. It may contain free macrogols.

CHARACTERS

Appearance

Clear, colourless or light yellow, viscous liquid.

Solubility

Miscible with water, with ethanol (96 per cent) and with vegetable oils.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *octoxinol 10 CRS*.

Preparation Film between *sodium chloride R* plates.

B. Cloud point (see Tests).

TESTS

Acidity or alkalinity

Boil 1.0 g with 20 mL of *carbon dioxide-free water R* for 1 min, with constant stirring. Cool and filter. To 10 mL of the filtrate, add 0.05 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the

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colour of the indicator.

Hydroxyl value (*2.5.3, Method A*)

85 to 101.

Cloud point

63 °C to 70 °C.

Dissolve 1.0 g in 99 g of *water R*. Transfer about 30 mL of this solution to a test-tube, heat on a water-bath and stir continuously until the solution becomes cloudy. Remove the test-tube from the water-bath (ensuring that the temperature does not increase more than 2 °C), and continue to stir. The cloud point is the temperature at which the solution becomes sufficiently clear that the entire thermometer bulb is plainly seen.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 2.00 g.

Total ash (*2.4.16*)

Maximum 0.4 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

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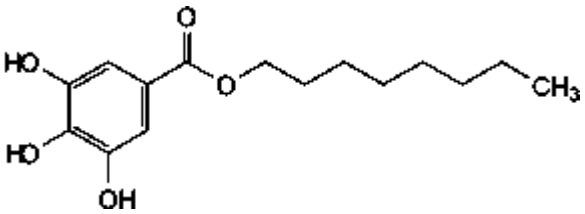
Octyl Gallate

General Notices

(Ph. Eur. monograph 2057)



$C_{15}H_{22}O_5$ 282.3 *1034-01-1*

Action and use

Used in treatment of alcohol dependence.

Ph Eur

DEFINITION

Octyl 3,4,5-trihydroxybenzoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Melting point (*2.2.14*).

Determine the melting point of the substance to be examined. Mix equal parts of the substance to be examined and *octyl gallate CRS* and determine the melting point of the mixture. The difference between the melting points (which are about 101 °C) is not greater than 2 °C.

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B. Examine the chromatograms obtained in the test for impurity A.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Impurity A

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.20 g of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20 mL with *acetone R*.

Reference solution (a) Dissolve 10 mg of *octyl gallate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *gallic acid R* in *acetone R* and dilute to 20 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10 mL with *acetone R*.

Reference solution (d) Dilute 1.0 mL of reference solution (b) to 5 mL with test solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *anhydrous formic acid R*, *ethyl formate R*, *toluene R* (10:40:50 *V/V/V*).

Application 5 µL of test solutions (a) and (b) and reference solutions (a), (c) and (d).

Development Over 2/3 of the plate.

Drying In air for 10 min.

Detection Spray with a mixture of 1 volume of *ferric chloride solution R1* and 9 volumes of *ethanol (96 per cent) R*.

System suitability Reference solution (d):

— the chromatogram shows 2 clearly separated principal spots.

Limit Test solution (a):

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.5 per cent).

Chlorides (2.4.4)

Maximum 100 ppm.

To 1.65 g add 50 mL of *water R*. Shake for 5 min. Filter. 15 mL of the filtrate complies with the test.

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Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 70 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in *methanol R* and dilute to 250.0 mL with the same solvent. Dilute 5.0 mL of the solution to 200.0 mL with *methanol R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 275 nm.

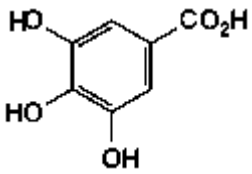
Calculate the content of $C_{15}H_{22}O_5$ taking the specific absorbance to be 387.

STORAGE

In a non-metallic container, protected from light.

IMPURITIES

Specified impurities *A.*



A. 3,4,5-trihydroxybenzoic acid (gallic acid).

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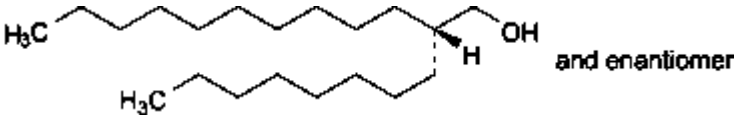
Octyldodecanol

General Notices

(Ph. Eur. monograph 1136)



5333-42-6

Action and use

Excipient.

Ph Eur

DEFINITION

Condensation product of saturated liquid fatty alcohols.

Content

Minimum 90 per cent of (2*RS*)-2-octyldodecan-1-ol ($C_{20}H_{42}O$; M_r 298.6), the remainder consisting mainly of related alcohols.

CHARACTERS

Appearance

Clear, colourless or yellowish, oily liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent).

Relative density

About 0.840.

Refractive index

About 1.455.

IDENTIFICATION

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A. Hydroxyl value (see Tests).

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in *toluene R* and dilute to 20 mL with the same solvent.

Reference solution Dissolve 0.20 g of *octyldodecanol CRS* in *toluene R* and dilute to 20 mL with the same solvent.

Plate Suitable silica gel plate.

Mobile phase *ethyl acetate R*, *toluene R* (5:95 *V/V*).

Application 2 µL.

Development Over a path of 12 cm.

Drying In air.

Detection Spray with about 7 mL of a mixture of 1 volume of a 25 g/L solution of *vanillin R* in *ethanol (96 per cent) R* and 4 volumes of *sulfuric acid R* and heat at 130 °C for 5-10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Acidity or alkalinity

Mix 5.0 g thoroughly for 1 min with a mixture of 0.1 mL of *bromothymol blue solution R1*, 2 mL of *heptane R* and 10 mL of *water R*. If the aqueous layer is blue, not more than 0.15 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to yellow. If the aqueous layer is yellow, add 0.45 mL of *0.01 M sodium hydroxide* and shake vigorously. After standing to ensure complete separation, the aqueous layer is blue.

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 2.50 g in *ethanol (96 per cent) R* and dilute to 25 mL with the same solvent.

Hydroxyl value (2.5.3, Method A)

175 to 190.

Iodine value (2.5.4, Method A)

Maximum 8.0.

Peroxide value (2.5.5, Method A)

Maximum 5.0.

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Saponification value (2.5.6)

Maximum 5.0.

Water (2.5.12)

Maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (2.2.28).

Internal standard solution Dissolve 0.4 g of *tetradecane R* in *hexane R* and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 0.100 g of the substance to be examined in the internal standard solution and dilute to 10.0 mL with the same solution.

Reference solution Dissolve 0.100 g of *octyldodecanol CRS* in the internal standard solution and dilute to 10.0 mL with the same solution.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.25 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 0.68 mL/min.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	180
	2 - 22	180 → 280
	22 - 52	280
Injection port		290
Detector		300

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Detection Flame ionisation.

Injection 1 µL.

Calculate the content of $C_{20}H_{42}O$ in the substance to be examined.

STORAGE

Protected from light.

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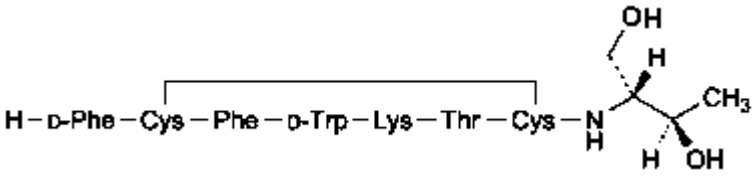
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Octreotide

General Notices

(Ph. Eur. monograph 2414)



$C_{49}H_{66}N_{10}O_{10}S_2$ 1019 *83150-76-9*

Action and use

Somatostatin analogue; treatment of neuroendocrine tumours and acromegaly.

Ph Eur

DEFINITION

D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninol cyclic (2→7)-disulfide.

Synthetic octapeptide analogue of the natural hormone somatostatin. It is available as an acetate.

Content

95.0 per cent to 103.0 per cent (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Freely soluble in water, in acetic acid and in methanol.

IDENTIFICATION

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Carry out either tests A, B or tests A, C.

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

B. Nuclear magnetic resonance spectrometry (*2.2.64*).

Preparation 2 mg/mL solution in a mixture of 10 volumes of *deuterated acetic acid R* and 90 volumes of *deuterium oxide R* containing 30 µg/mL of *deuterated sodium trimethylsilylpropionate R*.

Comparison 2 mg/mL solution of *octreotide for NMR identification CRS* in a mixture of 10 volumes of *deuterated acetic acid R* and 90 volumes of *deuterium oxide R* containing 30 µg/mL of *deuterated sodium trimethylsilylpropionate R*.

Operating conditions:

— *field strength*: minimum 300 MHz;

— *temperature*: 25 °C.

Results Examine the ^{1}H NMR spectrum from 0 to 8 ppm. The ^{1}H NMR spectrum obtained is qualitatively similar to the ^{1}H NMR spectrum obtained with *octreotide for NMR identification CRS*.

C. Amino acid analysis (*2.2.56*). Method 1 for hydrolysis and method 1 for analysis are suitable.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids taking 1/4 of the sum of the number of moles of phenylalanine, threonine and lysine as equal to 1. The values fall within the following limits: threonine: 0.7 to 1.1; threoninol: 0.7 to 1.2; lysine: 0.9 to 1.3; half-cystine: 1.0 to 2.2; phenylalanine: 1.8 to 2.2. Not more than traces of other amino acids are present.

TESTS

Specific optical rotation (*2.2.7*)

-18.5 to -14.5 (anhydrous and acetic acid-free substance).

Dissolve the substance to be examined in a 1 per cent *V/V* solution of *glacial acetic acid R* to obtain a concentration of 2.0 mg/mL.

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Solvent mixture Mix 10 volumes of *acetonitrile R* and 90 volumes of *water R*, then adjust to pH 3.5 with *acetic acid R*.

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution Dissolve the contents of a vial of *octreotide CRS* in the solvent mixture to obtain a concentration of 1.0 mg/mL.

Resolution solution Dissolve the contents of a vial of *octreotide impurity mixture CRS* (containing impurities F and G) in 1.0 mL of the reference solution.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 4.5 g of *tetramethylammonium hydroxide R* in 800 mL of *water for chromatography R* and adjust to pH 2.0 with *phosphoric acid R*; dilute to 900 mL with *water for chromatography R* and add 100 mL of *acetonitrile R1*;

— *mobile phase B*: dissolve 4.5 g of *tetramethylammonium hydroxide R* in 300 mL of *water for chromatography R* and adjust to pH 2.0 with *phosphoric acid R*; dilute to 400 mL with *water for chromatography R* and add 600 mL of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 80	10 → 20
15 - 40	80 → 55	20 → 45
40 - 45	55 → 30	45 → 70

Flow rate 1.8 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *octreotide impurity mixture CRS* and the chromatogram obtained with the resolution solution to identify the peaks due to impurities F and G.

Relative retention With reference to octreotide (retention time = about 20 min): impurity A = about 0.76; impurity B = about 0.89; impurity C = about 0.94; impurity E = about 1.13; impurity F = about 1.30; impurity G = about 1.33; impurity H = about 1.66; impurity I = about 1.88.

System suitability Resolution solution:

— *resolution*: minimum 2.0 between the peaks due to impurities F and G;

— *symmetry factor*: maximum 3.5 for the peak due to octreotide.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.5 per cent;

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— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.1 per cent.

Acetic acid (*2.5.34*)

5.0 per cent to 12.8 per cent.

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

Water (*2.5.32*)

Maximum 10.0 per cent, determined on 20.0 mg.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution.

Calculate the percentage content of octreotide ($C_{49}H_{66}N_{10}O_{10}S_2$) taking into account the assigned content of $C_{49}H_{66}N_{10}O_{10}S_2$ in *octreotide CRS*.

STORAGE

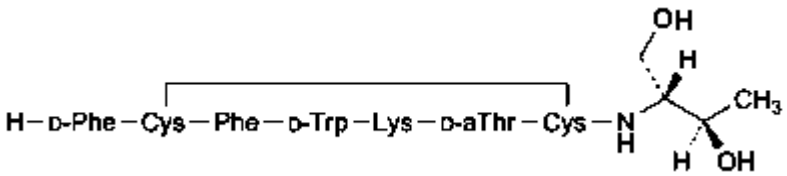
In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

LABELLING

The label states the octreotide content ($C_{49}H_{66}N_{10}O_{10}S_2$).

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, F, G, H, I.*



A. [6-D-allothreonine]octreotide,

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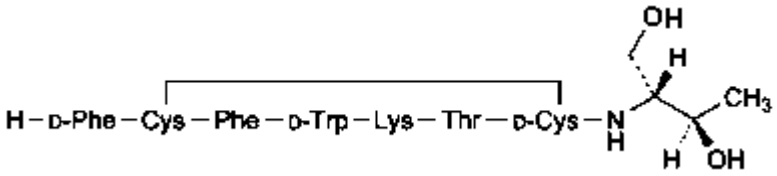
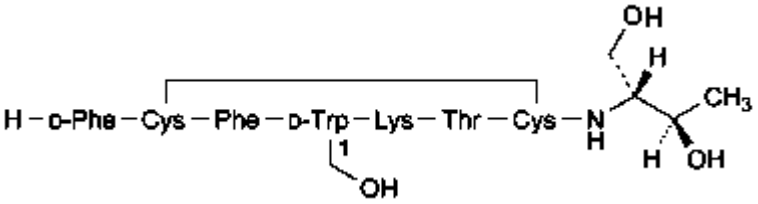
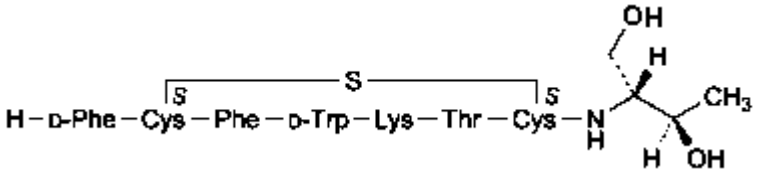


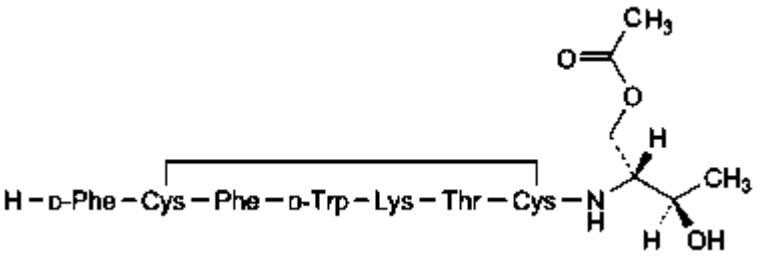
B. [7-D-cysteine]octreotide,



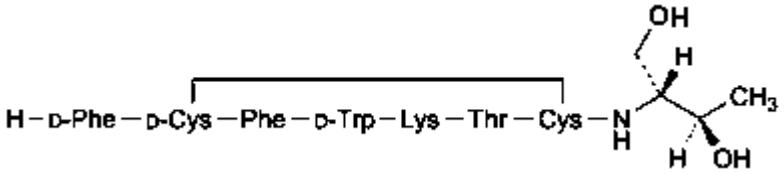
C. $N^{1.4}$-(hydroxymethyl)octreotide,



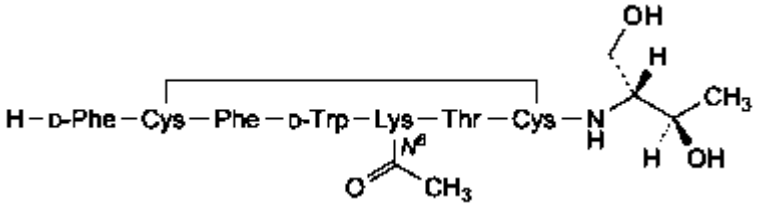
E. D-phenylalanyl-*S*-sulfanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninol cyclic (2 → 7)-trisulfide,



F. $O^{1.8}$-acetyloctreotide,



G. [2-D-cysteine]octreotide,



H. $N^{6.5}$-acetyloctreotide,

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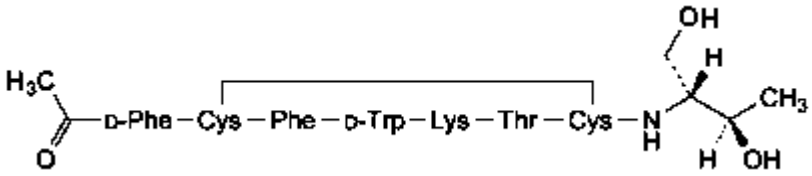

I. $N^{2.1}$-acetyloctreotide.

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Oily Phenol Injection

General Notices

DEFINITION

Oily Phenol Injection is a sterile solution containing 5% w/v of Phenol in a suitable fixed oil.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phenol, C_6H_6O

4.75 to 5.25% w/v.

ASSAY

Dissolve 8 g in 50 mL of *ether* and extract with successive 10 mL quantities of 2M *sodium hydroxide* until extraction is complete, boil the combined extracts for 2 minutes, cool and dilute to 250 mL with *water*. To 20 mL of this solution in a glass-stoppered flask add 30 mL of *0.05M bromine VS* and 6 mL of *hydrochloric acid*, stopper, shake repeatedly during 15 minutes and allow to stand for a further 15 minutes. Add 30 mL of *dilute potassium iodide solution*, taking care to avoid loss of bromine, and titrate the liberated iodine with 0.1M *sodium thiosulfate VS*. Repeat the operation without the injection. The difference between the titrations represents the amount of bromine required. Each mL of *0.05M bromine VS* is equivalent to 1.569 mg of C_6H_6O. Determine the *weight per mL*, Appendix V G, and calculate the percentage w/v of C_6H_6O.

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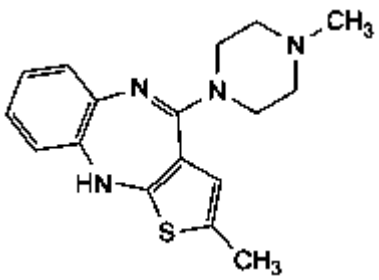
Olanzapine

General Notices

(Ph. Eur. monograph 2258)



$C_{17}H_{20}N_4S$ 312.4 *132539-06-1*

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

Preparation

Olanzapine Orodispersible Tablets

Ph Eur

DEFINITION

2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison olanzapine CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in ethyl acetate R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the test and reference solutions immediately before use or keep them refrigerated and inject within 20 h of preparation.*

Solution A Dissolve 13 g of sodium dodecyl sulfate R in about 1450 mL of water R, add 5 mL of phosphoric acid R and adjust to pH 2.5 by slowly adding strong sodium hydroxide solution R. If a precipitate is formed, this precipitate has to be re-dissolved prior to final pH adjustment. Dilute to 1500 mL with water R.

Solvent mixture Mix 4 volumes of acetonitrile R1 with 6 volumes of a 37 mg/L solution of sodium edetate R in solution A.

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 4 mg of olanzapine for system suitability CRS (containing impurities B, C and D) in 10.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R1, solution A (48:52 *V/V*);

— *mobile phase B*: solution A, acetonitrile R1 (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
10 - 20	100 → 0	0 → 100
20 - 25	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *olanzapine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C and D.

Relative retention With reference to olanzapine (retention time = about 13 min): impurity B = about 0.3; impurity D = about 0.9; impurity C = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity D and olanzapine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.4;

— *impurities B, C, D*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.250 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 10.0 mL with the mobile phase.

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Reference solution (a) Dissolve 50.0 mg of *olanzapine CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of the substance to be examined and 1 mg of *olanzapine impurity A CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 1 volume of *acetonitrile R* with 1 volume of a 6.9 g/L solution of *sodium dihydrogen phosphate monohydrate R* adjusted to pH 2.5 with *phosphoric acid R* and containing 12 g/L of *sodium dodecyl sulfate R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time 1.2 times the retention time of olanzapine.

Relative retention With reference to olanzapine (retention time = about 7 min): impurity A = about 0.8.

System suitability Reference solution (b):

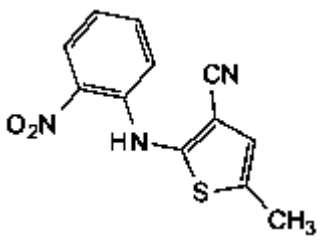
— *resolution*: minimum 2.0 between the peaks due to impurity A and olanzapine.

Calculate the percentage content of $C_{17}H_{20}N_4S$ using the chromatogram obtained with reference solution (a) and the declared content of *olanzapine CRS*.

IMPURITIES

Specified impurities *B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



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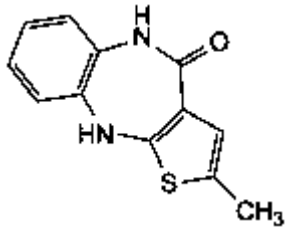
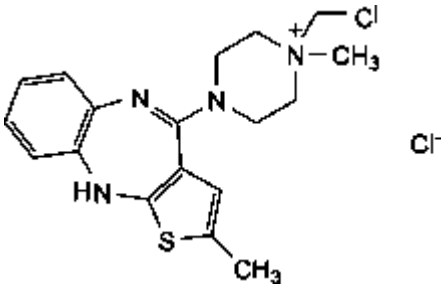
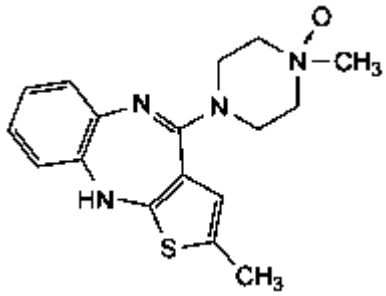
A. 5-methyl-2-[(2-nitrophenyl)amino]thiophene-3-carbonitrile,



B. 2-methyl-5,10-dihydro-4*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-one,



C. 1-(chloromethyl)-1-methyl-4-(2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-yl)piperazin-1-ium chloride,



D. 1-methyl-4-(2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-yl)piperazin-1-oxide.

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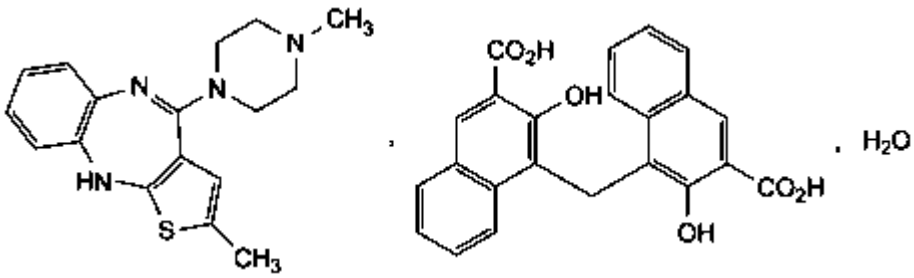
Olanzapine Embonate Monohydrate

General Notices

(Ph. Eur. monograph 3047)



$C_{40}H_{36}N_4O_6S,H_2O$ 719 *221373-18-8*

Action and use

Dopamine D2 receptor antagonist; serotonin 5HT2 receptor antagonist; antipsychotic.

Ph Eur

DEFINITION

2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine 4,4′-methylenebis(3-hydroxynaphthalene-2-carboxylate) monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is produced by methods of manufacture designed to guarantee the proper hydrate form and it complies, if tested, with a suitable test that demonstrates its monohydrate nature (e.g. X-ray powder diffraction (2.9.33)).

CHARACTERS

Appearance

Yellow, slightly hygroscopic powder.

Solubility

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Practically insoluble in water, freely soluble in dimethyl sulfoxide, very slightly soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *olanzapine embonate monohydrate CRS*.

B. Water (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the test and reference solutions immediately before use.*

Solution A A 1.15 g/L solution of *phosphoric acid R*, adjusted to pH 7.0 using a 330 g/L solution of *potassium hydroxide R*.

Test solution Dissolve 25.0 mg of the substance to be examined in 5.0 mL of *dimethyl sulfoxide R* and dilute to 25.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *olanzapine for system suitability CRS* (containing impurities B and D) in 1 mL of *dimethyl sulfoxide R* and dilute to 5 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of *olanzapine embonate for peak identification CRS* (containing impurities E and F) in 1 mL of *dimethyl sulfoxide R* and dilute to 5 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, solution A (40:60 *V/V*);

— *mobile phase B*: solution A, *methanol R* (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
5 - 15	100 → 0	0 → 100
15 - 19	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 259 nm.

Autosampler Set at 5 °C.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *olanzapine for system suitability CRS* and the chromatogram obained with reference solution (b) to identify the peaks due to impurities B and D; use the chromatogram supplied with *olanzapine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to embonic acid and impurities E and F.

Relative retention With reference to olanzapine (retention time = about 18 min): embonic acid = about 0.2; impurity E = about 0.3; impurity F = about 0.4; impurity D = about 0.6; impurity B = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities D and B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 0.7;

— for each impurity, use the concentration of olanzapine embonate monohydrate in reference solution (a).

Limits:

— *impurities B, E, F*: for each impurity, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to embonic acid.

Water (*2.5.32*)

2.4 per cent to 4.0 per cent, determined on 50.0 mg using the evaporation technique at 200 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Solution A A 1.15 g/L solution of *phosphoric acid R*, adjusted to pH 7.0 using a 330 g/L solution of *potassium hydroxide R*.

Test solution Dissolve 25.0 mg of the substance to be examined in 10.0 mL of *dimethyl sulfoxide R* and dilute to 100.0 mL with the mobile phase.

Reference solution Dissolve 20.0 mg of *olanzapine CRS* in 20.0 mL of *dimethyl sulfoxide R* and dilute to 200.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase Solution A, *methanol R* (40:60 *V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 259 nm.

Injection 10 µL.

Run time 1.3 times the retention time of olanzapine (retention time = about 8 min).

Calculate the percentage content of $C_{40}H_{36}N_4O_6S$ taking into account the assigned content of $C_{17}H_{20}N_4S$ in *olanzapine CRS* and a conversion factor of 2.243.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *B, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*

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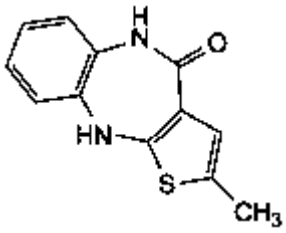
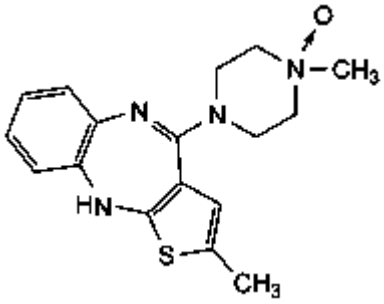
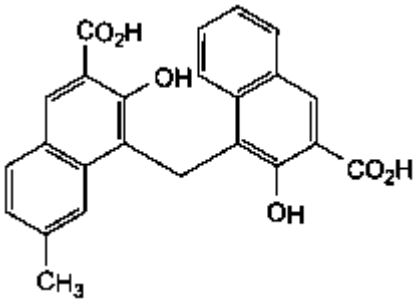


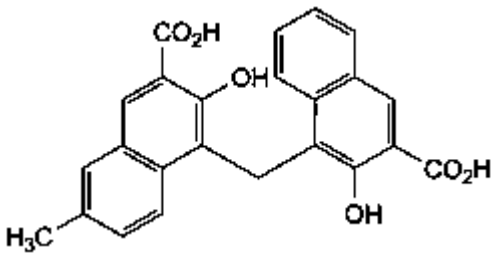
B. 2-methyl-5,10-dihydro-4*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-one,



D. 1-methyl-4-(2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine-4-yl)piperazine 1-oxide,



E. 4-[(3-carboxy-2-hydroxynaphthalen-1-yl)methyl]-3-hydroxy-6-methylnaphthalene-2-carboxylic acid,



F. 4-[(3-carboxy-2-hydroxynaphthalen-1-yl)methyl]-3-hydroxy-7-methylnaphthalene-2-carboxylic acid.

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Olanzapine Orodispersible Tablets

General Notices

Orodispersible Olanzapine Tablets

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

DEFINITION

Olanzapine Orodispersible Tablets contain Olanzapine in a suitable orodispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of Olanzapine, $C_{17}H_{20}N_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 60 mg of Olanzapine with 20 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of olanzapine (*RS 477*).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

(1) After 15 minutes withdraw a sample of the medium, filter and dilute with the dissolution medium, if necessary, to produce a solution expected to contain 0.00028% w/v of Olanzapine. Measure the *absorbance* of this solution in a 4-cm cell, at 260 nm, Appendix II B using dissolution medium in the reference cell.

(2) 0.00028% w/v solution of *olanzapine BPCRS* in the dissolution medium. Measure the *absorbance* in a 4-cm cell, at 260 nm, Appendix II B using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of olanzapine, $C_{17}H_{20}N_4S$, in the medium from the absorbances obtained and using the declared content of $C_{17}H_{20}N_4S$ in *olanzapine BPCRS*.

LIMITS

The amount of olanzapine released is not less than 75%(Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Disperse a quantity of powdered tablets containing 25 mg of Olanzapine in 5 mL of *water*. Add 40 mL of *acetonitrile*, mix with the aid of ultrasound, add 40 mL of *water* and shake for 20 minutes, add sufficient *water* to produce 100 mL and filter through a 0.45-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*. Dilute 1 volume of the resulting solution to 5 volumes with the same solvent mixture.
(3) 0.025% w/v of *olanzapine for system suitability EPCRS* with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Inertsil ODS-3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 250 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 45 volumes of a mixture of equal volumes of *acetonitrile* and *methanol* and 55 volumes of a 0.345% w/v buffer solution of *sodium dihydrogen orthophosphate monohydrate* adjusted to pH 6.8 with *dilute sodium hydroxide*.

Mobile phase B 25 volumes of the buffer solution described under Mobile phase A and 75 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-7	100→60	0→40	linear gradient
7-13	60	40	isocratic
13-17	60→0	40→100	linear gradient
17-30	0	100	isocratic
30-31	0→100	100→0	linear gradient
31-34	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to olanzapine (retention time about 15 minutes) are; impurity 2, about 0.13; impurity 3, about 0.34; impurity C, about 0.37; impurity D, about 0.40; impurity B, about 0.6 and impurity 1, about 0.61.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity D is at least 6.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B and D using solution (3) and multiply the areas of these peaks by the corresponding correction factors; impurity B, 0.63, impurity D, 1.52.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity B is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity D is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity 1 is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity 3 is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of all the *secondary peaks* is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Disperse a quantity of powdered tablets containing 25 mg of Olanzapine in 5 mL of *water*. Add 40 mL of *acetonitrile* and mix with the aid of ultrasound. Add 40 mL of *water* and shake for 20 minutes, dilute to 100 mL and filter through a 0.45-µm PTFE filter. Discard the first 2 mL of the filtrate.

(2) 0.025% w/v of *olanzapine BPCRS* in a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

(3) 0.025% w/v of *olanzapine for system suitability EPCRS* with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Inertsil ODS-3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 250 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of a 0.345% w/v solution of *sodium dihydrogen orthophosphate monohydrate* previously adjusted to pH 6.8 with *dilute sodium hydroxide* and 75 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and olanzapine is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{20}N_4S$ in the tablets using the declared content of $C_{17}H_{20}N_4S$ in *olanzapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Olanzapine and:

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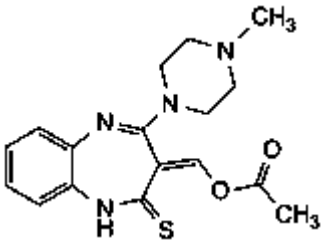
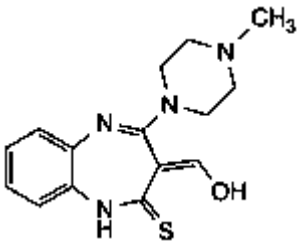
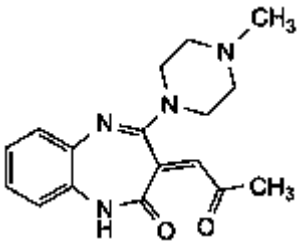


1. [4-(4-methylpiperazin-1-yl)-2-thioxo-2,3-dihydro-1*H*-1,4-benzodiazopin-3-ylidene]ethen-1-yl acetate; acetoxymethylidene thione;



2. 1-[(3*Z*)-4-(4-methylpiperazin-1-yl)-2-thioxo-2,3-dihydro-1*H*-1,4-benzodiazopin-3-ylidene]propan-2-one;



3. 4-(4-methylpiperazin-1-yl)-3-(2-oxopropylidene)-1*H*-1,4-benzodiazopin-2(3*H*)-one.

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Olanzapine Tablets

General Notices

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

DEFINITION

Olanzapine Tablets contain Olanzapine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of olanzapine, $C_{17}H_{20}N_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 60 mg of Olanzapine with 20 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of olanzapine *(RS 477)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter and dilute with the dissolution medium, if necessary, to produce a solution expected to contain 0.00028% w/v of Olanzapine. Measure the *absorbance* of this solution in a 4-cm cell, at 260 nm, Appendix II B using dissolution medium in the reference cell.

(2) 0.00028% w/v solution of *olanzapine BPCRS* in the dissolution medium. Measure the *absorbance* in a 4-cm cell, at 260 nm, Appendix II B using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of olanzapine, $C_{17}H_{20}N_4S$, in the medium from the absorbances obtained and using the declared content of $C_{17}H_{20}N_4S$ in *olanzapine BPCRS*.

LIMITS

The amount of olanzapine released is not less than 75%(Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Disperse a quantity of powdered tablets containing 25 mg of Olanzapine in 5 mL of *water*. Add 40 mL of *acetonitrile*, mix with the aid of ultrasound, add 40 mL of *water* and shake for 20 minutes, add sufficient *water* to produce 100 mL and filter through a 0.45-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*. Dilute 1 volume of the resulting solution to 5 volumes with the same solvent mixture.
(3) 0.025% w/v of *olanzapine for system suitability EPCRS* with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Inertsil ODS-3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 250 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 45 volumes of a mixture of equal volumes of *acetonitrile* and *methanol* and 55 volumes of a 0.345% w/v buffer solution of *sodium dihydrogen orthophosphate monohydrate* adjusted to pH 6.8 with *dilute sodium hydroxide*.

Mobile phase B 25 volumes of the buffer solution described under Mobile phase A and 75 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-7	100→60	0→40	linear gradient
7-13	60	40	isocratic
13-17	60→0	40→100	linear gradient
17-30	0	100	isocratic
30-31	0→100	100→0	linear gradient
31-34	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to olanzapine (retention time about 15 minutes) are; impurity 2, about 0.13; impurity 3, about 0.34; impurity C, about 0.37; impurity D, about 0.40; impurity B, about 0.6 and impurity 1, about 0.61.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity D is at least 6.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B and D using solution (3) and multiply the areas of these peaks by the corresponding correction factors; impurity B, 0.63, impurity D, 1.52.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity B is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity D is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity 1 or 2 is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

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ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Disperse a quantity of powdered tablets containing 25 mg of Olanzapine in 5 mL of *water*. Add 40 mL of *acetonitrile* and mix with the aid of ultrasound. Add 40 mL of *water* and shake for 20 minutes, dilute to 100 mL and filter through a 0.45-µm PTFE filter. Discard the first 2 mL of the filtrate.

(2) 0.025% w/v of *olanzapine BPCRS* in a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

(3) 0.025% w/v of *olanzapine for system suitability EPCRS* with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Inertsil ODS-3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 250 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of a 0.345% w/v solution of *sodium dihydrogen orthophosphate monohydrate* previously adjusted to pH 6.8 with *dilute sodium hydroxide* and 75 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*.

SYSTEM SUITABILITY

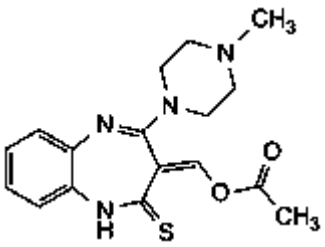
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and olanzapine is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{20}N_4S$ in the tablets using the declared content of $C_{17}H_{20}N_4S$ in *olanzapine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Olanzapine and:



1. [4-(4-methylpiperazin-1-yl)-2-thioxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3-ylidene]ethen-1-yl acetate; acetoxymethylidene thione;

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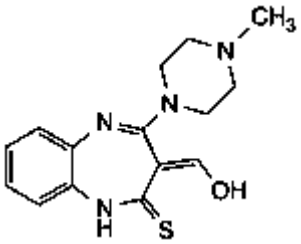
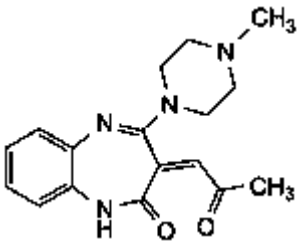


2. 1-[(3*Z*)-4-(4-methylpiperazin-1-yl)-2-thioxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3-ylidene]propan-2-one;



3. 4-(4-methylpiperazin-1-yl)-3-(2-oxopropylidene)-1*H*-1,4-benzodiazepin-2(3*H*)-one.

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Oleic Acid

General Notices

(Ph. Eur. monograph 0799)

112-80-1

Action and use

Excipient.

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DEFINITION

(*Z*)-Octadec-9-enoic acid ($C_{18}H_{34}O_2$; M_r 282.5), together with varying amounts of saturated and other unsaturated fatty acids. A suitable antioxidant may be added.

Content

65.0 per cent to 88.0 per cent of $C_{18}H_{34}O_2$.

CHARACTERS

Appearance

Clear, yellowish or brownish, oily liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent) and with methylene chloride.

Relative density

About 0.892.

IDENTIFICATION

A. Acid value (see Tests).

B. Iodine value (see Tests).

C. Composition of fatty acids (see Tests).

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Margaric acid Maximum 0.2 per cent for oleic acid of vegetable origin and maximum 4.0 per cent for oleic acid of animal origin.

TESTS

Appearance

The substance to be examined is not more intensely coloured than reference solution Y_1 or BY_1 (*2.2.2, Method I*).

Acid value (*2.5.1*)

195 to 204, determined on 0.5 g.

Iodine value (*2.5.4*)

89 to 105.

Peroxide value (*2.5.5*)

Maximum 10.0.

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*).

Test solution Prepare as described in the method but omitting the initial hydrolysis.

Composition of the fatty acid fraction of the substance:

— *myristic acid*: maximum 5.0 per cent,

— *palmitic acid*: maximum 16.0 per cent,

— *palmitoleic acid*: maximum 8.0 per cent,

— *stearic acid*: maximum 6.0 per cent,

— *oleic acid*: 65.0 per cent to 88.0 per cent,

— *linoleic acid*: maximum 18.0 per cent,

— *linolenic acid*: maximum 4.0 per cent,

— *fatty acids of chain length greater than* C_{18}: maximum 4.0 per cent.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 2.00 g.

STORAGE

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In an airtight, well-filled container, protected from light.

LABELLING

The label states the origin of oleic acid (animal or vegetable).

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Oleoyl Macrogolglycerides

General Notices

(Ph. Eur. monograph 1249)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of macrogols.

They are obtained by partial alcoholysis of an unsaturated oil mainly containing triglycerides of oleic ((9*Z*)-octadec-9-enoic) acid, using macrogol with a mean relative molecular mass between 300 and 400, or by esterification of glycerol and macrogol with unsaturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of this unsaturated oil.

CHARACTERS

Appearance

Amber oily liquid, which may give rise to a deposit after prolonged periods at 20 °C.

Solubility

Practically insoluble but dispersible in water, freely soluble in methylene chloride.

Relative density

About 0.95 at 20 °C.

Refractive index

About 1.47 at 20 °C.

Viscosity

About 35 mPa·s at 40 °C.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

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Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine B R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The chromatogram shows a spot due to triglycerides with an R_F value of about 0.9 (R_{st} 1) and spots due to 1,3-diglycerides (R_{st} 0.7), to 1,2-diglycerides (R_{st} 0.6), to monoglycerides (R_{st} 0.1) and to esters of macrogol (R_{st} 0).

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 2.0, determined on 2.0 g.

Hydroxyl value (*2.5.3, Method A*)

45 to 65, determined on 1.0 g.

Iodine value (*2.5.4, Method A*)

75 to 95.

Peroxide value (*2.5.5, Method A*)

Maximum 12.0, determined on 2.0 g.

Saponification value (*2.5.6*)

150 to 170, determined on 2.0 g.

Alkaline impurities

Introduce 5.0 g into a test tube and carefully add a mixture, neutralised if necessary with *0.01 M hydrochloric acid* or with *0.01 M sodium hydroxide*, of 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*, 0.3 mL of *water R* and 10 mL of *ethanol*

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(96 per cent) R. Shake and allow to stand. Not more than 1.0 mL of *0.01 M hydrochloric acid* is required to change the colour of the upper layer to yellow.

Free glycerol

Maximum 3.0 per cent.

Dissolve 1.20 g in 25.0 mL of *methylene chloride R*. Heat if necessary. After cooling, add 100 mL of *water R*. Shake and add 25.0 mL of *periodic acetic acid solution R*. Shake and allow to stand for 30 min. Add 40 mL of a 75 g/L solution of *potassium iodide R*. Allow to stand for 1 min. Add 1 mL of *starch solution R*. Titrate the iodine with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 2.3 mg of glycerol.

Composition of fatty acids (*2.4.22, Method A*)

Composition of the fatty-acid fraction of the substance:

— *palmitic acid*: 4.0 per cent to 9.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: 58.0 per cent to 80.0 per cent;

— *linoleic acid*: 15.0 per cent to 35.0 per cent;

— *linolenic acid*: maximum 2.0 per cent;

— *arachidic acid*: maximum 2.0 per cent;

— *eicosenoic acid*: maximum 2.0 per cent.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use a mixture of 30 volumes of *anhydrous methanol R* and 70 volumes of *methylene chloride R* as solvent.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

STORAGE

Protected from light.

LABELLING

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The label states the type of macrogol used (mean relative molecular mass) or the number of units of ethylene oxide per molecule (nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for oleoyl macrogolglycerides used as self-emulsifying agents and solubilisers.

Hydroxyl value

(see Tests).

Saponification value

(see Tests).

Composition of fatty acids

(see Tests).

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Oleyl Alcohol

General Notices

(Ph. Eur. monograph 2073)

Action and use

Nonionic surfactant.

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DEFINITION

Mixture of unsaturated and saturated long-chain fatty alcohols consisting mainly of octadec-9-enol (oleyl alcohol and elaidyl alcohol; $C_{18}H_{36}O$; M_r 268.5). It may be of vegetable or animal origin.

CHARACTERS

Appearance

Colourless or light yellow liquid.

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Composition of fatty alcohols (see Tests).

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

Refractive index (*2.2.6*)

1.458 to 1.461, determined at 25 °C.

Cloud point

Maximum 10 °C.

Introduce about 60 g into a cylindrical flat-bottomed container, 30-33.5 mm in internal diameter and 115-125 mm high. Heat to 30 °C, cool, and immerse the container in iced water with the surfaces of the water and the sample at the same level. Insert a thermometer and, using it

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as a stirring rod, begin stirring rapidly and steadily when the temperature falls below 20 °C. Keep the thermometer immersed throughout the test, and remove and examine the container at regular intervals. The cloud point is the temperature at which the immersed portion of the thermometer, positioned vertically in the centre of the container, is no longer visible when viewed horizontally through the container and sample.

Acid value (2.5.1)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (2.5.3, Method A)

205 to 215.

Saponification value (2.5.6)

Maximum 2.0.

Composition of fatty alcohols

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Mix 25 mg of the substance to be examined with 1.0 mL of *methylene chloride R*.

Reference solution (a) Dissolve 25 mg of each of *arachidyl alcohol R*, *linolenyl alcohol R*, *linoleyl alcohol R*, *oleyl alcohol R*, *palmityl alcohol R* and *stearyl alcohol R* in *methylene chloride R* and dilute to 5 mL with the same solvent. Dilute 1 mL of this solution to 5 mL with *methylene chloride R*.

Reference solution (b) Dissolve 10 mg of *linoleyl alcohol R* and 1 g of *oleyl alcohol R* in *methylene chloride R* and dilute to 40 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:11.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 1	170
	1 - 9	170 → 210
	9 - 65	210
Injection port		270
Detector		280

Detection Flame ionisation.

Injection 1 µL.

Identify the peaks using the chromatogram obtained with reference solution (a).

Relative retention With reference to oleyl alcohol (retention time = about 30 min): palmityl alcohol = about 0.6; linolenyl alcohol = about 0.8; linoleyl alcohol = about 0.9; stearyl alcohol = about 1.1; arachidyl alcohol = about 1.9 (elaidyl alcohol co-elutes with oleyl alcohol).

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to linoleyl alcohol and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to oleyl alcohol.

Limits:

— *palmityl alcohol*: maximum 8.0 per cent;

— *stearyl alcohol*: maximum 5.0 per cent;

— *oleyl alcohol* (sum of oleyl and elaidyl alcohols): minimum 80.0 per cent;

— *linoleyl alcohol*: maximum 3.0 per cent;

— *linolenyl alcohol*: maximum 0.5 per cent;

— *arachidyl alcohol*: maximum 0.3 per cent.

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Olive Oil Ear Drops

General Notices

DEFINITION

Olive Oil Ear Drops are Virgin Olive Oil in a suitable container.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

IDENTIFICATION

Carry out the test for the *identification of fatty oils by thin-layer chromatography*, Appendix X N. The chromatogram obtained from the oil being examined shows spots corresponding to those in the *typical chromatogram* for olive oil. For certain types of olive oil the difference in the sizes of spots E and F is less pronounced than in the figure.

TESTS

Acid value

Not more than 2.0, Appendix X B. Use 5 g.

Light absorption

The *absorbance* of a 1% w/v solution in *cyclohexane* at the maximum at 270 nm is not more than 0.20, Appendix II B. The ratio of the *absorbance* at 232 nm to that at 270 nm is greater than 8.

Peroxide value

Not more than 20.0, Appendix X F.

Relative density

0.910 to 0.916, Appendix V G.

Unsaponifiable matter

Not more than 1.5% w/w when determined by the following method. To 5 g of the oil in a 150-mL flask add 50 mL of 2M *ethanolic potassium hydroxide* and heat under a reflux condenser on a water bath for 1 hour, shaking frequently. Add 50 mL of *water* through the condenser, shake, allow to cool and transfer the contents of the flask to a separating funnel, rinsing the flask with 50 mL of *petroleum spirit* (*boiling range, 40° to 60°*) in portions and adding the rinsings to the separating funnel. Shake vigorously for 1 minute, allow to separate and transfer the aqueous layer to a second separating funnel. If an emulsion forms add small quantities of *ethanol* (*96%*) or a concentrated solution of *potassium hydroxide*. Extract the aqueous layer with two 50-mL quantities of *petroleum spirit* (*boiling range, 40° to 60°*) and combine the organic layers in a third separating funnel. Wash with three 50-mL quantities of *ethanol* (*50%*), transfer the petroleum spirit layer to a

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weighed 250-mL flask, rinse the separating funnel with small quantities of *petroleum spirit* (*boiling range, 40° to 60°*) and add the rinsings to the flask. Evaporate the solvent on a water bath, dry at 100° to 105° for 15 minutes with the flask in a horizontal position, allow to cool and weigh. Repeat the drying for successive 15-minute periods until the loss in weight between two successive weighings does not exceed 0.1%. Dissolve the residue in 20 mL of *ethanol* (*96%*) previously neutralised to 0.1 mL of *bromophenol blue solution* and, if necessary, titrate with *0.1M hydrochloric acid VS*. Calculate the percentage content of unsaponifiable matter from the expression:

$100(a-0.032b)/w$

where *a* is the weight, in g, of the residue, *b* is the volume, in mL, of *0.1M hydrochloric acid VS* required and *w* is the weight, in g, of oil taken. The test is not valid if $0.032b$ is greater than 5% of *a* and must be repeated.

Foreign fixed oils

Carry out the test for *composition of fatty acids by gas chromatography*, Appendix X N. The fatty-acid fraction of the oil has the following composition.

Saturated fatty acids of chain length less than C_{16}: Not more than 0.1%.

Palmitic acid: 7.5 to 20.0%.

Palmitoleic acid (equivalent chain length on polyethylene glycol adipate, 16.3): Not more than 3.5%.

Stearic acid: 0.5 to 5.0%.

Oleic acid (equivalent chain length on polyethylene glycol adipate, 18.3): 56.0 to 85.0%.

Linoleic acid (equivalent chain length on polyethylene glycol adipate, 18.9): 3.5 to 20.0%.

Linolenic acid (equivalent chain length on polyethylene glycol adipate, 19.7): Not more than 1.2%.

Arachidic acid: Not more than 0.7%.

Eicosenoic acid (equivalent chain length on polyethylene glycol adipate, 20.3): Not more than 0.4%.

Behenic acid: Not more than 0.2%.

Lignoceric acid: Not more than 0.2%.

Sterols

Carry out the test for the *determination of sterols*, Appendix X N. The sterol fraction of the oil has the following composition:

sum of contents of β-sitosterol, Δ5,23-stigmastadienol, clerosterol, sitostanol, Δ5-avenasterol and Δ5,24-stigmastadienol: not less than 93.0%.

cholesterol: not more than 0.5%.

Δ7-stigmasterol: not more than 0.5%.

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campesterol: not more than 4.0%.

and the content of stigmasterol is not more than that of campesterol.

Sesame oil

Shake 10 mL for about 1 minute with a mixture of 0.5 mL of a 0.35% v/v solution of *furfuraldehyde* in *acetic anhydride* and 4.5 mL of *acetic anhydride* in a cylinder closed with a ground-glass stopper, filter through paper impregnated with *acetic anhydride* and add 0.2 mL of *sulfuric acid* to the filtrate. No bluish green colour develops.

STORAGE

Olive Oil Ear Drops should be kept in a well-filled container and protected from light.

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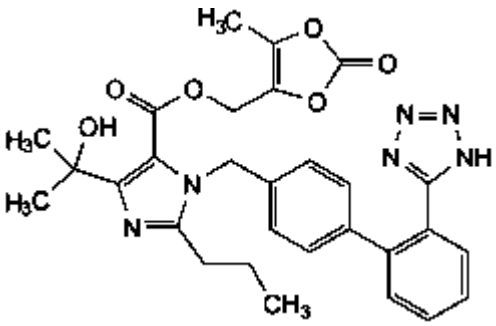
Olmesartan Medoxomil

General Notices

(Ph. Eur. monograph 2600)



$C_{29}H_{30}N_6O_6$ 558.6 *144689-63-4*

Action and use

Angiotensin II (AT_1) receptor antagonist.

Preparation

Olmesartan Tablets

Ph Eur

DEFINITION

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in olmesartan medoxomil should be avoided or limited as much as possible. For this reason, manufacturers of olmesartan medoxomil for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-

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nitrosamine impurities in olmesartan medoxomil. The general chapter 2.5.42. *N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison olmesartan medoxomil CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 25 mg of the substance to be examined in acetonitrile R and dilute to 25.0 mL with the same solvent.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in acetonitrile R and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of olmesartan medoxomil for system suitability CRS (containing impurities A, B and C) in acetonitrile R and dilute to 5 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with acetonitrile R. Dilute 1.0 mL of this solution to 10.0 mL with acetonitrile R.

Reference solution (c) Dissolve 25.0 mg of olmesartan medoxomil CRS in acetonitrile R and dilute to 50.0 mL with the same solvent.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 20 volumes of acetonitrile R and 80 volumes of a 2.04 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 3.4 with a 1.73 g/L solution of phosphoric acid R;

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— *mobile phase B*: mix 20 volumes of a 2.04 g/L solution of *potassium dihydrogen phosphate R*, previously adjusted to pH 3.4 with a 1.73 g/L solution of *phosphoric acid R*, and 80 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	75	25
10 - 35	75 → 0	25 → 100
35 - 45	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *olmesartan medoxomil for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to olmesartan medoxomil (retention time = about 10 min): impurity A = about 0.2; impurity B = about 0.7; impurity C = about 1.5.

System suitability Reference solution (a):

— *resolution*: minimum 3.5 between the peaks due to impurity B and olmesartan medoxomil.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Acetone

Head-space gas chromatography (2.2.28): use the direct calibration method.

Internal standard solution Dilute 1.0 mL of *butanol R* to 100.0 mL with *dimethyl sulfoxide R*.

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Test solution Dissolve 0.250 g of the substance to be examined in *dimethyl sulfoxide R*, add 2.0 mL of the internal standard solution and dilute to 10.0 mL with *dimethyl sulfoxide R*.

Reference solution Dilute 0.50 mL of *acetone R* to 200.0 mL with *dimethyl sulfoxide R*. Dilute 15.0 mL of the solution to 100.0 mL with *dimethyl sulfoxide R*. To 25.0 mL of this solution add 10.0 mL of the internal standard solution and dilute to 50.0 mL with *dimethyl sulfoxide R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 1 µm).

Carrier gas *nitrogen for chromatography R* or *helium for chromatography R*.

Flow rate 4.0 mL/min.

Split ratio 1:5.

Static head-space conditions that may be used:

— *equilibration temperature*: 80 °C;

— *equilibration time*: 30 min.

Temperature:

	Time (min)	Temperature (°C)
Column	5	50
	5 - 18	50 → 180
	18 - 23	180
Injection port		200
Detection		200

Detection Flame ionisation.

Injection 1 mL.

Calculate the content of acetone, taking its relative density to be 0.79 at 20 °C.

Limit:

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— *acetone*: maximum 0.6 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (25:75 *V/V*).

Injection Test solution (b) and reference solution (c).

Retention time Olmesartan medoxomil = about 10 min.

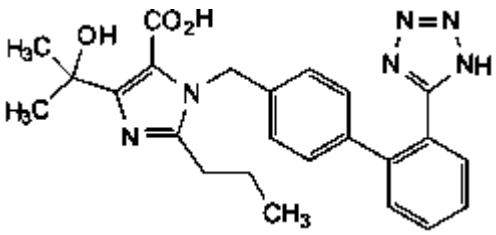
Run time 1.5 times the retention time of olmesartan medoxomil.

Calculate the percentage content of $C_{29}H_{30}N_6O_6$ taking into account the assigned content of *olmesartan medoxomil CRS*.

IMPURITIES

Specified impurities *A, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D.*



A. 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (olmesartan),

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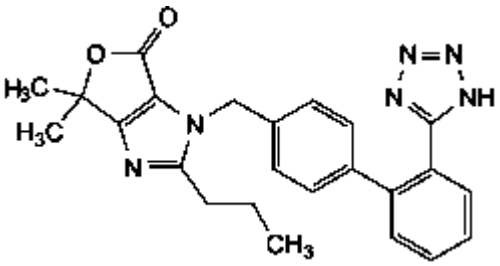
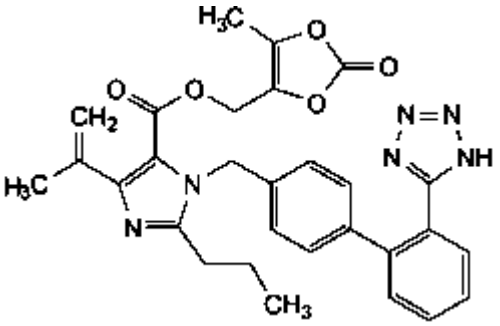
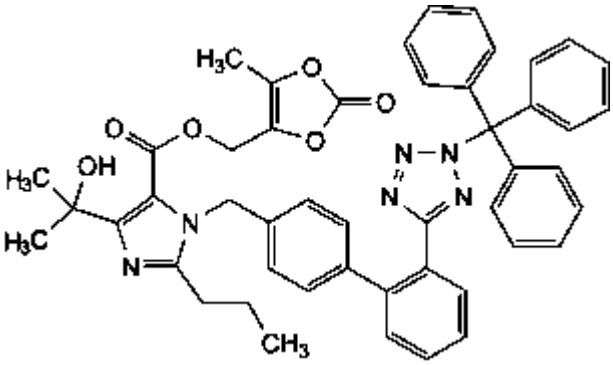


B. 6,6-dimethyl-2-propyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3,6-dihydro-4*H*-furo[3,4-*d*]imidazol-4-one,



C. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-methylethenyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate,



D. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2′-[(2-triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate.

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Olmesartan Tablets

General Notices

Action and use

Angiotensin II (AT_1) receptor antagonist.

DEFINITION

Olmesartan Tablets contain Olmesartan Medoxomil.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of olmesartan medoxomil, $C_{29}H_{30}N_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a tablet in sufficient of 60% v/v of *acetonitrile* to prepare a solution containing 0.02% w/v of Olmesartan Medoxomil and mix with the aid of ultrasound. Centrifuge and dilute 5 mL of the supernatant liquid to 100 mL with 60% v/v of *acetonitrile*. The light absorption of the resulting solution, Appendix II B, in the range 200 to 360 nm exhibits a maximum at about 258 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a solution prepared by dissolving 6.80 g of *potassium dihydrogen orthophosphate* and 0.944 g of *sodium hydroxide* in *water* and dilute to 1000 mL with *water*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

(1) After 45 minutes, withdraw a sample of the medium, filter and dilute the filtrate with sufficient of the dissolution medium to give a solution expected to contain about 0.001% w/v of Olmesartan Medoxomil. Measure the *absorbance* of this solution, Appendix II B, at 258 nm using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.001% w/v solution of *olmesartan medoxomil BPCRS* using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of olmesartan medoxomil, $C_{29}H_{30}N_6O_6$, in the medium from the absorbances obtained and using the declared content of $C_{29}H_{30}N_6O_6$, in *olmesartan medoxomil BPCRS*.

LIMITS

The amount of olmesartan medoxomil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of tablets in sufficient of 90% v/v of *acetonitrile* to prepare a solution containing 0.1% w/v of Olmesartan Medoxomil, mix with the aid of ultrasound, centrifuge and filter the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 50 volumes with 90% v/v of *acetonitrile* and dilute 1 volume of the resulting solution to 10 volumes with the same solvent.
(3) Dissolve 5 mg of *olmesartan medoxomil for system suitability EPCRS* in 90% v/v of *acetonitrile* and dilute to 5 mL with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (10 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (3.5 µm) (Waters Symmetry C8 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 250 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *acetonitrile* and 80 volumes of a 0.015M potassium dihydrogen orthophosphate buffer solution prepared in the following manner. Dissolve 4.08 g of *potassium dihydrogen orthophosphate* in *water*, dilute to 2000 mL and adjust the pH to 3.4 with a 0.173% w/v solution of *orthophosphoric acid*.

Mobile phase B 20 volumes of a 0.015M potassium dihydrogen orthophosphate buffer solution prepared as described under mobile phase A, and 80 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	75	25	isocratic
10-35	75→0	25→100	linear gradient
35-45	0	100	isocratic
45-60	0→75	100→25	re-equilibration

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When the chromatograms are recorded under the prescribed conditions the retention times relative to olmesartan medoxomil (retention time, about 10 minutes) are: impurity A, about 0.2; impurity B, about 0.7; impurity C, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and olmesartan medoxomil is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 4.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.9%);

the area of any peak corresponding to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 8.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.7%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To 10 whole tablets add 80 mL of 60% v/v *acetonitrile* and shake. Dilute to 100 mL with 60% v/v *acetonitrile* and dissolve with the aid of ultrasound. Centrifuge the resulting solution and dilute a suitable quantity of the supernatent with 60% v/v *acetonitrile* to produce a solution containing 0.004% w/v Olmesartan medoximil.

(2) 0.004% w/v of *olmesartan medoxomil BPCRS* in 60% v/v of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (L-Column ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 249 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

34 volumes of *acetonitrile* and 66 volumes of a 0.015M *potassium dihydrogen orthophosphate* buffer solution prepared in the following manner. Dissolve 4.08 g of *potassium dihydrogen orthophosphate* in *water*, dilute to 2000 mL and adjust the pH to 3.4 with a 0.173% w/v

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solution of *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{30}N_6O_6$ in the tablets from the chromatograms obtained using the declared content of $C_{29}H_{30}N_6O_6$ in *olmesartan medoxomil BPCRS*

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Olmesartan Medoxomil.

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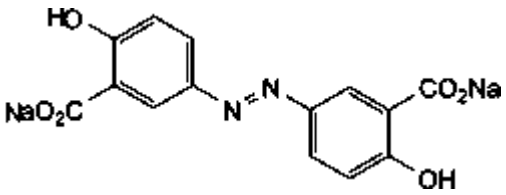
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Olsalazine Sodium

General Notices

(Ph. Eur. monograph 1457)



$C_{14}H_8N_2Na_2O_6$ 346.2 *6054-98-4*

Action and use

Aminosalicylate; treatment of ulcerative colitis.

Ph Eur

DEFINITION

Disodium 3,3′-diazenediylbis(6-hydroxybenzoate).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, fine, crystalline powder.

Solubility

Sparingly soluble in water, soluble in dimethyl sulfoxide, very slightly soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

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First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 40.0 mg in 5 mL of *0.1 M sodium hydroxide* and dilute to 100.0 mL with a 7.8 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 7.2 with *strong sodium hydroxide solution R* (buffer solution). Dilute 2.0 mL of the solution to 100.0 mL with the buffer solution.

Spectral range 240 nm to 400 nm.

Absorption maxima At 255 nm and 362 nm.

Absorbance ratio A_{255}/A_{362} = 0.53 to 0.56.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *olsalazine sodium CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 1 volume of *dilute ammonia R2* and 4 volumes of *ethanol (96 per cent) R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (a) Dissolve 10 mg of *olsalazine sodium CRS* in a mixture of 1 volume of *dilute ammonia R2* and 4 volumes of *ethanol (96 per cent) R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b) Dissolve 5 mg of *sulfasalazine CRS* in reference solution (a) and dilute to 5 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *acetone R*, *methylene chloride R* (5:50:60 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 separated spots.

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Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To 0.5 g add 2 mL of *sulfuric acid R*. Progressively heat to ignition and continue heating until an almost white or at most greyish residue is obtained. Carry out the ignition at a temperature up to 800 ± 50 °C. Dissolve the residue in 10 mL of boiling *water R* and filter. 2 mL of the filtrate gives reaction (a) of sodium (*2.3.1*).

TESTS

Acetate

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.125 g of the substance to be examined in 25.0 mL of *water R* and add 1.0 mL of *dilute hydrochloric acid R*. Centrifuge and then filter the solution through a 0.45 µm filter and also through an appropriate filter for removal of chlorides.

Reference solution (a) Dissolve 0.140 g of *sodium acetate R*, 0.150 g of *sodium formate R* and 0.180 g of *dipotassium sulfate R* in 100.0 mL of *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (b) Use suitable amounts of *sodium acetate R* to prepare not fewer than 5 reference solutions containing 10-50 µg/mL of acetate.

Column:

— *size*: *l* = 0.25 m, Ø = 9 mm;

— *stationary phase*: *ion-exclusion resin for chromatography R* with a capacity of about 27 meq/column.

Suppressor column.

Mobile phase *0.0001 M hydrochloric acid*.

Flow rate 0.9 mL/min.

Detection Conductivity detector at 10 µS·cm^{-1}.

Injection 0.1 mL.

System suitability Reference solution (a):

— the chromatogram shows 3 separated peaks.

Determine the concentration of acetate in the test solution using the calibration curve generated by the average of the readings obtained with the reference solutions. Measure the peak area for acetate. Calculate the percentage content of acetate using the following expression:

$$\frac{2.6\,c}{m}$$

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c	=	concentration of acetate in the test solution, in micrograms per millilitre, determined by linear interpolation of the standard curve for reference solution (b);
m	=	mass of sample, in milligrams.

Limit:

— *acetate*: maximum 1.0 per cent.

Methanesulfonic acid

Liquid chromatography (2.2.29).

Test solution Dissolve 0.25 g of the substance to be examined in 20 mL of *water R*, add 1.0 mL of *dilute hydrochloric acid R* and dilute to 25.0 mL with *water R*. Centrifuge and then filter the solution through a 0.45 µm filter and also through an appropriate filter for removal of chlorides.

Reference solution (a) Dissolve 0.25 g of *methanesulfonic acid R* in 50 mL of *water R*. Add 0.58 g of *sodium acetate R* and 0.08 g of *sodium chloride R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 0.10 g of *methanesulfonic acid R* in *water R* and dilute to 100.0 mL with *water R*. Dilute 3.0 mL of this solution to 100.0 mL with *water R*.

Precolumn:

— *size*: *l* = 0.035 m, Ø = 4 mm;

— *stationary phase*: *resin for reversed-phase ion chromatography R* (10 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *resin for reversed-phase ion chromatography R* (10 µm).

Mobile phase Mix 10 volumes of *acetonitrile for chromatography R* and 990 volumes of a solution containing 1.6 g/L of *tetrabutylammonium hydroxide R* and 0.053 g/L of *anhydrous sodium carbonate R*.

Flow rate 1.0 mL/min.

Detection Conductivity detector at 50 $\mu S \cdot cm^{-1}$.

Injection 100 µL.

System suitability Reference solution (a):

— the chromatogram shows 3 separated peaks.

Limit:

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— *methanesulfonic acid*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in mobile phase A and dilute to 25.0 mL with mobile phase A.

Reference solution (a) Dilute 0.5 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (b) Dissolve 20.0 mg of *olsalazine sodium for performance test CRS* in mobile phase A and dilute to 25.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 2.38 g of *tetrabutylammonium hydrogen sulfate R* and 3.6 g of *disodium hydrogen phosphate dihydrate R* in 900 mL of *water R*, adjust to pH 7.6 with *dilute sodium hydroxide solution R* and dilute to 1000.0 mL with *water R*; mix 700 mL of this buffer solution with 300 mL of *methanol R*;

— *mobile phase B*: dissolve 4.75 g of *tetrabutylammonium hydrogen sulfate R* and 3.6 g of *disodium hydrogen phosphate dihydrate R* in 900 mL of *water R*, adjust to pH 7.6 with *dilute sodium hydroxide solution R* and dilute to 1000.0 mL with *water R*; mix 350 mL of this buffer solution with 650 mL of *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	55	45
15 - 45	55 → 0	45 → 100
45 - 50	0 → 55	100 → 45
50 - 65	55	45

Flow rate 1 mL/min.

Detection Spectrophotometer at 360 nm.

Injection 20 µL.

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System suitability Reference solution (b):

— the chromatogram is similar to the chromatogram obtained with *olsalazine sodium for performance test CRS*.

Limits:

— *impurities A, B, C, D, E, F, G, H, I*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), and not more than one of the peaks has an area greater than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.025 per cent).

Loss on drying (2.2.32)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 150 °C.

ASSAY

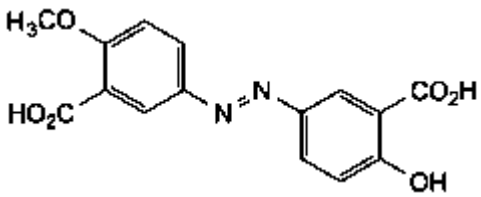
Dissolve 0.100 g in 15 mL of *ethylene glycol R*. Add 40 mL of *dioxan R* and 0.2 mL of a 224 g/L solution of *potassium chloride R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

Correct the volume consumed for the content of acetate, taking the molecular mass of acetate to be 59.0.

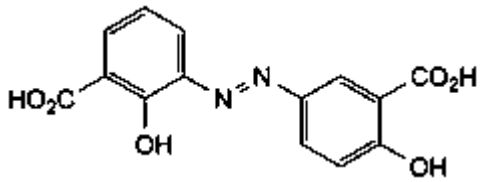
1 mL of *0.1 M hydrochloric acid* is equivalent to 17.31 mg of $C_{14}H_8N_2Na_2O_6$.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I.*



A. 6-hydroxy-6′-methoxy-3,3′-diazenediyldibenzoic acid,



B. 2,6′-dihydroxy-3,3′-diazenediyldibenzoic acid,

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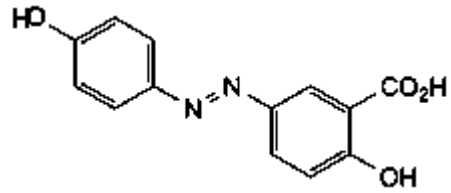
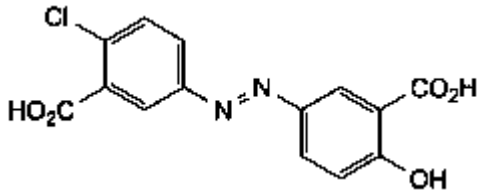
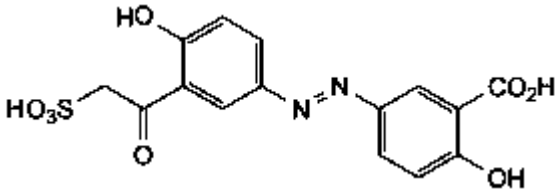


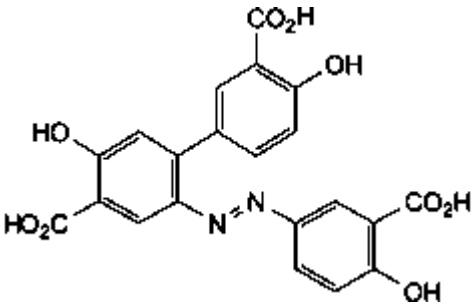
C. 2-hydroxy-5-[(4-hydroxyphenyl)diazenyl]benzoic acid,



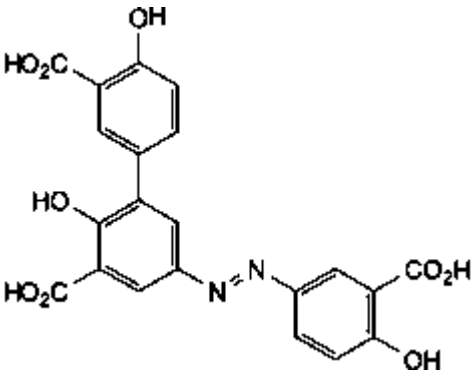
D. 6-chloro-6′-hydroxy-3,3′-diazenediyldibenzoic acid,



E. 2-hydroxy-5-[[4-hydroxy-3-(sulfoacetyl)phenyl)diazenyl]benzoic acid,



F. 2′-[(3-carboxy-4-hydroxyphenyl)diazenyl]-4,5′-dihydroxybiphenyl-3,4′-dicarboxylic acid,



G. 5-[(3-carboxy-4-hydroxyphenyl)diazenyl]-2,4′-dihydroxybiphenyl-3,3′-dicarboxylic acid,

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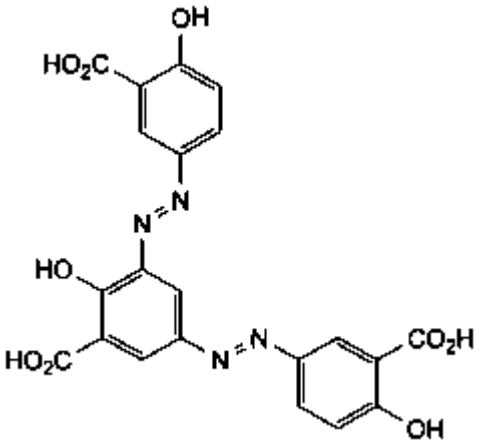
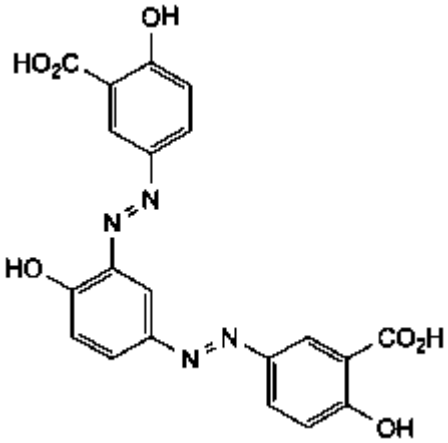


H. 3,3′-[5-carboxy-4-hydroxy-1,3-phenylenebis(diazenediyl)]bis(6-hydroxybenzoic) acid,



I. 3,3′-[4-hydroxy-1,3-phenylenebis(diazenediyl)]bis(6-hydroxybenzoic) acid.

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Omega-3-Acid Ethyl Esters 60

General Notices

(Ph. Eur. monograph 2063)

Action and use

Lipid-regulating drug.

Ph Eur

DEFINITION

Ethyl esters of *alpha*-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic acid (C22:5 n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3; DHA). Omega-3-acid ethyl esters 60 are obtained by transesterification of the body oil obtained from fish of families such as *Engraulidae*, *Carangidae*, *Clupeidae*, *Osmeridae*, *Salmonidae* and *Scombridae* or from animals of the class *Cephalopoda* and subsequent physico-chemical purification processes, including molecular distillation. The minimum content of total omega-3-acid ethyl esters and the minimum content of the omega-3-acids EPA and DHA ethyl esters are indicated in Table 2063.-1.

Table 2063.-1

Total omega-3-acid ethyl esters	EPA and DHA ethyl esters	EPA ethyl esters	DHA ethyl esters
Minimum content (per cent)			
65	50	25	20
60	50	-	40
55	50	40	-

A suitable antioxidant may be added.

PRODUCTION

The content of dioxins and dioxin-like PCBs (polychlorinated biphenyls) is controlled using methods and limits in accordance with the requirements set in the European Union or other applicable regulations.

CHARACTERS

Appearance

Light yellow liquid.

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Slight fish-like odour.

Solubility

Practically insoluble in water, very soluble in acetone, in ethanol (96 per cent), in heptane and in methanol.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay for EPA and DHA ethyl esters.

Results The peaks due to eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the chromatogram obtained with test solution (b) are similar in retention time to the corresponding peaks in the chromatograms obtained with reference solutions (a_1) and (a_2).

B. It complies with the limits of the assay for total omega-3-acid ethyl esters.

TESTS

Absorbance (2.2.25)

Maximum 0.60 at 233 nm.

Dilute 0.300 g to 50.0 mL with *trimethylpentane R*. Dilute 2.0 mL of the solution to 50.0 mL with *trimethylpentane R*.

Acid value (2.5.1)

Maximum 2.0, determined on 10 g in 50 mL of the prescribed mixture of solvents.

Anisidine value (2.5.36)

Maximum 20.0.

Peroxide value (2.5.5, Method A)

Maximum 10.0.

Oligomers and partial glycerides

Size-exclusion chromatography (2.2.30).

Test solution Dilute 50.0 mg of the substance to be examined to 10.0 mL with *tetrahydrofuran R*.

Reference solution Dissolve 50 mg of *monodocosahexaenoin R*, 30 mg of *didocosahexaenoin R* and 20 mg of *tridocosahexaenoin R* in *tetrahydrofuran R* and dilute to 100.0 mL with the same solvent.

Column 3 columns to be connected in series:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

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— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with the following pore sizes:

— *column 1*: 50 nm;

— *column 2*: 10 nm;

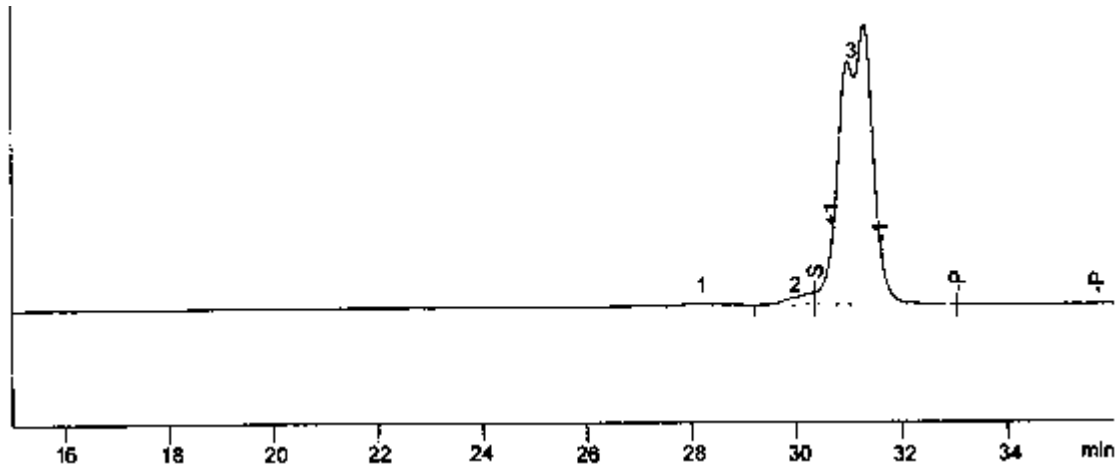
— *column 3*: 5 nm;

— *connection sequence*: injector – column 1 – column 2 – column 3 – detector.

Mobile phase *tetrahydrofuran R*.

Flow rate 0.8 mL/min.

Detection Differential refractometer.



1. oligomers 2. monoglycerides 3. fatty acid ethyl esters

Figure 2063.-1. – *Chromatogram for the test for oligomers and partial glycerides in omega-3-acid ethyl esters 60*

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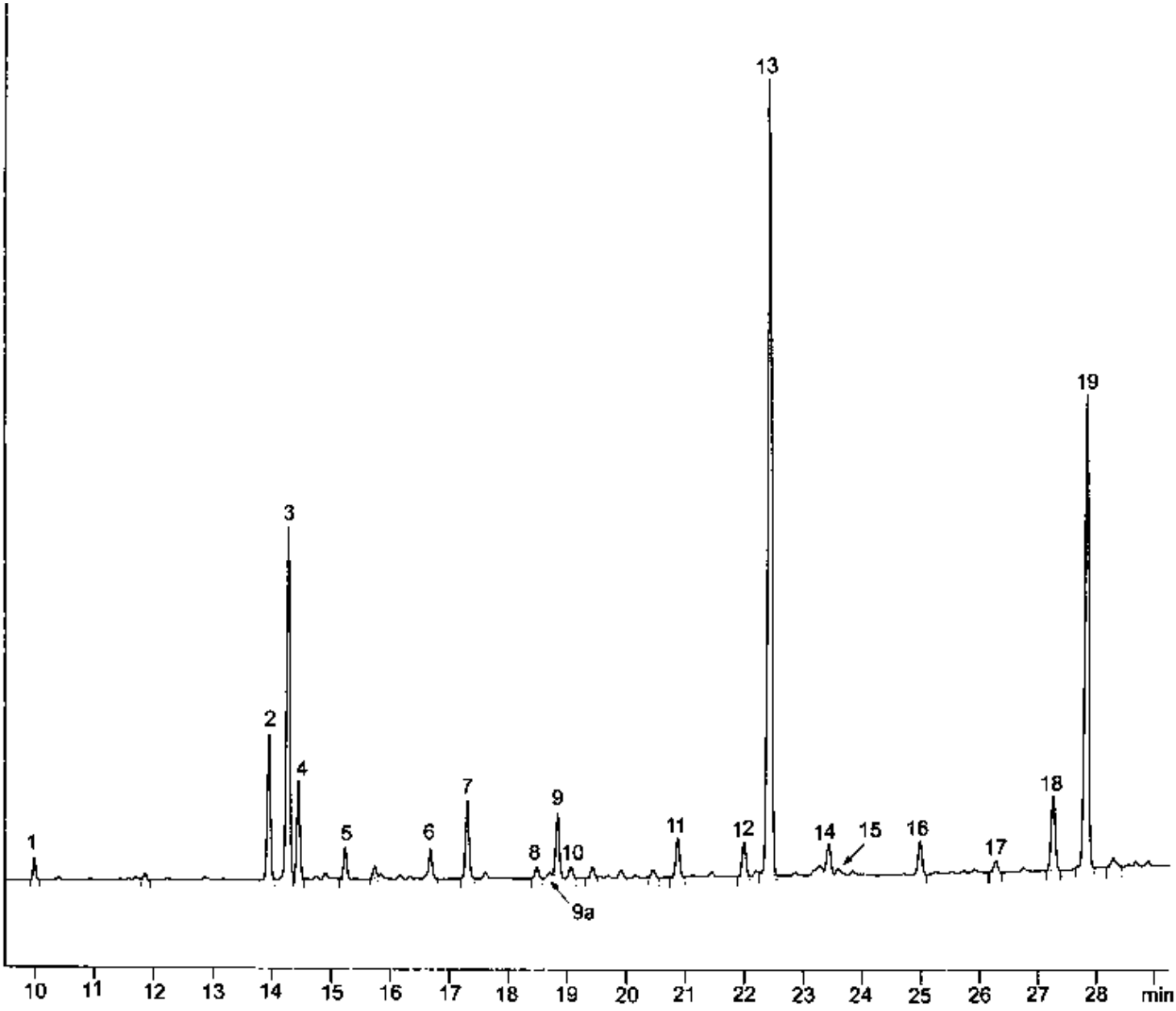

1. C16:0	4. C18:1 n-7	7. C18:4 n-3	9a. C20:1 n-11	12. C20:4 n-3	15. C22:1 n-9	18. C22:5 n-3
2. C18:0	5. C18:2 n-6	8. C20:0	10. C20:1 n-7	13. EPA	16. C21:5 n-3	19. DHA
3. C18:1 n-9	6. C18:3 n-3	9. C20:1 n-9	11. C20:4 n-6	14. C22:1 n-11	17. C22:5 n-6	

Figure 2063.-2. – *Chromatogram for the assays of omega-3-acid ethyl esters 60*

Injection 40 µL.

System suitability Reference solution:

— *elution order*: tridocosahexaenoin, didocosahexaenoin, monodocosahexaenoin;

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— *resolution*: minimum 2.0 between the peaks due to didocosahexaenoin and monodocosahexaenoin; minimum 1.0 between the peaks due to tridocosahexaenoin and didocosahexaenoin.

Calculate the percentage content of oligomers plus partial glycerides using the following expression:

$$\frac{B}{A} \times 100$$

A	=	sum of the areas of all the peaks in the chromatogram;
B	=	sum of the areas of the peaks with a retention time less than the retention time of the peaks due to ethyl esters.

The ethyl ester peaks, which may be present in the form of an unresolved double peak, are identified as the major peaks in the chromatogram (see Figure 2063.-1).

Limit:

— *sum of oligomers and partial glycerides*: maximum 7.0 per cent.

ASSAY

EPA and DHA ethyl esters (*2.4.29*)

For identification of the peaks, see Figure 2063.-2.

Total omega-3-acid ethyl esters (*2.4.29*)

See Figure 2063.-2.

STORAGE

Under an inert gas, in an airtight container, protected from light.

LABELLING

The label states:

— the content of total omega-3-acid ethyl esters;

— the content of EPA ethyl ester and DHA ethyl ester.

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Medicines & Healthcare products Regulatory Agency

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Omega-3-Acid Ethyl Esters 90

General Notices

(Ph. Eur. monograph 1250)

Action and use

Lipid-regulating drug.

Ph Eur

DEFINITION

Ethyl esters of *alpha*-linolenic acid (C18:3 n-3), moroctic (stearidonic) acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic (omega-3 docosapentaenoic) acid (C22:5 n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3; DHA). Omega-3-acid ethyl esters 90 are obtained by transesterification of the body oil obtained from fish of families such as *Engraulidae*, *Carangidae*, *Clupeidae*, *Osmeridae*, *Salmonidae* and *Scombridae* or from animals of the class *Cephalopoda* and subsequent physico-chemical purification processes, including urea fractionation followed by molecular distillation.

Content

— *EPA and DHA ethyl esters*: minimum 80.0 per cent and maximum 88.2 per cent, with minimum 43.0 per cent and maximum 49.5 per cent of EPA ethyl esters and minimum 34.7 per cent and maximum 40.3 per cent of DHA ethyl esters;

— *total omega-3-acid ethyl esters (corresponding to the sum of the ethyl esters listed under Definition)*: minimum 90 per cent.

A suitable antioxidant may be added.

PRODUCTION

The content of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDF), dioxin-like polychlorinated biphenyls (DLPCBs), non-dioxin-like polychlorinated biphenyls (NDLPCBs; 7PCB) and polybrominated diphenyl ethers (PBDEs) is controlled using suitable and validated methods, for example as outlined in Commission Regulation (EU) No 589/2014, Annex III, and in scientific publications of the European Food Safety Authority [EFSA, 2011].

Persistent organic pollutants	Maximum content
*Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/PCDF)**	1 pg/g (WHO-TEQ***)
Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/PCDF) and dioxin-like polychlorinated	5 pg/g (WHO-TEQ)

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Persistent organic pollutants	Maximum content
*biphenyls (DLPCBs)**	
*Non-dioxin-like polychlorinated biphenyls (NDLPCBs; 7PCB) (sum of congeners 28, 52, 101, 118, 138, 153 and 180)**	60 ng/g
*Polybrominated diphenyl ethers (PBDEs) (sum of congeners 28, 47, 49, 99, 100, 153 and 154)***	3 ng/g

*Commission Regulation (EU) No 589/2014, Annex III.

***EFSA Journal* 2011;9(5):2156, [274 pp.].

***WHO-TEQ = 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) toxic equivalent (TEQ) as agreed by WHO.

Calculate the upper-bound contents on the assumption that all values of the different congeners below the limit of quantification are equal to the limit of quantification.

CHARACTERS

Appearance

Light yellow liquid.

Solubility

Practically insoluble in water, very soluble in acetone, in ethanol (96 per cent), in heptane and in methanol.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay for EPA and DHA ethyl esters.

Results The peaks due to eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the chromatogram obtained with test solution (b) are similar in retention time to the corresponding peaks in the chromatograms obtained with reference solutions (a_1) and (a_2).

B. It complies with the limits of the assay for total omega-3-acid ethyl esters.

TESTS

Absorbance (2.2.25)

Maximum 0.55 at 233 nm.

Dilute 0.300 g to 50.0 mL with *trimethylpentane R*. Dilute 2.0 mL of the solution to 50.0 mL with *trimethylpentane R*.

Acid value (2.5.1)

Maximum 2.0, determined on 10 g in 50 mL of the prescribed mixture of solvents.

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Anisidine value (*2.5.36*)

Maximum 20.0.

Peroxide value (*2.5.5, Method B*)

Maximum 10.0.

Unidentified fatty acid ethyl esters (*2.4.29*)

Identify the peaks in the chromatogram obtained with test solution (b) in the assay, using Figure 1250.-2, integrating up to 1.3 times the retention time of DHA ethyl ester. Disregard any peak with an area less than 0.05 per cent of the total area.

Calculate the percentage content of the fatty acid ethyl ester corresponding to the largest single unidentified peak, using the following expression:

$$\frac{100 \times B}{A}$$

A	=	sum of the areas of all peaks, excluding those due to solvents, butylhydroxytoluene and the internal standard;
B	=	area of the largest single unidentified peak, excluding those due to solvents, butylhydroxytoluene and the internal standard.

Calculate the percentage content of total unidentified fatty acid ethyl esters, using the following expression:

$$100 - \frac{100 \times C}{A}$$

C	=	sum of the areas of the peaks due to ethyl esters identified in Figure 1250.-2.

Limits:

— *fatty acid ethyl ester corresponding to the largest single unidentified peak*: maximum 0.5 per cent;

— *total unidentified fatty acid ethyl esters*: maximum 2 per cent.

Cholesterol (*2.4.32*)

Maximum 3.0 mg/g.

Oligomers

Size-exclusion chromatography (*2.2.30*).

Test solution Dilute 50.0 mg of the substance to be examined to 10.0 mL with *tetrahydrofuran R*.

Reference solution Dissolve 50 mg of *monodocosahexaenoin R*, 30 mg of *didocosahexaenoin R* and 20 mg of *tridocosahexaenoin R* in *tetrahydrofuran R* and dilute to 100.0 mL with the same solvent.

Column 3 columns to be connected in series:

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— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with the following pore sizes:

— *column 1*: 50 nm;

— *column 2*: 10 nm;

— *column 3*: 5 nm;

— *connection sequence*: injector – column 1 – column 2 – column 3 – detector.

Mobile phase *tetrahydrofuran R*.

Flow rate 0.8 mL/min.

Run time 38 min.

Detection Differential refractometer.

Injection 40 µL.

System suitability Reference solution:

— *elution order*: tridocosahexaenoin, didocosahexaenoin, monodocosahexaenoin;

— *resolution*: minimum 2.0 between the peaks due to didocosahexaenoin and monodocosahexaenoin; minimum 1.0 between the peaks due to tridocosahexaenoin and didocosahexaenoin.

Calculate the percentage content of oligomers using the following expression:

$$\frac{B}{A} \times 100$$

A	=	sum of the areas of all the peaks in the chromatogram;
B	=	sum of the areas of the peaks with a retention time less than the retention time of the peaks due to ethyl esters.

The ethyl ester peaks, which may be present in the form of an unresolved double peak, are identified as the major peaks in the chromatogram (see Figure 1250.-1).

Where the result obtained exceeds the limit due to the presence of monoglycerides, the following procedure is carried out.

Test solution Weigh 50.0 mg of the substance to be examined into a quartz tube. Add 1.5 mL of a 20 g/L solution of *sodium hydroxide R* in *methanol R*, cover with *nitrogen R*, cap tightly with a polytetrafluoroethylene-lined cap, mix and heat on a water-bath for 7 min. Allow to cool. Add 2 mL of *boron trichloride-methanol solution R*, cover with *nitrogen R*, cap tightly, mix and heat on a water-bath for 30 min. Cool to 40-50 °C, add 1 mL of *trimethylpentane R*, cap and shake vigorously for at least 30 s. Immediately add 5 mL of *saturated sodium chloride solution R*, cover with *nitrogen R*, cap and shake thoroughly for at least 15 s. Transfer the upper layer to a separate tube. Shake the methanol layer once more with 1 mL of *trimethylpentane R*. Wash the combined trimethylpentane extracts with 2 quantities, each of 1 mL,

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of *water R*. Carefully evaporate the solvent under a current of *nitrogen R* then add 10.0 mL of *tetrahydrofuran R* to the residue. Add a small amount of *anhydrous sodium sulfate R* and filter.

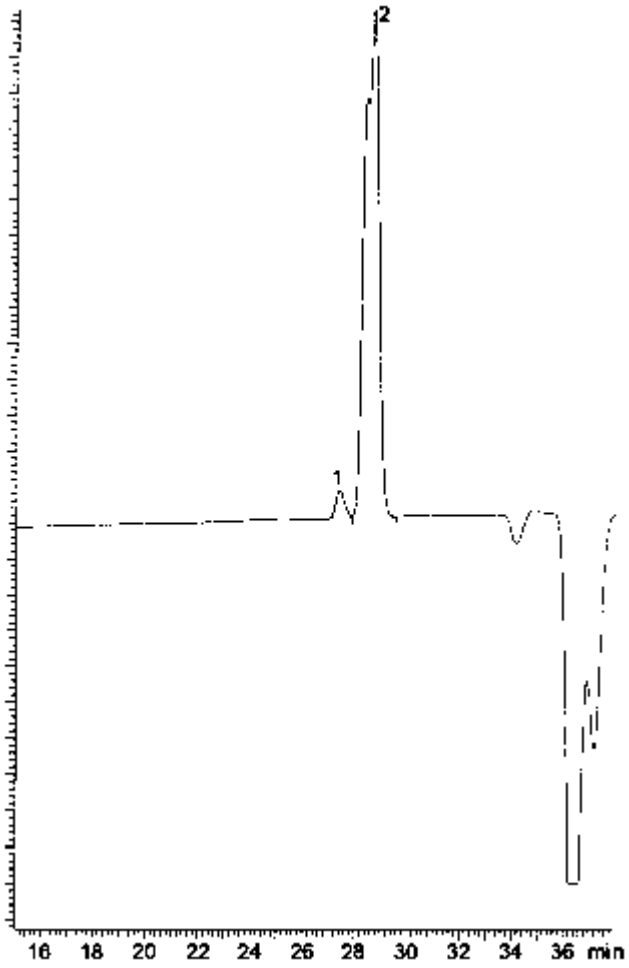
Calculate the percentage content of oligomers using the following expression:

$$\frac{B'}{A} \times 100$$

A	=	sum of the areas of all the peaks in the chromatogram;
B'	=	sum of the areas of the peaks with a retention time less than the retention time of the peaks due to methyl esters.

Limit:

— *oligomers*: maximum 1.0 per cent.



1. oligomers 2. ethyl esters

Figure 1250.-1. – *Chromatogram for the test for oligomers in omega-3-acid ethyl esters 90: spiked sample*

ASSAY

EPA and DHA ethyl esters (*2.4.29*)

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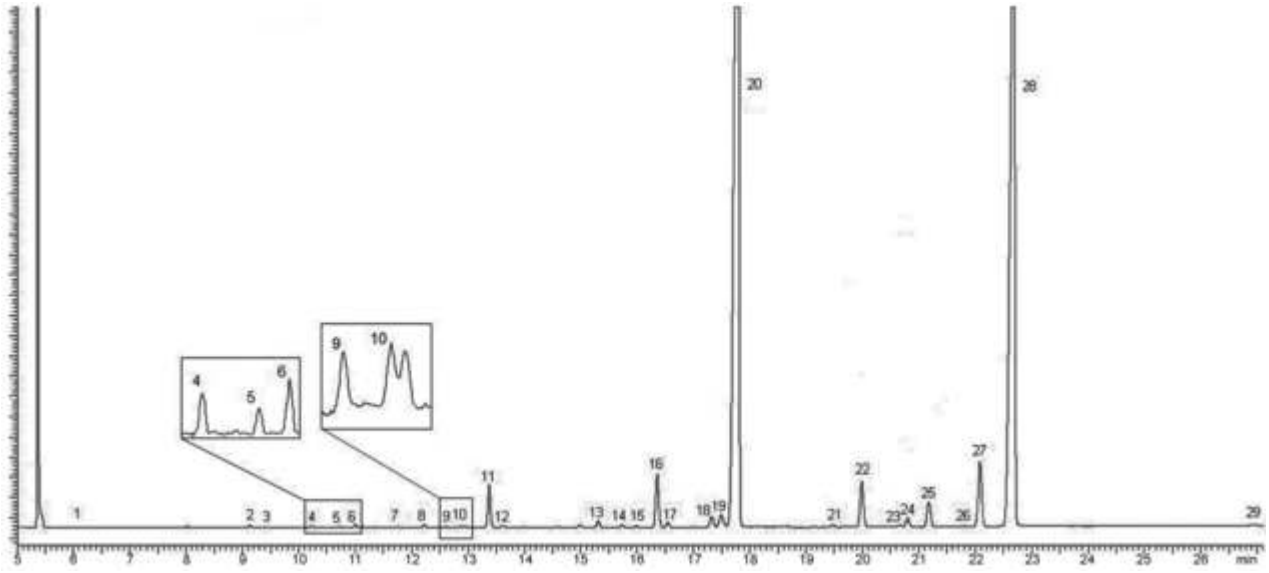
For identification of the peaks, see Figure 1250.-2.



Fatty acid	*r*	Fatty acid	*r*	Fatty acid	*r*	Fatty acid	*r*
1. C14:0	0.278	8. C18:3 *n*-6	0.557	15. C20:3 *n*-6	0.720	22. C21:5 *n*-3	0.889
2. Phytanic acid	0.416	9. C18:3 *n*-4	0.574	16. C20:4 *n*-6	0.736	23. C22:4 *n*-6	0.917
3. C16:3 *n*-4	0.431	10. C18:3 *n*-3	0.585	17. Furan acid 7	0.744	24. Furan acid 10	0.922
4. C16:4 *n*-1	0.468	11. C18:4 *n*-3	0.608	18. C20:4 *n*-3	0.777	25. C22:5 *n*-6	0.939
5. C18:0	0.488	12. C18:4 *n*-1	0.618	19. Furan acid 8	0.783	26. Furan acid 11	0.963
6. C18:1 *n*-9	0.501	13. Furan acid 5	0.691	20. EPA	0.796	27. C22:5 *n*-3	0.977
7. C18:2 *n*-6	0.535	14. C19:5	0.710	21. Furan acid 9	0.867	28. DHA	1.000
						29. C24:6	1.183

r: relative retention with reference to DHA ethyl ester (retention time = about 23 min).

Figure 1250.-2. – *Chromatogram for the assay of omega-3-acid ethyl esters 90 and the test for unidentified fatty acid ethyl esters*

Total omega-3-acid ethyl esters (2.4.29)

See Figure 1250.-2.

STORAGE

Under an inert gas, in an airtight container, protected from light.

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Omega-3-Marine Triglycerides

General Notices

(Omega-3-Acid Triglycerides, Ph. Eur. monograph 1352)

Action and use

Lipid-regulating drug.

Ph Eur

DEFINITION

Mixture of mono-, di- and triesters of omega-3 acids with glycerol, containing mainly triesters and obtained either by esterification of concentrated and purified omega-3 acids with glycerol or by transesterification of the omega-3 acid ethyl esters with glycerol. The origin of the omega-3 acids is the body oil obtained from fish of families such as *Engraulidae*, *Carangidae*, *Clupeidae*, *Osmeridae*, *Salmonidae* and *Scombridae* or from animals of the class *Cephalopoda*. The omega-3 acids are identified as the following acids: *alpha*-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic acid (C22:5 n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3; DHA).

Content

— *sum of the contents of the omega-3 acids EPA and DHA, expressed as triglycerides*: minimum 45 per cent;

— *total omega-3 acids, expressed as triglycerides*: minimum 60 per cent.

A suitable antioxidant may be added.

PRODUCTION

The content of dioxins and dioxin-like PCBs (polychlorinated biphenyls) is controlled using methods and limits in accordance with the requirements set in the European Union or other applicable regulations.

CHARACTERS

Appearance

Pale yellow liquid.

Solubility

Practically insoluble in water, very soluble in acetone and in heptane, slightly soluble in anhydrous ethanol.

IDENTIFICATION

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IDENTIFICATION

Examine the chromatograms obtained in the assay for EPA and DHA.

Results The peaks due to eicosapentaenoic acid methyl ester and docosahexaenoic acid methyl ester in the chromatogram obtained with test solution (b) are similar in retention time to the corresponding peaks in the chromatograms obtained with reference solutions (a_1) and (a_2).

TESTS

Absorbance (2.2.25)

Maximum 0.70 at 233 nm.

Dilute 0.300 g to 50.0 mL with *trimethylpentane R*. Dilute 2.0 mL of the solution to 50.0 mL with *trimethylpentane R*.

Acid value (2.5.1)

Maximum 3.0, determined on 10.0 g in 50 mL of the prescribed mixture of solvents.

Anisidine value (2.5.36)

Maximum 20.0.

Peroxide value (2.5.5, Method A)

Maximum 5.0.

Oligomers, triglycerides, ethyl esters and free fatty acids

Size-exclusion chromatography (2.2.30).

Test solution Dilute 50.0 mg of the substance to be examined to 10.0 mL with *tetrahydrofuran R*.

Reference solution Dissolve 50 mg of *monodocosahexaenoin R*, 30 mg of *didocosahexaenoin R* and 20 mg of *tridocosahexaenoin R* in *tetrahydrofuran R* and dilute to 100.0 mL with the same solvent.

Column 3 columns to be connected in series:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with the following pore sizes:

  — *column 1*: 50 nm;

  — *column 2*: 10 nm;

  — *column 3*: 5 nm;

— *connection sequence*: injector - column 1 - column 2 - column 3 - detector.

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Mobile phase tetrahydrofuran R.

Flow rate 0.8 mL/min.

Detection Differential refractometer.

Injection 40 µL.

System suitability Reference solution:

— *elution order*: tridocosahexaenoin, didocosahexaenoin, monodocosahexaenoin;

— *resolution*: minimum 2.0 between the peaks due to didocosahexaenoin and monodocosahexaenoin; minimum 1.0 between the peaks due to tridocosahexaenoin and didocosahexaenoin.

Identify the peaks using the chromatogram shown in Figure 1352.-1. Calculate the percentage content of oligomers using the following expression:

$$\frac{B}{A} \times 100$$

A = sum of the areas of all the peaks in the chromatogram;

B = area of the peak with a retention time less than the retention time of the peak due to the triglycerides.

Calculate the percentage content of triglycerides using the following expression:

$$\frac{C}{A} \times 100$$

A = sum of the areas of all the peaks in the chromatogram;

C = (sum of the) area(s) of the peak(s) due to triglycerides.

Calculate the percentage content of ethyl esters and free fatty acids using the following expression:

$$\frac{D}{A} \times 100$$

A = sum of the areas of all the peaks in the chromatogram;

D = (sum of the) area(s) of the peak(s) due to ethyl esters and free fatty acids.

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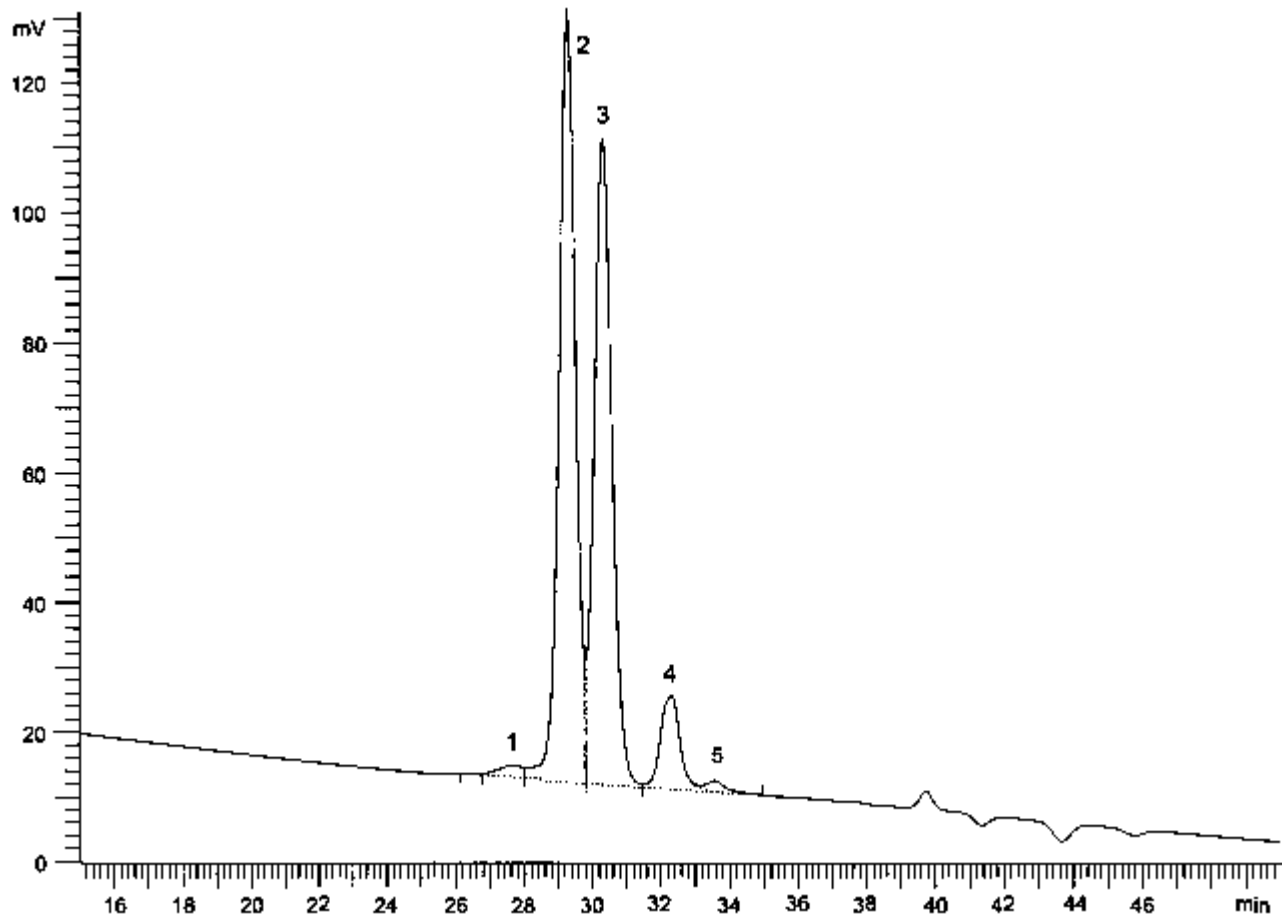

1. oligomers 2. triglycerides 3. diglycerides 4. monoglycerides 5. ethyl esters and free fatty acids

Figure 1352.-1. – *Chromatogram for the test for oligomers, triglycerides, ethyl esters and free fatty acids in omega-3 acids triglycerides*

Limits:

— *oligomers*: maximum 3.0 per cent;

— *triglycerides*: minimum 50.0 per cent;

— *ethyl esters and free fatty acids*: maximum 5.0 per cent.

ASSAY

EPA and DHA (2.4.29)

For identification of the peaks, see Figure 1352.-2.

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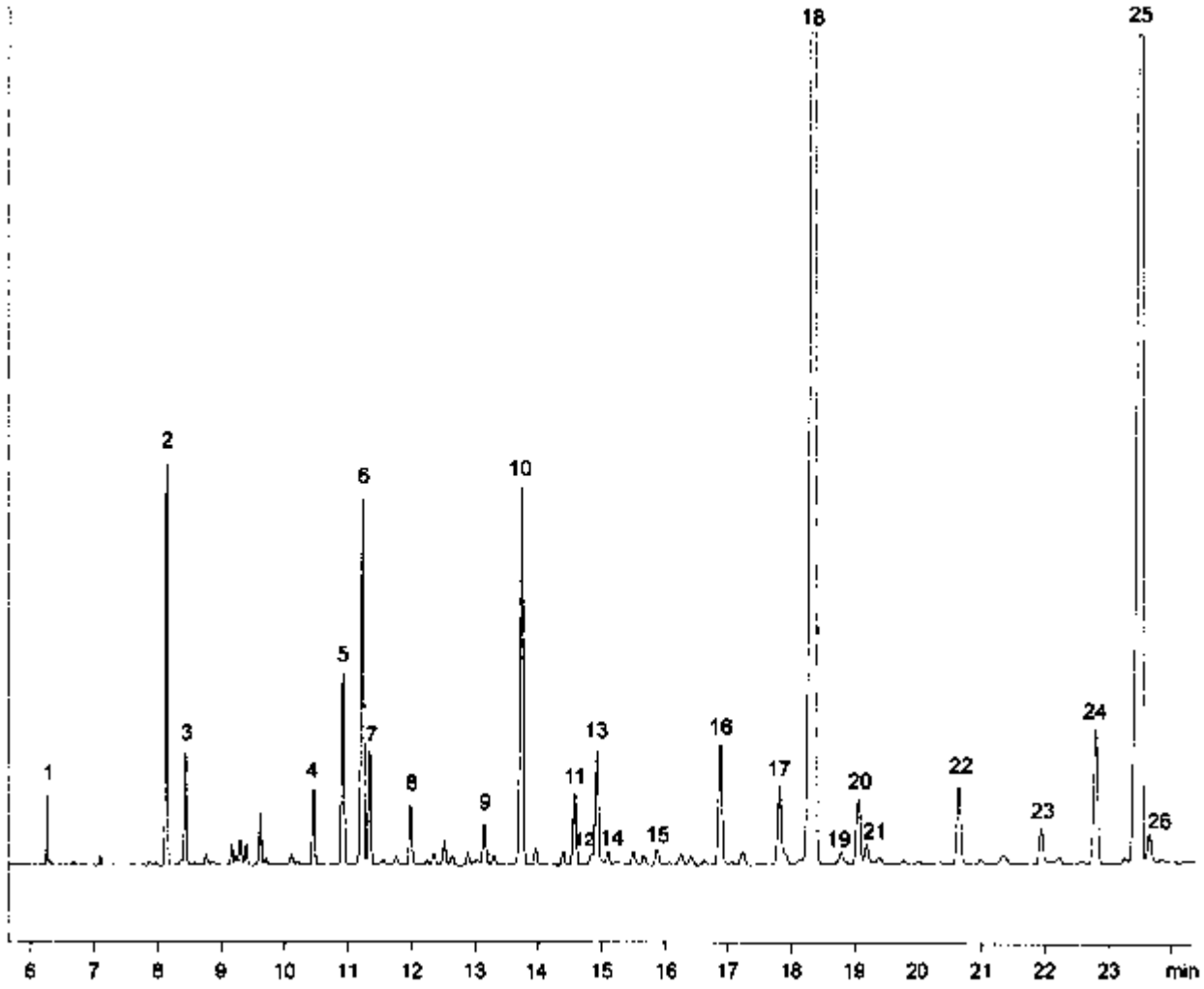

1. C14:0	4. C16:4 n-1	7. C18:1 n-7	10. C18:4 n-3	13. C20:1 n-9	16. C20:4 n-6	19. C22:0	22. C21:5 n-3	25. DHA
2. C16:0	5. C18:0	8. C18:2 n-6	11. C20:0	14. C20:1 n-7	17. C20:4 n-3	20. C22:1 n-11	23. C22:5 n-6	26. C24:1 n-9
3. C16:1 n-7	6. C18:1 n-9	9. C18:3 n-3	12. C20:1 n-11	15. C20:2 n-6	18. EPA	21. C22:1 n-9	24. C22:5 n-3	

Figure 1352.-2. – *Chromatogram for the assays of omega-3 acids in omega-3 acids triglycerides*

Total omega-3 acids (*2.4.29*)

See Figure 1352.-2.

STORAGE

Under an inert gas, in a well-filled, airtight container, protected from light.

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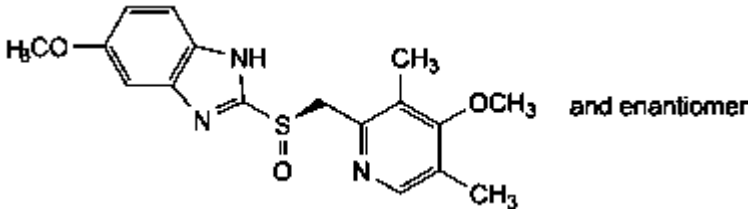
Omeprazole

General Notices

(Ph. Eur. monograph 0942)



$C_{17}H_{19}N_3O_3S$ 345.4 *73590-58-6*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Preparations

Omeprazole Gastro-resistant Tablets

Omeprazole Oral Suspension

Ph Eur

DEFINITION

5-Methoxy-2-[(*RS*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96 per cent) and in methanol. It dissolves in dilute solutions of alkali hydroxides.

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It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison omeprazole CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Solution S

Dissolve 0.50 g in methylene chloride R and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1).

Impurities F and G

Maximum 350 ppm for the sum of the contents.

The absorbance (2.2.25) of solution S determined at 440 nm is not greater than 0.10.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 3 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 1 mg of omeprazole CRS and 1 mg of omeprazole impurity D CRS in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 3 mg of omeprazole for peak identification CRS (containing impurity E) in the mobile phase and dilute to 20 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm).

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Mobile phase Mix 27 volumes of *acetonitrile R* and 73 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate dodecahydrate R* previously adjusted to pH 7.6 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 40 µL.

Run time 5 times the retention time of omeprazole.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D; use the chromatogram supplied with *omeprazole for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity E.

Relative retention With reference to omeprazole (retention time = about 9 min): impurity E = about 0.6; impurity D = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity D and omeprazole; if necessary, adjust the pH of the aqueous part of the mobile phase or the concentration of *acetonitrile R*; an increase in the pH will improve the resolution.

Limits:

— *impurities D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 10 mL of *water R* and 40 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 34.54 mg of $C_{17}H_{19}N_3O_3S$.

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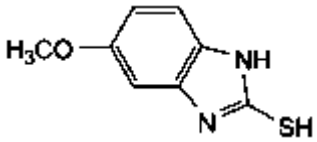
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

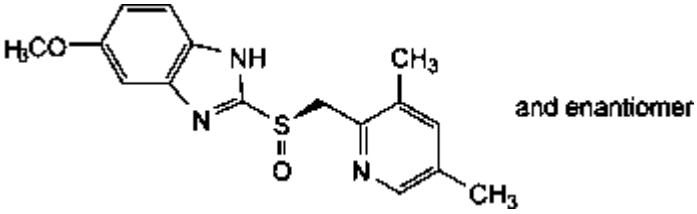
IMPURITIES

Specified impurities *D, E, F, G*.

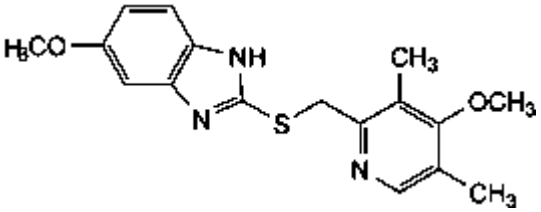
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, H, I*.



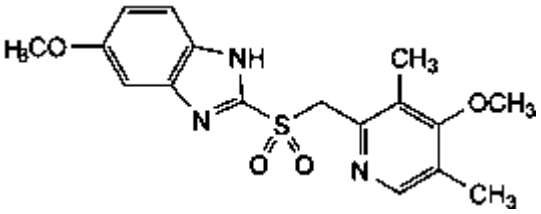
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),



D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole sulfone),

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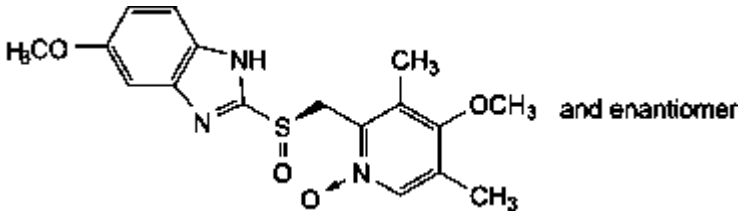
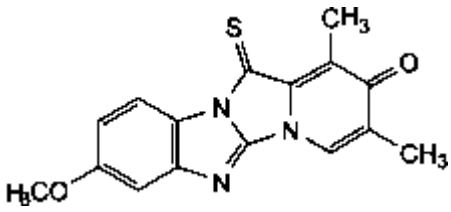
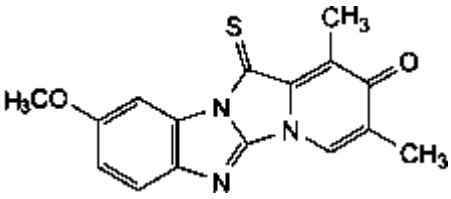


and enantiomer

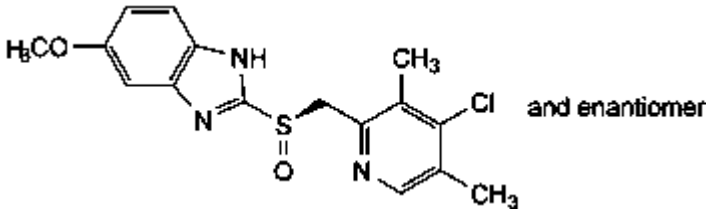
E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide,



F. 8-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one,

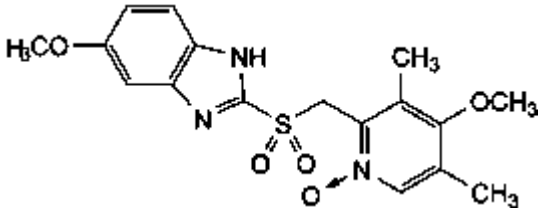


G. 9-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one,



and enantiomer

H. 2-[(*RS*)-[(4-chloro-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



I. 4-methoxy-2-[[(5-methoxy-1*H*-benzimidazol-2-yl)sulfonyl]methyl]-3,5-dimethylpyridine 1-oxide.

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Omeprazole Gastro-resistant Capsules

General Notices

Gastro-resistant Omeprazole Capsules

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Omeprazole Gastro-resistant Capsules contain Omeprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of omeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the finely powdered contents of the capsules containing 20 mg of Omeprazole with 50 mL of 0.1M *sodium hydroxide*, dilute to 100 mL, filter and further dilute 10 mL to 100 mL. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 276 nm and 305 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

Mix 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 1000 volumes with *water* and adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution C).

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First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use as the medium 700 mL of *0.05M phosphate buffer solution pH 4.5*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw 5 mL of the medium, filter the aliquot, dilute to 25 mL with solution A and retain the samples for analysis. Proceed immediately to the final stage.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 302 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 8 times the retention time of omeprazole.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*. Adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 5 minutes of medium withdrawal at the first stage, add 200 mL of solution B at 37° to the vessel.

PROCEDURE

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute 1 volume to 5 volumes with solution A and retain the samples for analysis.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released after the final stage is not less than 65% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. The solutions should be prepared immediately before use.

(1) Disperse a quantity of finely powdered capsule contents containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter.

(2) Dilute 5 volumes of solution (1) to 100 volumes. Dilute 1 volume of this solution to 10 volumes.

(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil RP8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 40 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of omeprazole.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.14% w/v solution of *disodium hydrogen orthophosphate* previously adjusted to pH 7.6 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with respect to omeprazole (retention time about 9 minutes) are: impurity D, about 0.8; impurity C, about 3.4.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%)

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Weigh and powder the contents of 20 capsules. Shake a quantity of the mixed capsule contents containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter and further dilute 1 volume to 10 volumes.
(2) 0.0012% w/v of *omeprazole BPCRS*.
(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but with a detection wavelength of 305 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O_3S$ in the capsules using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

IMPURITIES

The impurities limited by this monograph include those listed under Omeprazole.

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Omeprazole Gastro-resistant Tablets

General Notices

Gastro-resistant Omeprazole Tablets

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Omeprazole Gastro-resistant Tablets contain Omeprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of omeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of powdered tablets containing 20 mg of Omeprazole with 50 mL of 0.1M *sodium hydroxide*, dilute to 100 mL, filter and further dilute 10 mL to 100 mL. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits two maxima at 276 nm and 305 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

Mix 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 1000 volumes with *water* and adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution C).

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First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use as the medium 700 mL of *0.05M phosphate buffer solution pH 4.5*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw 5 mL of the medium, filter the aliquot, dilute to 25 mL with solution A and retain the samples for analysis. Proceed immediately to the final stage.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 302 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 8 times the retention time of omeprazole.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*. Adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 5 minutes of medium withdrawal at the first stage, add 200 mL of solution B at 37° to the vessel.

PROCEDURE

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute 1 volume to 5 volumes with solution A and retain the samples for analysis.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released after the final stage is not less than 65% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase. The solutions should be prepared immediately before use.

(1) Disperse a quantity of the powdered tablets containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter.

(2) Dilute 5 volumes of solution (1) to 100 volumes. Dilute 1 volume of this solution to 10 volumes.

(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil RP8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 40 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of omeprazole.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.14% w/v solution of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.6 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with respect to omeprazole (retention time about 9 minutes) are: impurity D, about 0.8; impurity C, about 3.4.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is greater than 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%)

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Disperse a quantity of the powdered tablets containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix, filter and further dilute 1 volume to 10 volumes.
(2) 0.0012% w/v of *omeprazole BPCRS*.
(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but with a detection wavelength of 305 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is greater than 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O_3S$ in the tablets from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

IMPURITIES

The impurities limited by this monograph include those listed under Omeprazole.

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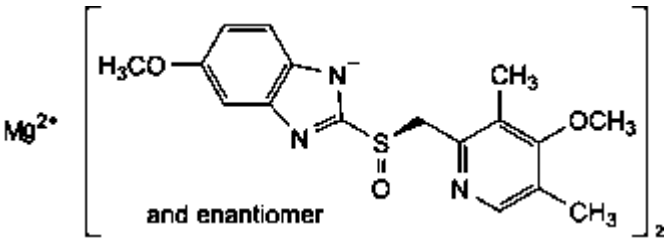
Omeprazole Magnesium

General Notices

(Ph. Eur. monograph 2374)



$C_{34}H_{36}MgN_6O_6S_2$ 713 *95382-33-5*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Ph Eur

DEFINITION

Magnesium bis[5-methoxy-2-[(*RS*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazol-1-ide]. It contains a variable quantity of water.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Very slightly soluble in water, sparingly soluble in methanol, practically insoluble in heptane.

IDENTIFICATION

Carry out either tests A, B, C or tests A, B, D.

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A. Optical rotation (2.2.7): -0.10° to + 0.10°.

Dissolve 0.250 g in methanol R and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison omeprazole magnesium CRS.

C. Atomic absorption spectrometry (2.2.23) as described in the test for magnesium.

The test solution shows the absorption maximum at 285.2 nm.

D. Ignite about 0.5 g of the substance to be examined according to the procedure for the sulfated ash test (2.4.14). Dissolve the residue in 10 mL of water R. 2 mL of this solution gives the reaction of magnesium (2.3.1).

TESTS

Absorbance (2.2.25)

Maximum 0.10 at 440 nm.

Dissolve 0.500 g in methanol R and dilute to 25.0 mL with the same solvent. Filter the solution through a membrane filter (nominal pore size 0.45 µm).

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Prepare the solutions immediately before use.*

Test solution Dissolve 3.5 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 1 mg of omeprazole CRS and 1 mg of omeprazole impurity D CRS in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 3 mg of omeprazole for peak identification CRS (containing impurity E) in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 27 volumes of acetonitrile R and 73 volumes of a 1.4 g/L solution of disodium hydrogen phosphate dodecahydrate R previously adjusted to pH 7.6 with phosphoric acid R.

Flow rate 1 mL/min.

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Detection Spectrophotometer at 280 nm.

Injection 40 µL.

Run time 5 times the retention time of omeprazole.

Identification of impurities:

— use the chromatogram supplied with *omeprazole for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity E;

— use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to omeprazole (retention time = about 9 min): impurity E = about 0.6, impurity D = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity D and omeprazole; if necessary, adjust the pH of the aqueous part of the mobile phase or its proportion of acetonitrile; an increase in the pH will improve the resolution.

Limits:

— *impurities D, E*: for each impurity, maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *disregard limit*: half the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Magnesium

3.30 per cent to 3.55 per cent (anhydrous substance).

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 0.250 g in 20.0 mL of a 103 g/L solution of *hydrochloric acid R* by slow addition of the acid and dilute to 100.0 mL with *water R*. Dilute 10.0 mL of the solution to 200.0 mL with *water R*. To 10.0 mL of this solution add 4 mL of *lanthanum chloride solution R* and dilute to 100.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *magnesium standard solution (1000 ppm Mg) R*, diluting with a mixture of 1 mL of a 103 g/L solution of *hydrochloric acid R* and 1000.0 mL of *water R*.

Wavelength 285.2 nm.

Water (*2.5.12*)

7.0 per cent to 10.0 per cent, determined on 0.200 g.

ASSAY

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Liquid chromatography (2.2.29).

Buffer pH 11.0 Mix 11 mL of a 95.0 g/L solution of *trisodium phosphate dodecahydrate R* and 22 mL of a 179.1 g/L solution of *disodium hydrogen phosphate dodecahydrate R*. Dilute to 100.0 mL with *water R*.

Test solution Dissolve 10.0 mg of the substance to be examined in about 10 mL of *methanol R*. Add 10 mL of buffer pH 11.0 and dilute to 200.0 mL with *water R*.

Reference solution Dissolve 10.0 mg of *omeprazole CRS* in about 10 mL of *methanol R*. Add 10 mL of buffer pH 11.0 and dilute to 200.0 mL with *water R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate dodecahydrate R* previously adjusted to pH 7.6 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 1.5 times the retention time of omeprazole.

Retention time Omeprazole = about 4 min.

Calculate the percentage content of $C_{34}H_{36}MgN_6O_6S_2$ from the declared content of *omeprazole CRS*.

1 g of omeprazole is equivalent to 1.032 g of omeprazole magnesium.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*

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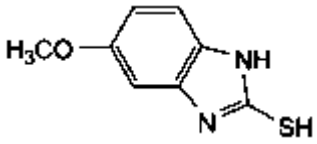
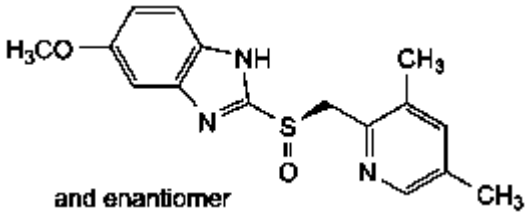
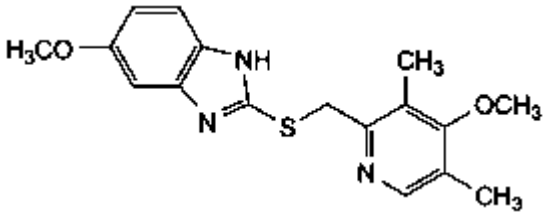


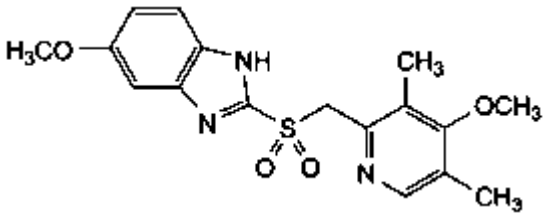
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



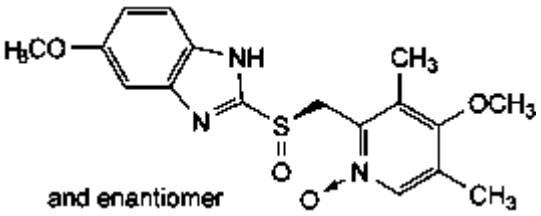
B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole,



D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole,



E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide.

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Omeprazole Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Omeprazole Oral Suspension is a suspension containing Omeprazole in a suitable alkaline vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of omeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Disperse a volume of the oral suspension containing 2 mg of Omeprazole in 0.1M *sodium hydroxide* and dilute to 100 mL with the same solution. Mix with the aid of ultrasound for 10 minutes and filter the resulting suspension. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits absorption maxima at 276 nm and at 305 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

The requirement stated under Unlicensed Medicines, Oral Suspensions does not apply to Omeprazole Oral Suspension.

Buffer capacity

Not less than 400, when determined by the following method.

Measure the pH of 30 mL of the oral suspension, Appendix V L. Add sufficient 0.5M *hydrochloric acid* to change the initial pH by 1 unit. Calculate the buffer capacity (β) [the amount of strong acid or base that must be added to 1 litre of the solution to change the pH by one unit] using the following expression:

$$\beta = V_A \times 1000 / V_S \times C$$

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where,

V_A	=	the volume of 0.5M *hydrochloric acid* required to change the pH by 1 unit (in mL),
V_S	=	the volume of oral suspension (in mL),
C	=	the concentration of 0.5M *hydrochloric acid* (in moles per litre).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the oral suspension containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter.
(2) Dilute 1 volume of solution (1) to 20 volumes with the mobile phase. Dilute 1 volume of this solution to 10 volumes with the mobile phase.
(3) Mix 10 mg of each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS* in the mobile phase and dilute to 100 mL with the same solvent.
(4) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil RP8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 40 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of omeprazole.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.14% w/v solution of *disodium hydrogen orthophosphate* previously adjusted to pH 7.6 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of omeprazole is about 9 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak due to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a weighed quantity of the oral suspension containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(2) 0.0012% w/v of *omeprazole BPCRS* in the mobile phase.
(3) Mix 10 mg of each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS* in the mobile phase and dilute to 100 mL with the same solvent.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using a detection wavelength of 305 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 3.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{17}H_{19}N_3O_3S$, weight in volume, from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

STORAGE

Omeprazole Oral Suspension should be protected from light and stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Omeprazole.

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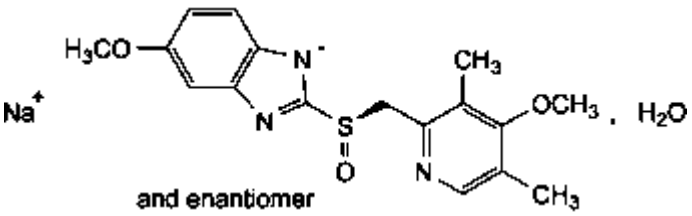
Omeprazole Sodium

General Notices

(Ph. Eur. monograph 1032)



$C_{17}H_{18}N_3NaO_3S,H_2O$ 385.4 *95510-70-6*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Ph Eur

DEFINITION

Sodium 5-methoxy-2-[(*RS*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole monohydrate.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), soluble in propylene glycol, very slightly soluble in methylene chloride.

IDENTIFICATION

A. Optical rotation (2.2.7): -0.10° to + 0.10°, determined on solution S.

B. Infrared absorption spectrophotometry (2.2.24).

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Preparation Dissolve 0.50 g of the substance to be examined in 1.50 mL of *water R*, add 3.0 mL of *methanol R* and stir; while stirring, adjust to pH 8-9 by adding, dropwise, *dilute acetic acid R* (about 0.4 mL); continue stirring until crystallisation and isolate the crystalline precipitate by filtration; wash with 5 mL of *water R*, then 2 mL of *methanol R*, and dry *in vacuo* at 40 °C for 30 min.

Comparison *omeprazole CRS*.

If the spectra obtained in the solid state show differences, dissolve the crystalline precipitate and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Ignite 1 g and cool. Add 1 mL of *water R* to the residue and neutralise with *hydrochloric acid R*. Filter and dilute the filtrate to 4 mL with *water R*. 0.1 mL of the solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

pH (*2.2.3*)

10.3 to 11.3 for solution S.

Related substances

Liquid chromatography (*2.2.29*). *Prepare solutions immediately before use.*

Test solution Dissolve 3 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 1 mg of *omeprazole CRS* and 1 mg of *omeprazole impurity D CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 3 mg of *omeprazole for peak identification CRS* (containing impurity E) in the mobile phase and dilute to 25.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

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Mobile phase Mix 27 volumes of *acetonitrile R* and 73 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate dodecahydrate R*, previously adjusted to pH 7.6 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 40 µL.

Run time 5 times the retention time of omeprazole.

Identification of impurities Use the chromatogram supplied with *omeprazole for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to omeprazole (retention time = about 9 min): impurity E = about 0.6; impurity D = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity D and omeprazole; if necessary adjust the pH of the aqueous part of the mobile phase or the concentration of *acetonitrile R*; an increase in the pH will improve the resolution.

Limits:

— *impurities D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

4.5 per cent to 10.0 per cent, determined on 0.300 g.

ASSAY

Dissolve 0.300 g in 50 mL of *water R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* corresponds to 36.74 mg of $C_{17}H_{18}N_3NaO_3S$.

STORAGE

In an airtight container, protected from light.

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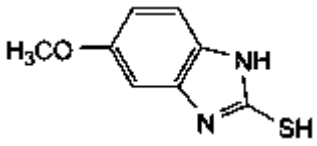
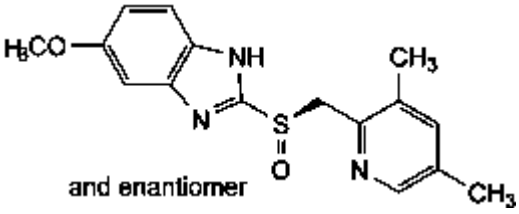
IMPURITIES

Specified impurities D, E.

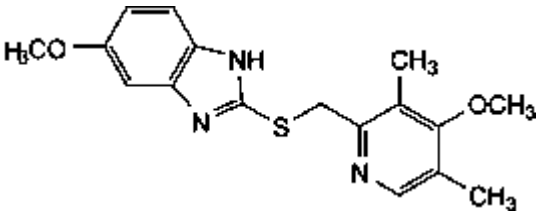
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.



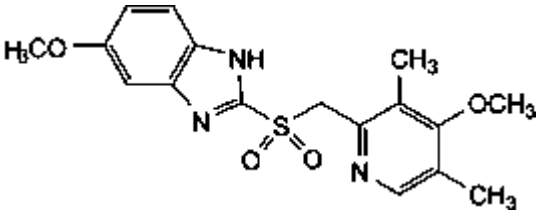
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



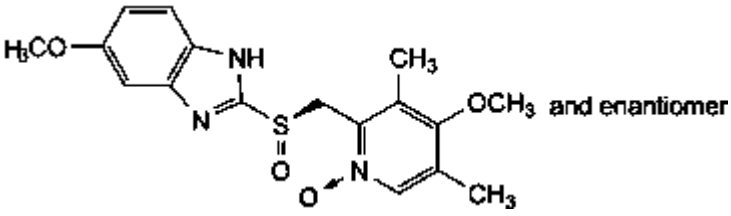
B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),



D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole-sulfone),



E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide.

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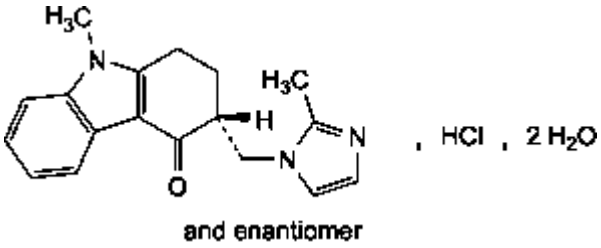
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Ondansetron Hydrochloride Dihydrate

General Notices

(Ph. Eur. monograph 2016)



$C_{18}H_{20}ClN_3O,2H_2O$ 365.9 *103639-04-9*

Action and use

Serotonin 5-HT_3 antagonist; treatment of nausea and vomiting.

Preparations

Ondansetron Injection

Ondansetron Tablets

Ph Eur

DEFINITION

(3*RS*)-9-Methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one hydrochloride dihydrate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Sparingly soluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ondansetron hydrochloride dihydrate CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Impurity B

Thin-layer chromatography (2.2.27).

Solvent mixture *concentrated ammonia R*, *ethanol (96 per cent) R*, *methanol R* (0.5:100:100 *V/V/V*).

Test solution Dissolve 0.125 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 12.5 mg of *ondansetron for TLC system suitability CRS* (containing impurities A and B) in the solvent mixture and dilute to 1 mL with the solvent mixture.

Reference solution (b) Dilute 1 mL of the test solution to 100 mL with the solvent mixture. Dilute 4.0 mL of this solution to 10.0 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *ethyl acetate R*, *methylene chloride R* (2:40:50:90 *V/V/V/V*).

Application 20 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Impurity A = about 0.3; impurity B = about 0.4; ondansetron = about 0.6.

System suitability Reference solution (a):

— the chromatogram shows 3 clearly separated spots.

Limit:

— *impurity B*: any spot due to impurity B is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.4 per cent).

Related substances

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Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Test solution (b) Dissolve 90.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *ondansetron impurity E CRS* and 5 mg of *ondansetron impurity A CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *ondansetron for LC system suitability CRS* (containing impurities C and D) in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (d) Dissolve 5.0 mg of *ondansetron impurity D CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (e) Dissolve 90.0 mg of *ondansetron hydrochloride dihydrate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (f) Dissolve 5.0 mg of *ondansetron impurity F CRS* and 5 mg of *ondansetron impurity G CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (g) To 1.0 mL of reference solution (b) add 1.0 mL of reference solution (f) and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 20 volumes of *acetonitrile R1* and 80 volumes of a 2.8 g/L solution of *sodium dihydrogen phosphate monohydrate R* previously adjusted to pH 5.4 with a 40 g/L solution of *sodium hydroxide R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 216 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b), (c), (d), (f) and (g).

Run time 1.5 times the retention time of ondansetron.

Identification of impurities:

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— use the chromatogram supplied with *ondansetron for LC system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and D;

— use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and E;

— use the chromatogram obtained with reference solution (f) to identify the peaks due to impurities F and G.

Relative retention With reference to ondansetron (retention time = about 18 min): impurity E = about 0.17; impurity F = about 0.20 (E and F may coelute); impurity C = about 0.35; impurity D = about 0.45; impurity A = about 0.80; impurity G = about 0.89 (A and G may coelute or be inverted).

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurities C and D.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.6;

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of impurities A and G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of impurities E and F*: not more than the sum of the areas of the corresponding peaks in the chromatogram obtained with reference solution (g) (0.2 per cent);

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 0.4 per cent;

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

9.0 per cent to 10.5 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

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Injection Test solution (b) and reference solution (e).

System suitability Reference solution (e):

— *symmetry factor*: maximum 2.5 for the peak due to ondansetron.

Calculate the percentage content of $C_{18}H_{20}ClN_3O$ taking into account the assigned content of *ondansetron hydrochloride dihydrate CRS*.

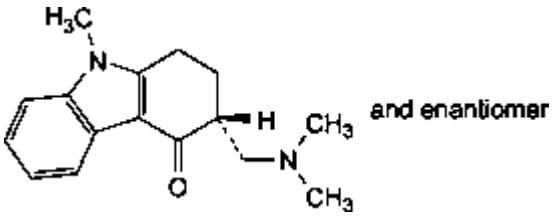
STORAGE

Protected from light.

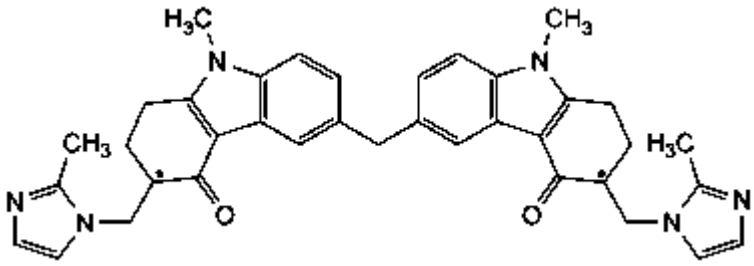
IMPURITIES

Specified impurities *A, B, C, D, E, F, G*.

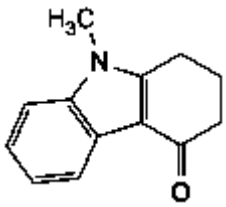
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H*.



A. (3*RS*)-3-[(dimethylamino)methyl]-9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,



B. 6,6′-methylenebis[(3Ξ)-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one],



C. 9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,

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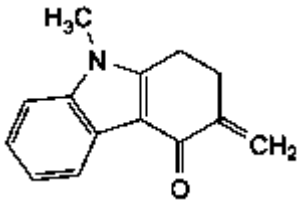
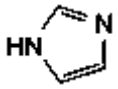
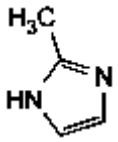


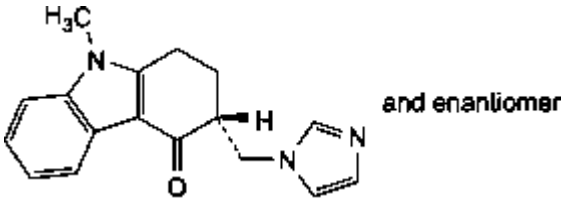
D. 9-methyl-3-methylidene-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,



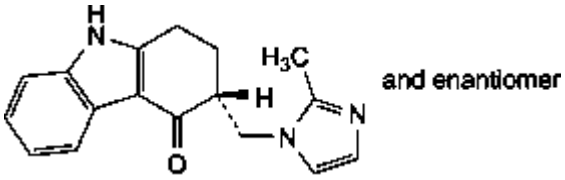
E. 1*H*-imidazole,



F. 2-methyl-1*H*-imidazole,



G. (3*RS*)-3-[(1*H*-imidazol-1-yl)methyl]-9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (*C*-demethylondansetron),



H. (3*RS*)-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (*N*-demethylondansetron).

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Ondansetron Injection

General Notices

Action and use

Serotonin $5HT_3$ antagonist; treatment of nausea and vomiting.

DEFINITION

Ondansetron Injection is a sterile solution of Ondansetron Hydrochloride Dihydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ondansetron, $C_{18}H_{19}N_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume of the injection containing the equivalent of 40 mg of ondansetron add 3 mL of 10M *sodium hydroxide*, shake and filter. Wash the precipitate with *water* and dry at 60° at a pressure of 2 kPa. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of ondansetron *(RS 418)*.

TESTS

Acidity

pH, 3.3 to 4.0, Appendix V L.

Impurity B

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in solution A.

Solution A: 0.5 volumes of 13.5M *ammonia*, 100 volumes of *ethanol (96%)* and 100 volumes of *methanol*.

(1) Dilute the injection, if necessary, to give a solution containing the equivalent of 0.2% w/v of ondansetron.

(2) Dilute 1 volume of solution (1) to 50 volumes and dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.25% w/v solution of *ondansetron for TLC system suitability BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use *silica gel F_{254}* as the coating.

(b) Use the mobile phase described below.

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(c) Apply 100 µL of each solution.

(d) Develop the plate to 15 cm.

(e) Remove the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 20 volumes of *methanol*, 25 volumes of *ethyl acetate* and 45 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots (impurity A, Rf value of about 0.3; impurity B, Rf value of about 0.4; ondansetron, Rf value of about 0.6).

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* corresponding to impurity B is not more intense than the spot obtained with solution (2) (0.4%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the injection, if necessary, to give a solution containing the equivalent of 0.1% w/v of ondansetron.

(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume of the resulting solution to 10 volumes.

(3) 0.0004% w/v each of *ondansetron impurity E EPCRS* and *ondansetron impurity F EPCRS*.

(4) 0.05% w/v of *ondansetron impurity standard BPCRS*.

(5) 0.005% w/v of *ondansetron impurity A EPCRS* and 0.005% w/v of *ondansetron impurity G EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 216 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile R1* and 80 volumes of 0.02M *sodium dihydrogen orthophosphate* *dihydrate*, previously adjusted to pH 5.4 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to impurity C and D is at least 2.5.

LIMITS

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Identify any peak corresponding to impurity C (the first eluting peak in solution (4)) and multiply the area of this peak by a correction factor of 0.6.

The peaks due to impurity E and impurity F in solution (3) and the peaks due to impurity A and impurity G in solution (5) may co-elute or may invert.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D (the second eluting peak in solution (4)) is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any peak corresponding to impurity C (the first eluting peak in solution (4)) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of the peaks corresponding to impurities E and F is not greater than the area of the corresponding peaks in the chromatogram obtained with solution (3) (0.4%);

the sum of the areas of the peaks corresponding to impurities A and G is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks*, apart from any peaks corresponding to impurity C and impurity D, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the injection to give a solution containing the equivalent of 0.01% w/v of ondansetron.
(2) 0.0125% w/v of *ondansetron hydrochloride dihydrate BPCRS*.
(3) 0.05% w/v of *ondansetron impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and impurity D is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{19}N_3O$ in the injection using the declared content of $C_{18}H_{19}N_3O$ in *ondansetron hydrochloride dihydrate BPCRS*.

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LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ondansetron.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ondansetron Hydrochloride Dihydrate.

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Ondansetron Tablets

General Notices

Action and use

Serotonin $5HT_3$ antagonist; treatment of nausea and vomiting.

DEFINITION

Ondansetron Tablets contain Ondansetron Hydrochloride Dihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ondansetron, $C_{18}H_{19}N_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 30 mg of ondansetron with 20 mL of *acetonitrile*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ondansetron hydrochloride *(RS 419)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes, withdraw a sample of the medium, and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 310 nm, Appendix II B, using *water* in the reference cell.
(2) Measure the *absorbance* of a 0.001% w/v solution of *ondansetron hydrochloride dihydrate BPCRS* using *water* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of ondansetron, $C_{18}H_{19}N_3O$, in the medium from the absorbances obtained and using the declared content of $C_{18}H_{19}N_3O$ in *ondansetron hydrochloride dihydrate BPCRS*.

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LIMITS

The amount of ondansetron released is not less than 75% (Q) of the stated amount.

Impurity B

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in solution A.

Solution A: 0.5 volumes of 13.5M *ammonia*, 100 volumes of *ethanol (96%)* and 100 volumes of *methanol*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 20 mg of ondansetron with 25 mL of *acetonitrile*, filter and evaporate the filtrate to dryness using a rotary evaporator. Dissolve the residue in 2 mL of solution A.

(2) Dilute 1 volume of solution (1) to 50 volumes and dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.25% w/v of *ondansetron for TLC system suitability BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) Remove the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 20 volumes of *methanol*, 25 volumes of *ethyl acetate* and 45 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows 3 clearly separated spots (impurity A, Rf value of about 0.3; impurity B, Rf value of about 0.4; ondansetron, Rf value of about 0.6).

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* corresponding to impurity B is not more intense than the spot in the chromatogram obtained with solution (2) (0.4%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 20 mg of ondansetron with 25 mL of *acetonitrile*, filter and evaporate the filtrate to dryness. Dissolve the residue in 20 mL of mobile phase.

(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(3) 0.0004% w/v each of *ondansetron impurity E EPCRS* and *ondansetron impurity F EPCRS*.

(4) 0.05% w/v of *ondansetron impurity standard BPCRS* (containing impurities C and D) in the mobile phase.

(5) 0.005% w/v of *ondansetron impurity A EPCRS* and 0.005% w/v of *ondansetron impurity G EPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 216 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile R1* and 80 volumes of 0.02M *sodium dihydrogen orthophosphate* *dihydrate*, previously adjusted to pH 5.4 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and impurity D is at least 2.5.

LIMITS

Identify any peak corresponding to impurity C (the first eluting peak in solution (4)) and multiply the area of this peak by a correction factor of 0.6.

The peaks due to impurity E and impurity F in solution (3) and the peaks due to impurity A and impurity G in solution (5) may co-elute or be inverted.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D (the second eluting peak in solution (4)) is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of the peaks corresponding to impurities E and F is not greater than the area of the corresponding peaks in the chromatogram obtained with solution (3) (0.4%);

the sum of the areas of any peaks corresponding to impurities A and G is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* apart from any peaks corresponding to impurity C and impurity D is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

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ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B.

Solution B: Equal volumes of *acetonitrile* and mobile phase.

(1) Mix a quantity of the powdered tablets containing the equivalent of 20 mg of ondansetron and 150 mL of solution B for 30 minutes with the aid of ultrasound, shaking every 5 minutes, and allow to cool. Add sufficient solution B to produce 200 mL and filter.

(2) 0.0125% w/v of *ondansetron hydrochloride dihydrate BPCRS*.

(3) 0.05% w/v of *ondansetron impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (1), the symmetry factor for the peak due to ondansetron is less than 3.0;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and impurity D is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{19}N_3O$ in the tablets using the declared content of $C_{18}H_{19}N_3O$ in *ondansetron hydrochloride dihydrate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ondansetron.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ondansetron Hydrochloride Dihydrate.

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Oral Rehydration Salts

General Notices

Oral Rehydration Oral Powder

Action and use

Prevention and treatment of dehydration.

DEFINITION

Oral Rehydration Salts are *oral powders* containing either Glucose or Glucose Monohydrate, Sodium Chloride, Potassium Chloride and Sodium Citrate or Sodium Bicarbonate. After being dissolved in the requisite volume of Water they are intended for the prevention and treatment of dehydration due to diarrhoea, including maintenance therapy. Oral Rehydration Salts may contain suitable flavouring agents. Where necessary they may also contain suitable flow agents in the minimum quantity required to achieve a satisfactory product.

The composition of one of the formulations in use is described below in terms of the amount in grams to be dissolved in sufficient Water to produce 1000 mL. It is that recommended by the Diarrhoeal Diseases Control Programme of the World Health Organization (WHO) and the United Nations Childrens Fund (UNICEF).

Sodium Chloride	2.6 g
Potassium Chloride	1.5 g
Sodium Citrate	2.9 g
Glucose	13.5 g

The oral powders comply with the requirements stated under Oral Powders and with the following requirements.

Content of potassium, K, sodium, Na, bicarbonate, HCO_3, chloride, Cl, and citrate, $C_6H_5O_7$, as appropriate,

90.0 to 110.0% of the requisite amount, the latter being calculated from the stated amounts of the relevant constituents.

Content of anhydrous glucose, $C_6H_{12}O_6$,

As appropriate 90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. When heated with *cupri-tartaric solution R1* a copious precipitate of copper(I) oxide is produced.

B. Yield reaction B characteristic of *potassium salts*, Appendix VI.

C. Yield reaction A characteristic of *sodium salts*, Appendix VI.

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D. Yield reaction A characteristic of *chlorides*, Appendix VI.

E. For preparations containing Sodium Citrate a quantity of the oral powder containing the equivalent of 50 mg of citric acid yields reactions A and B characteristic of *citrates*, Appendix VI.

F. For preparations containing Sodium Bicarbonate add 2 mL of *hydrochloric acid*. A vigorous effervescence is produced.

ASSAY

Carry out the following assays on the well-mixed contents of an individual sachet or on a suitable sample from the well-mixed contents of a bulk container. Where the amount in an individual sachet is insufficient to carry out all the assays, thoroughly mix the contents of sufficient sachets to provide enough material for all of the assays.

For the Assays for potassium, for sodium, for chloride and for bicarbonate dissolve 8 g in sufficient *water* to produce 500 mL (solution A).

For potassium

Dilute a suitable volume of solution A with a solution of *strontium chloride* such that there is a 1500- to 2000-fold excess of strontium ions in the final solution and determine by Method I for *atomic emission spectrophotometry*, Appendix II D, measuring at 767 nm. Use *potassium standard solution* (*600 ppm K*), suitably diluted with the strontium chloride solution, for the standard solutions. Each mg of Potassium Chloride is equivalent to 0.5245 mg of K.

For sodium

Dilute a suitable volume of solution A with a solution of *strontium chloride* such that there is a 1500- to 2000-fold excess of strontium ions in the final solution and determine by Method I for *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm. Use *sodium standard solution* (*200 ppm Na*), suitably diluted with the strontium chloride solution, for the standard solutions. Each mg of Sodium Chloride, of Sodium Bicarbonate and of Sodium Citrate is equivalent to 0.3934, 0.2737 and 0.2345 mg of Na respectively.

For chloride

Titrate a suitable volume (50 mL for the formula stated above) of solution A with *0.1M silver nitrate VS* using a 5% w/v solution of *potassium chromate* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 3.545 mg of Cl. Each mg of Potassium Chloride and of Sodium Chloride is equivalent to 0.4756 mg and 0.6066 mg of Cl respectively.

For citrate

Disperse 2.8 g in 80 mL of *anhydrous acetic acid*, heat to about 50°, cool, dilute to 100 mL with *anhydrous acetic acid*, allow to stand for 10 minutes and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 20 mL of the supernatant liquid and *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 6.303 mg of $C_6H_5O_7$. Each mg of Sodium Citrate is equivalent to 0.6430 mg of $C_6H_5O_7$.

For bicarbonate

Titrate 200 mL of solution A with *0.1M hydrochloric acid VS* using *methyl orange solution* as indicator. Each mL of *0.1M hydrochloric acid VS* is equivalent to 6.101 mg of HCO_3. Each mg of Sodium Bicarbonate is equivalent to 0.7263 mg of HCO_3.

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For glucose

Dissolve 7.5 g in 40 mL of *water*, add 0.5 mL of 1M *ammonia*, dilute to 50 mL with *water*, mix well and allow to stand for not less than 5 hours. If necessary use a suitable method of filtration to obtain a clear solution. Determine the *optical rotation* of the solution, Appendix V F. The observed rotation in degrees multiplied by 0.9477 represents the weight, in g, of $C_6H_{12}O_6$ in the weight taken for the Assay.

STORAGE

Oral Rehydration Salts should be protected from moisture. They should be kept in sachets, preferably made of aluminium foil, containing sufficient for a single dose or for a single day's treatment. Powders for use in hospitals may be presented in bulk containers containing sufficient to produce a volume of solution appropriate to the daily requirements of the establishment concerned.

LABELLING

The label states (1) for sachets the total weights, in grams, of each of the constituents; (2) for bulk containers the weights, in grams, of each of the constituents in a stated quantity, in grams, of the oral powder.

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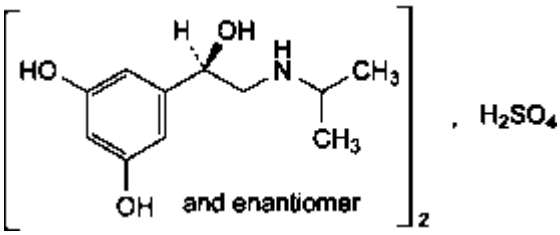
Orciprenaline Sulfate

General Notices

Orciprenaline Sulphate

(Ph. Eur. monograph 1033)



$C_{22}H_{36}N_2O_{10}S$ 520.6 *5874-97-5*

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

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DEFINITION

Bis[5-[(1*RS*)-1-hydroxy-2-[(1-methylethyl)amino]ethyl]benzene-1,3-diol] sulfate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, E.

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Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in a 0.04 per cent *V/V* solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution. Dilute 5.0 mL of this solution to 50.0 mL with a 0.04 per cent *V/V* solution of *hydrochloric acid R*.

Spectral range 240-350 nm.

Absorption maximum At 278 nm.

Specific absorbance at the absorption maximum 68.5 to 76.0 (anhydrous substance).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *orciprenaline sulfate CRS*.

If the spectra obtained show differences, dissolve separately, with heating, 50 mg of the substance to be examined and 50 mg of the reference substance, in the minimum volume of *water R*. Add 10 mL of *acetone R* and centrifuge. Dry the precipitates at 40 °C under reduced pressure for 3 h and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *orciprenaline sulfate CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *orciprenaline sulfate CRS* and 10 mg of *salbutamol CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ammonia R*, *water R*, *aldehyde-free methanol R* (1.5:10:90 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 10 g/L solution of *potassium permanganate R*.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

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D. Dissolve about 20 mg in 2 mL of *ethanol (96 per cent) R*. Add 2 mL of a 1 g/L solution of *dichloroquinonechlorimide R* in *ethanol (96 per cent) R* and 1 mL of *sodium carbonate solution R*. A violet colour is produced, turning to brown.

E. It gives reaction (a) of sulfates (*2.3.1*).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.0 to 5.5 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *orciprenaline for system suitability CRS* (containing impurities A and B) in 2.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Dissolve 9.1 g of *potassium dihydrogen phosphate R* and 4.6 g of *sodium octanesulfonate R* in *water R*, adjust to pH 4.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*. Add 140 mL of *acetonitrile R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Run time Twice the retention time of orciprenaline.

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Identification of impurities Use the chromatogram supplied with *orciprenaline for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to orciprenaline (retention time = about 7 min): impurity A = about 0.9; impurity B = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and orciprenaline.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.3;

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Phenone

Maximum 0.1 per cent.

Dissolve 0.50 g in a 0.04 per cent *V/V* solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution. The absorbance (*2.2.25*) of the solution measured at 328 nm is not greater than 0.16.

Iron (*2.4.9*)

Maximum 20 ppm.

The residue obtained in the test for sulfated ash complies with the test. Prepare the reference solution using *iron standard solution (2 ppm Fe) R*.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 5 mL of *anhydrous formic acid R* and add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* using 0.1 mL of *crystal violet solution R* as indicator.

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1 mL of *0.1 M perchloric acid* is equivalent to 52.06 mg of $C_{22}H_{36}N_2O_{10}S$.

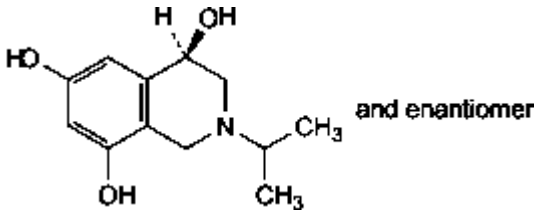
STORAGE

In an airtight container, protected from light.

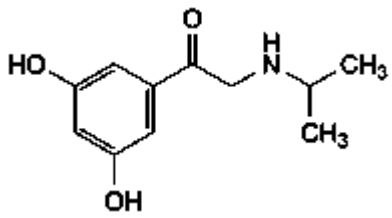
IMPURITIES

Specified impurities A, B.

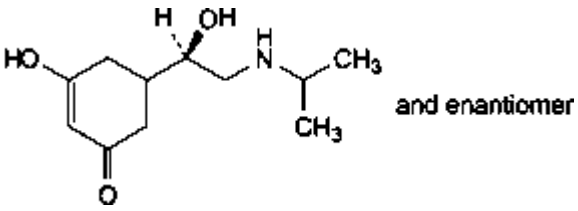
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. (4*RS*)-2-(1-methylethyl)-1,2,3,4-tetrahydroisoquinoline-4,6,8-triol,



B. 1-(3,5-dihydroxyphenyl)-2-[(1-methylethyl)amino]ethanone,



C. 3-hydroxy-5-[(1*RS*)-1-hydroxy-2-[(1-methylethyl)amino]ethyl]cyclohex-2-enone.

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Organ Preservation Solutions

General Notices

(Solutions for Organ Preservation, Ph. Eur. monograph 1264)

Ph Eur

DEFINITION

Solutions for organ preservation are sterile, aqueous preparations intended for the storage, protection and/or perfusion of mammalian body organs, particularly pending transplantation.

They contain electrolytes, typically in concentrations close to the intracellular electrolyte composition.

They may contain carbohydrates (such as glucose or mannitol), amino acids, calcium-complexing agents (such as citrate or phosphate), hydrocolloids (such as starch or gelatin derivatives) and other suitable excipients, in order, for example, to adjust the tonicity of the preparation relative to blood, to adjust or stabilise the pH or to stabilise the preparation. The excipients do not adversely affect the intended action of the preparation or, at the concentrations used, cause toxicity or undue local irritation. Solutions for organ preservation may also contain active substances or these may be added immediately before use.

Solutions for organ preservation, examined under suitable conditions of visibility, are clear and practically free from particles.

Solutions for organ preservation may also be supplied as concentrated solutions to be diluted to the prescribed volume with a prescribed liquid immediately before use. After dilution, they comply with the requirements for solutions for organ preservation.

Before use, solutions for organ preservation are cooled, typically to 2 °C to 6 °C, to lower the temperature of the organ and slow its metabolism.

Where applicable, containers for solutions for organ preservation comply with the requirements for *Materials used for the manufacture of containers* (*3.1* and subsections) and *Containers* (*3.2* and subsections).

Solutions for organ preservation are supplied in glass containers (*3.2.1*) or in other containers such as plastic containers (*3.2.2*) and prefilled syringes. The tightness of the container is ensured by suitable means. Closures ensure a good seal, prevent micro-organisms and other contaminants from entering the container and closure system and usually permit the withdrawal of part or all of the contents without removal of the closure. The plastic materials or elastomers (*3.2.9*) of which the closures are composed are sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles.

PRODUCTION

Solutions for organ preservation are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms; recommendations on this aspect are provided in general chapter *5.1.1*. *Methods of preparation of sterile products*.

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Unless otherwise justified and authorised, solutions for organ preservation are prepared from *water for injections R* and do not contain preservatives.

TESTS

pH (*2.2.3*)

5.0 to 8.0.

Osmolality (*2.2.35*)

250 mosmol/kg to 380 mosmol/kg.

Hydroxymethylfurfural

If the solution contains glucose, it complies with the following test. To a volume of the preparation to be examined containing the equivalent of 25 mg of glucose, add 5.0 mL of a 100 g/L solution of *p-toluidine R* in *2-propanol R* containing 10 per cent *V/V* of *glacial acetic acid R* and then add 1.0 mL of a 5 g/L solution of *barbituric acid R*. The absorbance (*2.2.25*), determined at 550 nm after allowing the mixture to stand for 2 min to 3 min, is not greater than that of a standard prepared at the same time and in the same manner using a solution containing 10 µg of *hydroxymethylfurfural R* in the same volume as the preparation to be examined.

Particulate contamination: sub-visible particles (*2.9.19*)

Use 50 mL of the preparation to be examined. The solution contains not more than 50 particles per millilitre larger than 10 µm in size and not more than 5 particles per millilitre larger than 25 µm.

Products whose labels state that the product is to be used with a final filter are exempted from these requirements.

Sterility (*2.6.1*)

The preparation complies with the test.

Bacterial endotoxins (*2.6.14*)

Less than 0.5 IU/mL.

Pyrogens (*2.6.8*)

Preparations for which a validated test for bacterial endotoxins cannot be carried out comply with the test for pyrogens. Inject 10 mL of the preparation per kilogram of the rabbit's mass, unless otherwise justified and authorised.

LABELLING

The label states:

— that the solution is not to be used for injection;

— the formula of the solution for organ preservation, expressed in grams per litre and in millimoles per litre;

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— the nominal volume of the solution for organ preservation in the container;

— the osmolality, expressed in milliosmoles per kilogram;

— that any unused portion of the ready-to-use solution, of the concentrated solution or of the diluted solution is to be discarded;

— the storage conditions;

— where applicable, that the solution is to be used in conjunction with a final filter;

— for concentrated solutions, that the solution is to be diluted with a suitable liquid immediately before use.

Ph Eur

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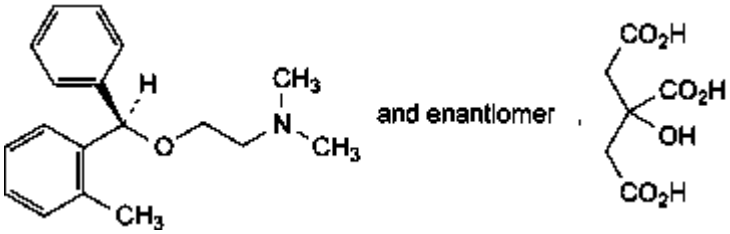
Orphenadrine Citrate

General Notices

(Ph. Eur. monograph 1759)



$C_{24}H_{31}NO_8$ 461.5 *4682-36-4*

Action and use

Anticholinergic.

Ph Eur

DEFINITION

(*RS*)-*N*,*N*-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent).

mp

About 137 °C.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison orphenadrine citrate CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 436 nm has a maximum of 0.050.

Dissolve 1.0 g in a 3.6 per cent *V/V* solution of hydrochloric acid R in ethanol (96 per cent) R and dilute to 10.0 mL with the same acid solution.

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Dissolve 0.500 g of the substance to be examined in water R and dilute to 50 mL with the same solvent. Add 2 mL of concentrated ammonia R and shake with 3 quantities, each of 10 mL, of toluene R. To the combined upper layers add anhydrous sodium sulfate R, shake, filter and evaporate the filtrate by suitable means, at a temperature not exceeding 50 °C. Take up the residue with toluene R and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 30 mg of orphenadrine citrate CRS and 30 mg of orphenadrine impurity E CRS in 20 mL of water R. Add 1 mL of concentrated ammonia R and shake with 3 quantities, each of 5 mL, of toluene R. To the combined upper layers add anhydrous sodium sulfate R, shake, filter and evaporate the filtrate by suitable means, at a temperature not exceeding 50 °C. Take up the residue with toluene R and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dissolve the contents of a vial of orphenadrine for peak identification CRS (containing impurities A, B, C, D and F) in 1.0 mL of toluene R.

Column:

— *size*: *l* = 60 m, Ø = 0.32 mm;

— *stationary phase*: phenyl(5)methyl(95)polysiloxane R (film thickness 1.0 µm).

Carrier gas helium for chromatography R.

Flow rate 1 mL/min.

Split ratio 1:25.

Temperature:

— *column*: 240 °C;

— *injection port and detector*: 290 °C.

Detection Flame ionisation.

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Injection 2 µL.

Run time 1.3 times the retention time of orphenadrine.

Identification of impurities Use the chromatogram supplied with *orphenadrine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and F. Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention With reference to orphenadrine (retention time = about 13 min): impurity B = about 0.5; impurity A = about 0.6; impurity D = about 0.8; impurity C = about 0.9; impurity E = about 0.98; impurity F = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum of 1.5 between the peaks due to impurity E and orphenadrine.

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, not more than 0.3 per cent;

— *unspecified impurities*: for each impurity, not more than 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *disregard limit*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 46.15 mg of $C_{24}H_{31}NO_8$.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container, protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*

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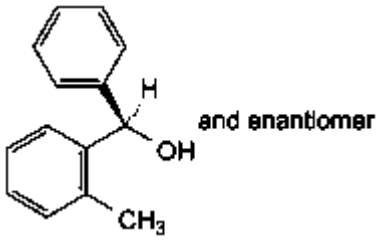
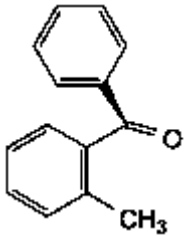
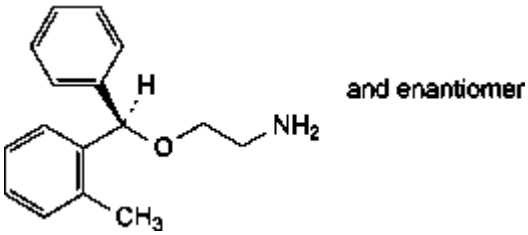


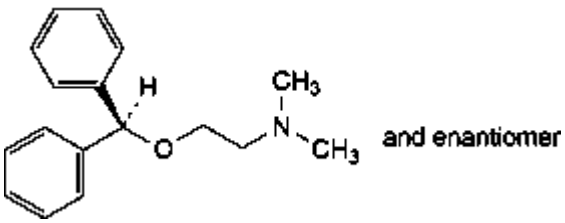
A. (*RS*)-(2-methylphenyl)phenylmethanol (2-methylbenzhydrol),



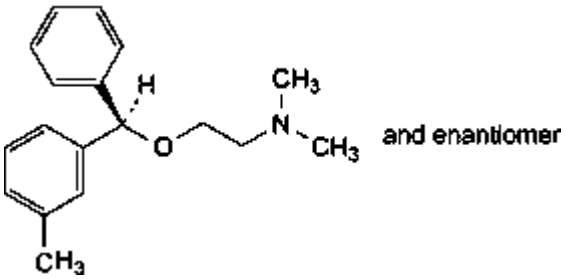
B. (2-methylphenyl)phenylmethanone (2-methylbenzophenone),



C. (*RS*)-2-[(2-methylphenyl)phenylmethoxy]ethanamine,



D. 2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine (diphenhydramine),



E. (*RS*)-*N*,*N*-dimethyl-2-[(3-methylphenyl)phenylmethoxy]ethanamine (*meta*-methylbenzyl isomer),

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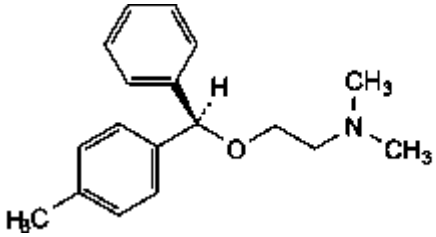

and enantiomer

F. (*RS*)-*N*,*N*-dimethyl-2-[(4-methylphenyl)phenylmethoxy]ethanamine (*para*-methylbenzyl isomer).

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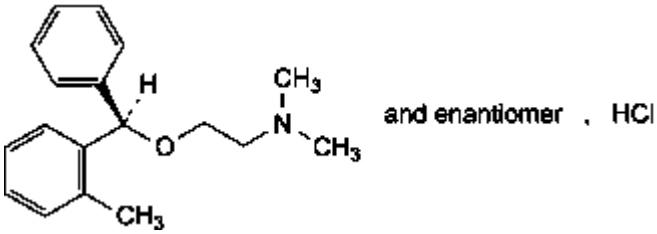
Orphenadrine Hydrochloride

General Notices

(Ph. Eur. monograph 1760)



$C_{18}H_{24}ClNO$ 305.9 *341-69-5*

Action and use

Anticholinergic.

Preparation

Orphenadrine Hydrochloride Tablets

Ph Eur

DEFINITION

(*RS*)-*N,N*-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

mp

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About 160 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *orphenadrine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 436 nm has a maximum of 0.050.

Dissolve 0.70 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Dissolve 0.300 g of the substance to be examined in *water R* and dilute to 50 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 10 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate by suitable means, at a temperature not exceeding 50 °C. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *orphenadrine hydrochloride CRS* and 20 mg of *orphenadrine impurity E CRS* in 20 mL of *water R*. Add 1 mL of *concentrated ammonia R* and shake with 3 quantities, each of 5 mL, of *toluene R*. To the combined upper layers add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate by suitable means, at a temperature not exceeding 50 °C. Take up the residue with *toluene R* and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dissolve the contents of a vial of *orphenadrine for peak identification CRS* (containing impurities A, B, C, D and F) in 1.0 mL of *toluene R*.

Column:

— *size*: *l* = 60 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 1.0 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:25.

Temperature:

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— *column*: 240 °C;

— *injection port and detector*: 290 °C.

Detection Flame ionisation.

Injection 2 µL.

Run time 1.3 times the retention time of orphenadrine.

Identification of impurities Use the chromatogram supplied with *orphenadrine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and F. Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention With reference to orphenadrine (retention time = about 13 min): impurity B = about 0.5; impurity A = about 0.6; impurity D = about 0.8; impurity C = about 0.9; impurity E = about 0.98; impurity F = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity E and orphenadrine.

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, not more than 0.3 per cent;

— *unspecified impurities*: for each impurity, not more than 0.10 per cent;

— *total*: not more than 1.0 per cent;

— *disregard limit*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 30.59 mg of $C_{18}H_{24}ClNO$.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container, protected from light.

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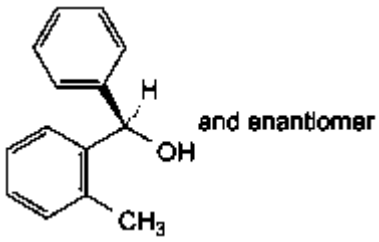
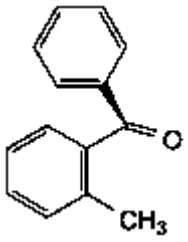
IMPURITIES

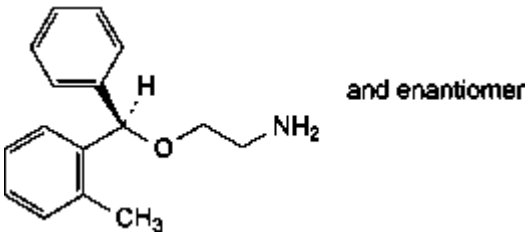
Specified impurities *A, B, C, D, E, F.*



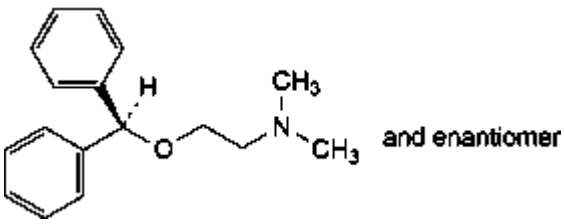
A. (*RS*)-(2-methylphenyl)phenylmethanol (2-methylbenzhydrol),



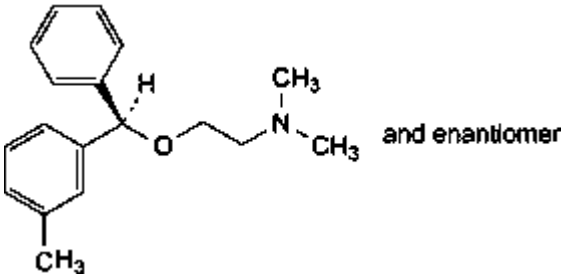
B. (2-methylphenyl)phenylmethanone (2-methylbenzophenone),



C. (*RS*)-2-[(2-methylphenyl)phenylmethoxy]ethanamine,



D. 2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine (diphenhydramine),



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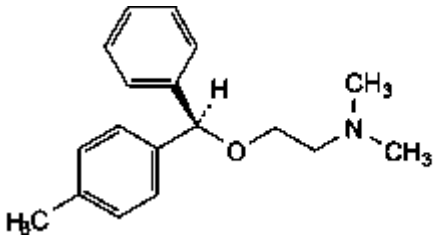
E. (*RS*)-*N*,*N*-dimethyl-2-[(3-methylphenyl)phenylmethoxy]ethanamine (*meta*-methylbenzyl isomer),



and enantiomer

F. (*RS*)-*N*,*N*-dimethyl-2-[(4-methylphenyl)phenylmethoxy]ethanamine (*para*-methylbenzyl isomer).

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Orphenadrine Hydrochloride Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Orphenadrine Hydrochloride Tablets contain Orphenadrine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of orphenadrine hydrochloride, $C_{18}H_{23}NO,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.15 g of Orphenadrine Hydrochloride with *chloroform*, filter and evaporate the filtrate to dryness. The residue complies with the following tests.

A. Dissolve 5 mg in 2 mL of *sulfuric acid*. An orange-red colour is produced.

B. Dissolve 50 mg in 10 mL of *ethanol* (*50%*), add 10 mL of *picric acid solution R1* and allow to stand. The *melting point* of the precipitate, after recrystallisation from *ethanol* (*96%*), is about 89° or about 107°, Appendix V A.

C. Yields reaction A characteristic of *chlorides*, Appendix VI.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 70 mg of Orphenadrine Hydrochloride as completely as possible in a mixture of 5 mL of *water* and 5 mL of *2M hydrochloric acid*. Without delay extract with four 15 mL quantities of *chloroform*, filter the combined extracts and evaporate to about 20 mL. Carry out Method I for *non-aqueous titration*, Appendix VIII A, using *0.02M perchloric acid VS*, adding 2 mL of *mercury(II) acetate solution* and determining the end point potentiometrically. Each mL of *0.02M perchloric acid VS* is equivalent to 6.118 mg of $C_{18}H_{23}NO,HCl$.

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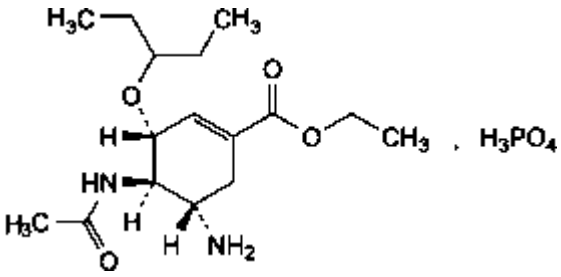
Oseltamivir Phosphate

General Notices

(Ph. Eur. monograph 2422)



$C_{16}H_{31}N_2O_8P$ 410.4 *204255-11-8*

Action and use

Treatment of influenza.

Preparation

Paediatric Oseltamivir Oral Solution

Ph Eur

DEFINITION

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylate phosphate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in methylene chloride.

It shows polymorphism (*5.9*).

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IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *oseltamivir phosphate (impurity B-free) CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Dissolve 200 mg in 10 mL of *water R*. It gives reaction (b) of phosphates (2.3.1).

TESTS

Specific optical rotation (2.2.7)

-30.7 to -32.6 (anhydrous substance), measured at 25 °C.

Dissolve 0.50 g in *water R* and dilute to 50.0 mL with the same solvent.

Impurity B

Liquid chromatography (2.2.29) coupled with mass spectrometry (2.2.43).

Test solution Dissolve 0.100 g of the substance to be examined in *water for chromatography R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2.5 mg of *oseltamivir impurity B CRS* in 5.0 mL of *anhydrous ethanol R* and dilute to 50.0 mL with *water for chromatography R*. Dilute 2.0 mL of the solution to 100.0 mL with *water for chromatography R*.

Reference solution (b) Dissolve 50.0 mg of *oseltamivir phosphate (impurity B-free) CRS* in reference solution (a) and dilute to 5.0 mL with the same solution.

Column:

— *size*: *l* = 0.05 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 10 volumes of a 1.54 g/L solution of *ammonium acetate R* in *water for chromatography R*, 30 volumes of *acetonitrile R1* and 60 volumes of *water for chromatography R*.

Flow rate 1.5 mL/min.

Post-column split ratio Use a split ratio suitable for the mass detector (e.g. 1:3).

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Detection:

— mass detector: the following settings have been found to be suitable and are given as examples; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criterion:

— ionisation: ESI-positive;

— detection *m/z*: 356.2;

— dwell: 580 ms;

— gain EMV: 1;

— fragmentator voltage: 120 V;

— gas temperature: 350 °C;

— drying gas flow: 13 L/min,

— nebuliser pressure: 345 kPa;

— capillary voltage (Vcap): 3 kV.

Injection 1 µL of the test solution and reference solution (b).

Run time 3 min.

System suitability Reference solution (b):

— *repeatability*: maximum relative standard deviation of 15 per cent determined on 6 injections.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (100 ppm).

Impurity H

Gas chromatography (*2.2.28*).

Silylation reagent Mix 1.0 mL of *chlorotrimethylsilane R*, 2.0 mL of *hexamethyldisilazane R* and 10.0 mL of *anhydrous pyridine R*.

Test solution Introduce 15.0 mg of the substance to be examined into a 2 mL vial and add 1.0 mL of the silylation reagent. Close the vial, shake and heat at 60 °C for 20 min. Centrifuge and discard the precipitate.

Reference solution Introduce 15.0 mg of *oseltamivir impurity H CRS* into a 2 mL vial and add 1.0 mL of *anhydrous pyridine R*. Close the vial and shake (solution A). (Note: impurity H is hygroscopic.) Introduce 15.0 mg of the substance to be examined into another 2 mL vial and add 1.0 mL of the silylation reagent. Close the vial, shake and heat at 60 °C for 20 min. Centrifuge and discard the precipitate (solution B). Introduce 10.0 µL of solution A and 10.0 µL of solution B into a volumetric flask and dilute to 10.0 mL with *anhydrous pyridine R*.

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Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.2 mL/min.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	180
	2 - 11	180 → 250
	11 - 21	250
Injection port		260
Detector		260

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to oseltamivir phosphate (retention time = about 10 min): impurity H = about 0.5.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 5 per cent for the peak due to impurity H after 6 injections.

Limit:

— *impurity H*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.15 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R1*, *methanol R2*, *water for chromatography R* (135:245:620 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *oseltamivir impurity A CRS* and 5.0 mg of *oseltamivir impurity C CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *oseltamivir phosphate (impurity B-free) CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase Mix 135 volumes of *acetonitrile R1*, 245 volumes of *methanol R2* and 620 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* in *water for chromatography R*, adjusted to pH 6.0 with a 1 M potassium hydroxide solution prepared from *potassium hydroxide R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 207 nm.

Injection 15 µL of the test solution and reference solutions (a) and (b).

Run time Twice the retention time of oseltamivir phosphate.

Relative retention With reference to oseltamivir phosphate (retention time = about 17 min): impurity A = about 0.16; impurity C = about 0.17.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and C.

Limits:

— *impurity C*: not more than 0.3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

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Maximum 0.5 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{16}H_{31}N_2O_8P$ from the declared content of *oseltamivir phosphate (impurity B-free) CRS*.

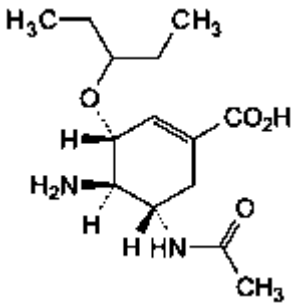
STORAGE

Protected from light.

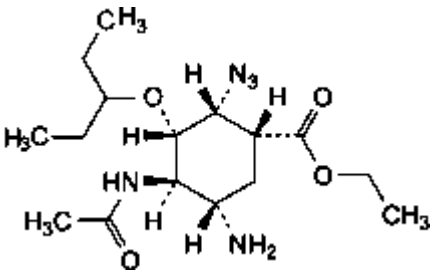
IMPURITIES

Specified impurities *B, C, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, F, G.*



A. (3*R*,4*R*,5*S*)-5-acetamido-4-amino-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylic acid,



B. ethyl (1*R*,2*R*,3*S*,4*R*,5*S*)-4-acetamido-5-amino-2-azido-3(1-ethylpropoxy)cyclohexanecarboxylate,

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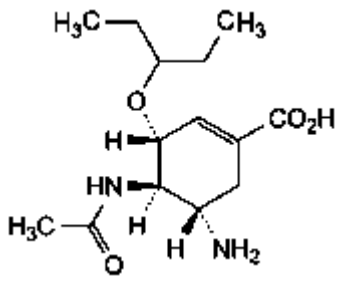
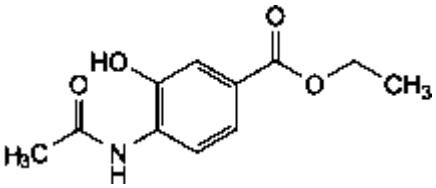
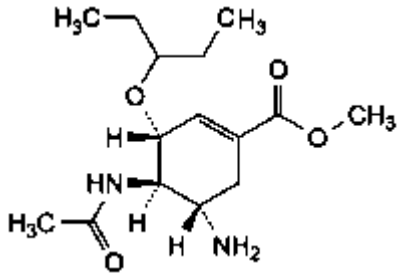


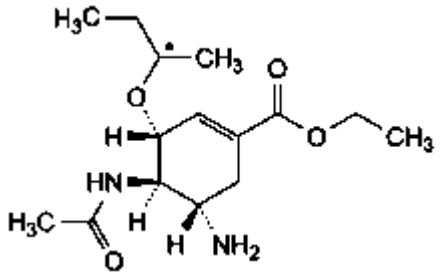
C. (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylic acid,



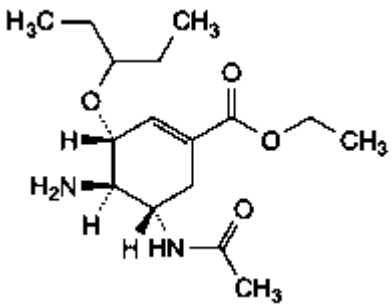
D. ethyl 4-acetamido-3-hydroxybenzoate,



E. methyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylate,



F. ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-methylpropoxy)cyclohex-1-ene-1-carboxylate,



G. ethyl (3*R*,4*R*,5*S*)-5-acetamido-4-amino-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylate,

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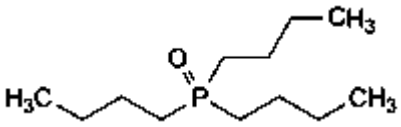

H. tributylphosphane oxide.

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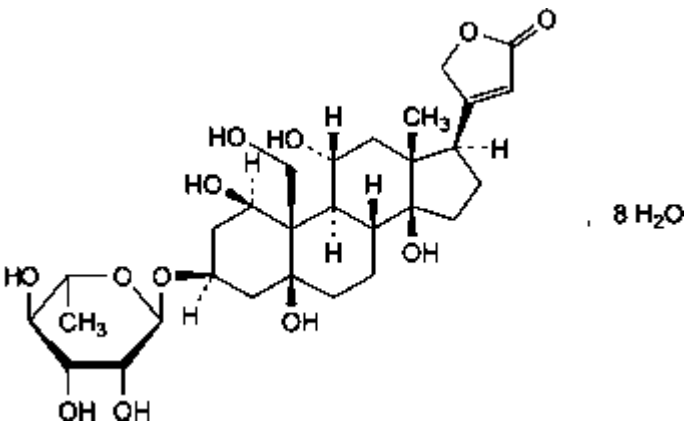
Ouabain

General Notices

(Ph. Eur. monograph 0048)



$C_{29}H_{44}O_{12},8H_2O$ 729 *11018-89-6*

Ph Eur

DEFINITION

3β-[(6-Deoxy-α-L-mannopyranosyl)oxy]-1β,5,11α,14,19-pentahydroxy-5β,14β-card-20(22)-enolide octahydrate.

Content

96.0 per cent to 104.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Sparingly soluble in water and in anhydrous ethanol, practically insoluble in ethyl acetate.

IDENTIFICATION

A. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the spot in the chromatogram obtained with reference solution (a).

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B. Dissolve 2 mg to 3 mg in 2 mL of *sulfuric acid R*; a pink colour develops which quickly changes to red. The solution shows green fluorescence in ultraviolet light.

C. Dissolve about 1 mg in 1 mL of *dinitrobenzene solution R* and add 0.2 mL of *dilute sodium hydroxide solution R*. An intense blue colour develops.

D. Dissolve 0.1 g in 5 mL of a 150 g/L solution of *sulfuric acid R* and boil for a few minutes. The solution becomes yellow and turbid. Filter and add to the filtrate 5 mL of a 120 g/L solution of *sodium hydroxide R* and 3 mL of *cupri-tartaric solution R*. Heat. A red precipitate is formed.

TESTS

Solution S

Dissolve 0.20 g in 15 mL of *water R*, heating on a water-bath. Allow to cool and dilute to 20.0 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

-33 to -30 (anhydrous substance), determined on solution S.

Related substances

Thin-layer chromatography (*2.2.27*).

Solvent mixture *water R*, *chloroform R*, *methanol R* (16:50:50 *V*/*V*/*V*).

Test solution Dissolve a quantity of the substance to be examined corresponding to 20 mg of the anhydrous substance in 1.0 mL of the solvent mixture.

Reference solution (a) Dissolve a quantity of *ouabain CRS* corresponding to 20 mg of the anhydrous substance in 1.0 mL of the solvent mixture.

Reference solution (b) Dissolve a quantity of *ouabain CRS* corresponding to 10 mg of the anhydrous substance in the solvent mixture and dilute to 25 mL with the solvent mixture.

Reference solution (c) Dilute 2.5 mL of reference solution (b) to 10 mL with the solvent mixture.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *dimethyl sulfoxide R*, *methanol R*, *chloroform R* (4:15:15:70 *V*/*V*/*V*/*V*); homogenise the mixture before use.

Application 5 µL.

Development Over a path of 13 cm.

Drying Immediately at 140 °C for 30 min in a ventilated oven.

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Detection Allow to cool, spray with *alcoholic solution of sulfuric acid R* and heat at 140 °C for 15 min.

System suitability:

— the principal spot in the chromatogram obtained with the test solution and the principal spot in the chromatogram obtained with reference solution (a) migrate over a distance sufficient to give unequivocal separation of the secondary spots;

— the chromatogram obtained with reference solution (c) shows a clearly visible spot.

Limit:

— *any impurity*: any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (2.0 per cent).

Alkaloids and strophanthin-K

To 5.0 mL of solution S add 0.5 mL of a 100 g/L solution of *tannic acid R*. No precipitate is formed.

Water (*2.5.12*)

18.0 per cent to 22.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Test solution Dissolve 40.0 mg in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*.

Reference solution Dissolve 40.0 mg of *ouabain CRS* in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*.

To 5.0 mL of each solution add 3.0 mL of *alkaline sodium picrate solution R*, allow to stand protected from bright light for 30 min and measure the absorbance (*2.2.25*) of both solutions at the absorption maximum at 495 nm using as the compensation liquid a mixture of 3.0 mL of *alkaline sodium picrate solution R* and 5.0 mL of *ethanol (96 per cent) R* prepared at the same time.

Calculate the percentage content of $C_{29}H_{44}O_{12}$ from the absorbances measured and the concentrations of the solutions.

STORAGE

Protected from light.

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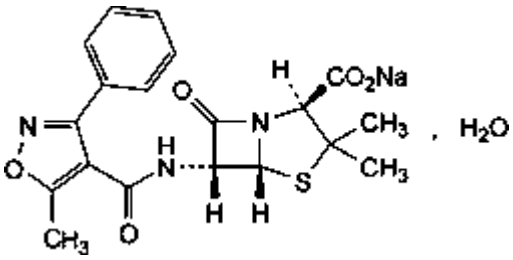
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Oxacillin Sodium Monohydrate

General Notices

(Ph. Eur. Monograph 2260)



$C_{19}H_{18}N_3NaO_5S,H_2O$ 441.4 *7240-38-2*

Action and use

Penicillin antibacterial.

Ph Eur

DEFINITION

Sodium (2*S*,5*R*,6*R*)-3,3-dimethyl-6-[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, soluble in methanol, practically insoluble in methylene chloride.

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *oxacillin sodium monohydrate CRS*.

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 430 nm is not greater than 0.10.

Dissolve 2.50 g in *water R* and dilute to 25.0 mL with the same solvent.

pH (2.2.3)

4.5 to 7.5.

Dissolve 0.30 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 196 to + 212 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *oxacillin sodium monohydrate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of test solution (b) to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *cloxacillin sodium CRS* (impurity E) and 5 mg of *oxacillin sodium monohydrate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (d) In order to prepare impurities B and D *in situ*, dissolve 25 mg of the substance to be examined in 1 mL of *0.05 M sodium hydroxide*, allow to stand for 3 min, then dilute to 100 mL with the mobile phase. Inject immediately.

Reference solution (e) Dissolve 5 mg of *oxacillin for peak identification CRS* (containing impurities E, F, G, I and J) in 5 mL of the mobile phase.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 25 volumes of *acetonitrile R* and 75 volumes of a 2.7 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *dilute sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c), (d) and (e).

Run time 7 times the retention time of oxacillin.

Identification of impurities:

— in the chromatogram obtained with reference solution (d), the 2 principal peaks eluting before the main peak are due to impurities B and D respectively;

— use the chromatogram supplied with *oxacillin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities E, F, G, I and J.

Relative retention With reference to oxacillin (retention time = about 5 min): impurity A = about 0.3; impurity B (isomer 1) = about 0.4; impurity B (isomer 2) = about 0.5; impurity C = about 0.65; impurity D (2 epimers) = about 0.9; impurity E = about 1.5; impurity F = about 1.9; impurity G = about 2.1; impurity I = about 3.8; impurity J = about 5.8.

System suitability:

— *resolution*: minimum 2.5 between the peaks due to oxacillin and impurity E in the chromatogram obtained with reference solution (c);

— the chromatogram obtained with reference solution (e) is similar to the chromatogram supplied with *oxacillin for peak identification CRS*.

Limits:

— *impurity B*: for the sum of the areas of the 2 isomer peaks, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurities D (sum of the 2 epimers), F, G, I, J*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

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— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Ethyl acetate and butyl acetate

Head-space gas chromatography (2.2.28).

Test solution Dissolve 0.200 g of the substance to be examined in 6.0 mL of *water R*.

Reference solution Dissolve 83 mg of *butyl acetate R* and 83 mg of *ethyl acetate R* in *water R* and dilute to 250.0 mL with the same solvent. Use 6.0 mL of this solution.

Close the vials immediately with a rubber membrane stopper coated with polytetrafluoroethylene and secured with an aluminium crimp cap. Mix to obtain a homogeneous solution.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2 mL/min.

Static head-space conditions that may be used:

— *equilibration temperature*: 80 °C;

— *equilibration time*: 60 min;

— *transfer-line temperature*: 140 °C;

— *pressurisation time*: 30 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	70
	6 - 16	70 → 220
	16 - 18	220
Injection port		140

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	Time (min)	Temperature (°C)
Detector		250

Detection Flame ionisation.

Retention time Ethyl acetate = about 10 min; butyl acetate = about 15.5 min.

Limits:

— *butyl acetate*: maximum 1.0 per cent;

— *ethyl acetate*: maximum 1.0 per cent.

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.8 per cent.

Water (*2.5.12*)

3.5 per cent to 5.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.20 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{19}H_{18}N_3NaO_5S$ taking into account the assigned content of *oxacillin sodium monohydrate CRS*.

IMPURITIES

Specified impurities *B, D, E, F, G, I, J.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*

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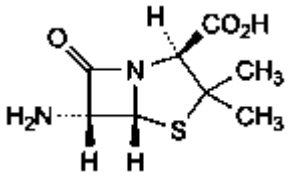
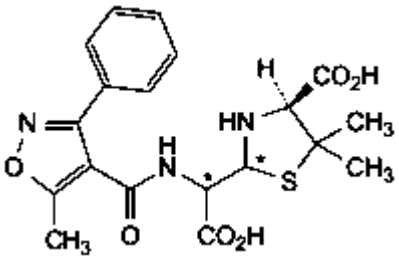
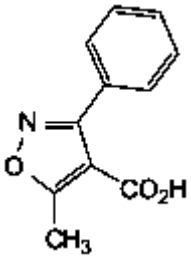


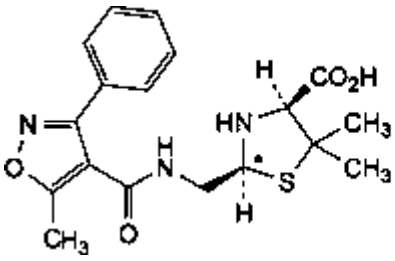
A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



B. (4*S*)-2-[carboxy[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of oxacillin),

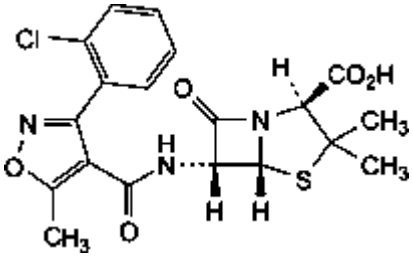


C. 5-methyl-3-phenylisoxazole-4-carboxylic acid,



and epimer at C*

D. (2*RS*,4*S*)-5,5-dimethyl-2-[[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]methyl]thiazolidine-4-carboxylic acid (penilloic acids of oxacillin),



E. (2*S*,5*R*,6*R*)-6-[[[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (cloxacillin),

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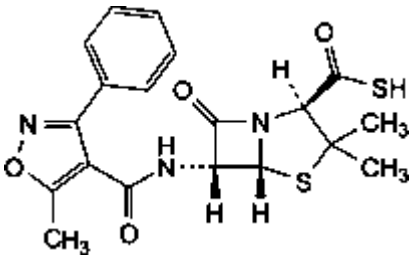
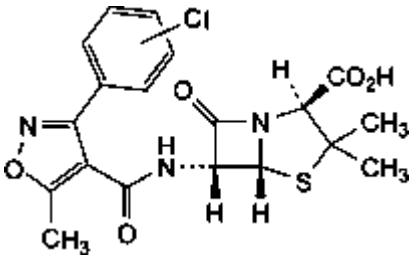
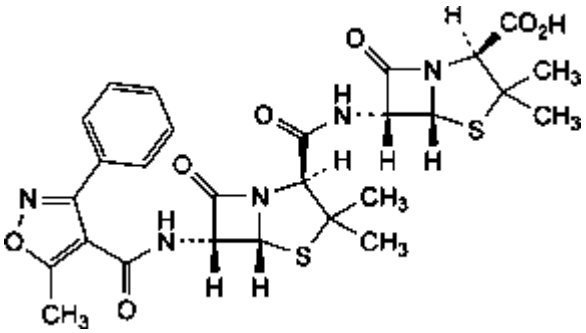


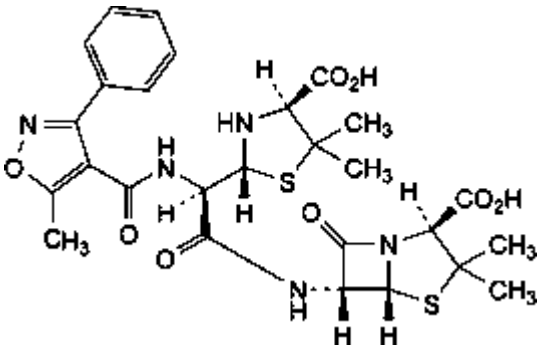
F. (2*R*,5*R*,6*R*)-3,3-dimethyl-6-[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carbothioic acid (thiooxacillin),



G. (2*S*,5*R*,6*R*)-6-[[[3-(chlorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (cloxacillin isomer),



I. (2*S*,5*R*,6*R*)-6-[[(2*S*,5*R*,6*R*)-3,3-dimethyl-6-[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-APA oxacillin amide),



J. (2*S*,5*R*,6*R*)-6-[[(2*R*)-[(2*R*,4*S*)-4-carboxy-5,5-dimethylthiazolidin-2-yl][[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (ozolamide of 6-APA dimer).

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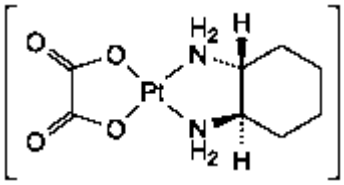
Oxaliplatin

General Notices

(Ph. Eur. monograph 2017)



$C_8H_{14}N_2O_4Pt$ 397.3 *61825-94-3*

Action and use

Platinum-containing cytotoxic.

Ph Eur

DEFINITION

(*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ^2*N*,*N*′][ethanedioato-κ^2*O*,*O*′(2-)]platinum.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, very slightly soluble in methanol, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *oxaliplatin CRS*.

B. Specific optical rotation (see Tests).

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TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.10 g in *water R* and dilute to 50 mL with the same solvent.

Acidity

Dissolve 0.10 g in *carbon dioxide-free water R*, dilute to 50 mL with the same solvent and add 0.5 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.60 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*)

+ 74.5 to + 78.0 (dried substance).

Dissolve 0.250 g in *water R* and dilute to 50.0 mL with the same solvent.

Impurity D

Liquid chromatography (*2.2.29*).

Test solution Dissolve 30 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *oxaliplatin impurity D CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 15.0 mL of reference solution (a) to 50.0 mL with *methanol R*.

Reference solution (c) Dissolve 75 mg of the substance to be examined in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (d) Dilute 5.0 mL of reference solution (c) to 100.0 mL with *methanol R*.

Reference solution (e) To 40 mL of reference solution (c) add 1.0 mL of reference solution (b) and dilute to 50.0 mL with *methanol R*.

Reference solution (f) To 4.0 mL of reference solution (a) add 5.0 mL of reference solution (d) and dilute to 50.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R*;

— *temperature*: 40 °C.

Mobile phase *anhydrous ethanol R*, *methanol R* (30:70 *V/V*).

Flow rate 0.3 mL/min.

Detection Spectrophotometer at 254 nm.

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Injection 20 µL of the test solution and reference solutions (e) and (f).

Run time Twice the retention time of oxaliplatin.

Retention time Oxaliplatin = about 14 min; impurity D = about 16 min.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to oxaliplatin and impurity D in the chromatogram obtained with reference solution (f);

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity D in the chromatogram obtained with reference solution (e).

Limit:

— *impurity D*: not more than 3 times the difference between the heights of the peaks due to impurity D in the chromatograms obtained with reference solution (e) and the test solution (0.15 per cent).

Related substances

A. Impurity A. Liquid chromatography (2.2.29). *Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation.*

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 14.0 mg of *oxalic acid R* (impurity A) in *water R* and dilute to 250.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 200.0 mL with *water R*.

Reference solution (c) Dissolve 12.5 mg of *sodium nitrate R* in *water R* and dilute to 250.0 mL with the same solvent. Dilute a mixture of 2.0 mL of this solution and 25.0 mL of reference solution (a) to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 20 volumes of *acetonitrile R1* and 80 volumes of a solution prepared as follows: to 10 mL of a 320 g/L solution of *tetrabutylammonium hydroxide R* add 1.36 g of *potassium dihydrogen phosphate R*, dilute to 1000 mL with *water for chromatography R* and adjust to pH 6.0 with *phosphoric acid R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

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Run time Twice the retention time of impurity A.

Retention times Nitrate = about 2.7 min; impurity A = about 4.7 min.

System suitability:

— *resolution*: minimum 9 between the peaks due to nitrate and impurity A in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity A in the chromatogram obtained with reference solution (b).

Limit:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent).

B. Impurity B. Liquid chromatography (2.2.29). *Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation. Use suitable polypropylene containers for the preparation and injection of all solutions. Glass pipettes may be used for diluting solutions.*

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Add 5.0 mg of *oxaliplatin impurity B CRS* to 25 mL of *methanol R* and dilute to 100.0 mL with *water R*. Sonicate for about 1.5 h until dissolved (solution A). Dilute 3.0 mL of solution A to 200.0 mL with *water R*.

Reference solution (b) In order to prepare impurity E *in situ*, adjust 50.0 mL of solution A to pH 6.0 with a 0.2 g/L solution of *sodium hydroxide R*, heat at 70 °C for 4 h and allow to cool.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 20 volumes of *acetonitrile R1* and 80 volumes of a solution prepared as follows: dissolve 1.36 g of *potassium dihydrogen phosphate R* and 1 g of *sodium heptanesulfonate R* in 1000 mL of *water for chromatography R* and adjust to pH 3.0 ± 0.05 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 2.5 times the retention time of impurity B.

Retention time Impurity B = about 4.3 min; impurity E = about 6.4 min.

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System suitability:

— *resolution*: minimum 7 between the peaks due to impurities B and E in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity B in the chromatogram obtained with reference solution (a).

Limit:

— *impurity B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent).

C. Impurity C and other related substances. Liquid chromatography (2.2.29). *Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation.*

Test solution (a) Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 500.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *oxaliplatin CRS* and 5.0 mg of *oxaliplatin impurity C CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with *water R*.

Reference solution (c) Dissolve 25.0 mg of *oxaliplatin CRS* in *water R* and dilute to 250.0 mL with the same solvent.

Reference solution (d) Dissolve 5.0 mg of *dichlorodiaminocyclohexaneplatinum CRS* in reference solution (c) and dilute to 50.0 mL with reference solution (c).

Reference solution (e) Dilute 5 mL of reference solution (d) to 50.0 mL with *water R*.

Reference solution (f) To 0.100 g of the substance to be examined add 1.5 mL of reference solution (a) and dilute to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 1 volume of *acetonitrile R1* and 99 volumes of a solution prepared as follows: dilute 0.6 mL of *dilute phosphoric acid R* in 1000 mL of *water for chromatography R* and adjust to pH 3.0 with either *sodium hydroxide solution R* or *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of test solution (a) and reference solutions (b), (e) and (f).

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Run time 3 times the retention time of oxaliplatin.

Retention time Impurity C = about 4.4 min; dichlorodiaminocyclohexaneplatinum = about 6.9 min; oxaliplatin = about 8.0 min.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to dichlorodiaminocyclohexaneplatinum and oxaliplatin in the chromatogram obtained with reference solution (e);

— *signal-to-noise ratio*: minimum 50 for the peak due to impurity C and minimum 10 for the peak due to oxaliplatin in the chromatogram obtained with reference solution (b).

Limits:

— *impurity C*: not more than 0.5 times the area of the peak due to impurity C in the chromatogram obtained with reference solution (f) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than twice the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *sum of unspecified impurities*: not more than 3 times the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *disregard limit*: the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak with a retention time less than 2 min.

D. Sum of impurities other than D: maximum 0.30 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Bacterial endotoxins (*2.6.14*)

Less than 1.0 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for impurity C and other related substances with the following modifications.

Injection 20 µL of test solution (b) and reference solutions (c) and (d).

System suitability:

— *resolution*: minimum 2.0 between the peaks due to dichlorodiaminocyclohexaneplatinum and oxaliplatin in the chromatogram obtained with reference solution (d);

— *repeatability*: reference solution (c).

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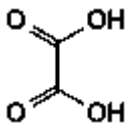
Calculate the percentage content of oxaliplatin using the chromatogram obtained with reference solution (c).

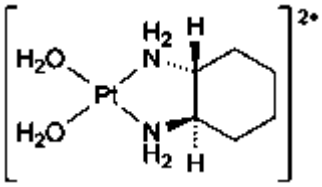
IMPURITIES

Specified impurities *A, B, C, D.*

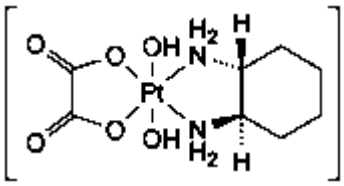
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E.*



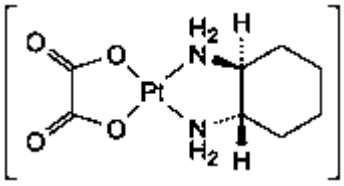
A. oxalic acid,



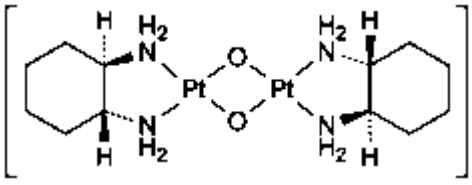
B. (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ^2*N*,*N*′]platinum (diaquodiaminocyclohexaneplatinum; supplied as dinitrate),



C. (*OC*-6-33)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ^2*N*,*N*′][ethanedioato-κ^2*O*,*O*′(2-)]dihydroxidoplatinum,



D. (*SP*-4-2)-[(1*S*,2*S*)-cyclohexane-1,2-diamine-κ^2*N*,*N*′][ethanedioato-κ^2*O*,*O*′(2-)]platinum (*S*,*S*-enantiomer of oxaliplatin),



E. (*SP*-4-2)-di-μ-oxidobis[(1*R*,2*R*)-cyclohexane-1,2-diamine-1κ^2*N*,2κ^2*N*′]diplatinum (diaquodiaminocyclohexaneplatinum dimer).

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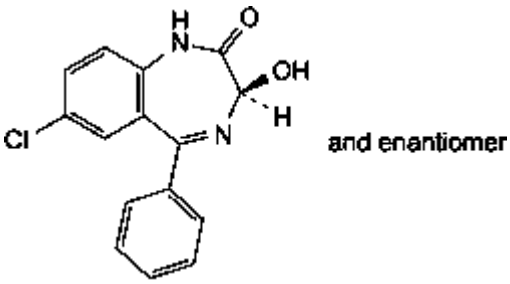
Oxazepam

General Notices

(Ph. Eur. monograph 0778)



$C_{15}H_{11}ClN_2O_2$ 286.7 *604-75-1*

Action and use

Benzodiazepine.

Preparation

Oxazepam Tablets

Ph Eur

DEFINITION

(3*RS*)-7-Chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *oxazepam CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 40.0 mg of the substance to be examined in 25 mL of a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*. Dilute 2.0 mL of this solution to 10.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Reference solution (b) Dissolve the contents of a vial of *oxazepam for peak identification CRS* (containing impurities A, B, C, D and E) in 1.0 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) resistant to bases up to pH 11.

Mobile phase:

— *mobile phase A*: dissolve 3.48 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 10.5 with a 40 g/L solution of *sodium hydroxide R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	75	25
4 - 34	75 → 25	25 → 75
34 - 45	25	75
45 - 50	25 → 75	75 → 25
50 - 60	75	25

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL.

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Identification of impurities Use the chromatogram obtained with reference solution (b) and the chromatogram supplied with *oxazepam for peak identification CRS* to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to oxazepam (retention time = about 15 min): impurity E = about 0.7; impurity A = about 0.8; impurity B = about 1.2; impurity C = about 1.4; impurity D = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities E and A.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 4.0; impurity B = 1.1;

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C at a pressure not exceeding 0.7 kPa.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 10 mL of *anhydrous acetic acid R* and 90 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 28.67 mg of $C_{15}H_{11}ClN_2O_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*

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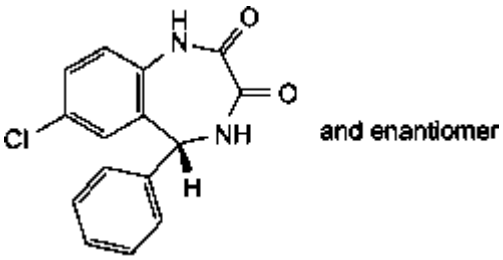
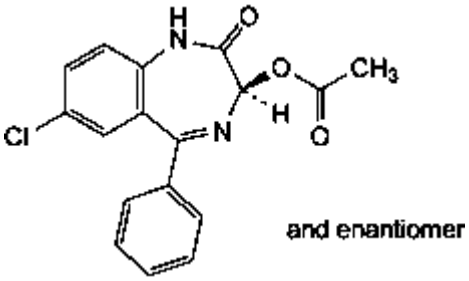


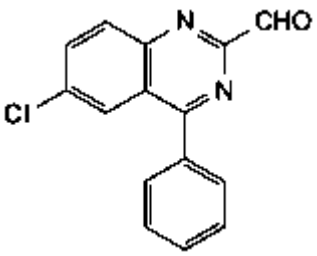
and enantiomer

A. (5*RS*)-7-chloro-5-phenyl-4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione,

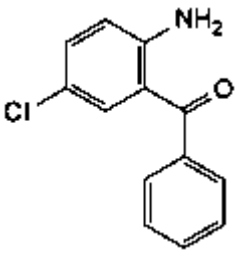


and enantiomer

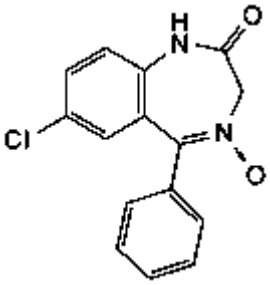
B. (3*RS*)-7-chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl acetate,



C. 6-chloro-4-phenylquinazoline-2-carbaldehyde,



D. (2-amino-5-chlorophenyl)phenylmethanone,



E. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide.

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Oxazepam Tablets

General Notices

Action and use

Benzodiazepine.

DEFINITION

Oxazepam Tablets contain Oxazepam.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of oxazepam, $C_{15}H_{11}ClN_2O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 20 mg of Oxazepam with 25 mL of *chloroform*, filter, evaporate to dryness and dry the residue at 60° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of oxazepam (*RS 253*).

B. The *light absorption*, Appendix II B, in the range 210 to 350 nm of the solution obtained in the Assay exhibits two maxima, at 230 nm and 316 nm.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 236 nm, Appendix II B using 0.01M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of oxazepam, $C_{15}H_{11}ClN_2O_2$, in the medium taking 1080 as the value of A(1%, 1 cm) at the maximum at 236 nm.

Related substances

Carry out the following procedure protected from light. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 30 mg of Oxazepam with 6 mL of *acetone* and centrifuge.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetone*.

(3) Dilute 1 volume of solution (1) to 500 volumes with *acetone*.

(4) 0.10% w/v of each of *oxazepam BPCRS* and *bromazepam EPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} is suitable). Before use, wash the plate with *methanol* allowing the solvent front to ascend 17 cm above the line of application.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *methanol* and 100 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (1%),

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 25 mg of Oxazepam add 150 mL of *ethanol* (*96%*) and shake for 30 minutes. Add sufficient *ethanol* (*96%*) to produce 250 mL, centrifuge, dilute 5 mL of the supernatant liquid to 100 mL with the same solvent and measure the *absorbance* of the resulting solution at the maximum at 230 nm, Appendix II B. Calculate the content of $C_{15}H_{11}ClN_2O_2$ taking 1250 as the value of A(1%, 1 cm) at the maximum at 230 nm.

STORAGE

Oxazepam Tablets should be protected from light.

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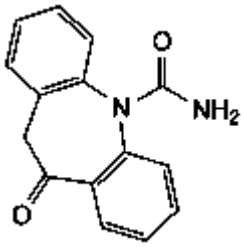
Oxcarbazepine

General Notices

(Ph. Eur. monograph 2577)



$C_{15}H_{12}N_2O_2$ 252.3 *28721-07-5*

Action and use

Antiepileptic.

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DEFINITION

10-Oxo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or faintly orange, crystalline powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *oxcarbazepine CRS*.

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TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Solvent mixture acetonitrile R, solution A (50:50 *V/V*).

Phosphate buffer solution Dissolve 0.54 g of potassium dihydrogen phosphate R and 8.9 g of disodium hydrogen phosphate dihydrate R in 1.0 L of water R.

Solution A 1.8 g/L solution of ascorbic acid R.

Solution B 1.8 g/L solution of sodium edetate R in a mixture of equal volumes of the phosphate buffer solution and water R.

Test solution (a) Dissolve 50.0 mg of the substance to be examined in 25 mL of acetonitrile R, sonicate for 10 min, cool to room temperature and dilute to 50.0 mL with solution A.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of oxcarbazepine impurity mixture CRS (impurities A, B, I and K) in 0.5 mL of acetonitrile R and dilute to 1.0 mL with solution A.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of oxcarbazepine CRS in 25 mL of acetonitrile R, sonicate for 10 min, cool to room temperature and dilute to 50.0 mL with solution A. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: phenylhexylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, solution B, tetrahydrofuran R, water R (5:10:10:75 *V/V/V/V*);

— *mobile phase B*: solution B, tetrahydrofuran R, water R, acetonitrile R (10:10:20:60 *V/V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	60	40

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
10 - 20	60 → 5	40 → 95
20 - 27	5	95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *oxcarbazepine impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, I and K.

Relative retention With reference to oxcarbazepine (retention time = about 6 min): impurity I = about 0.8; impurity A = about 1.3; impurities K and L = about 1.4; impurity B = about 1.6.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to impurities K and L and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of oxcarbazepine in reference solution (b).

Limits:

— *impurities B, I*: for each impurity, maximum 0.1 per cent;

— *sum of impurities K and L*: maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.03 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	60	40
7 - 8	60 → 5	40 → 95
8 - 13	5	95

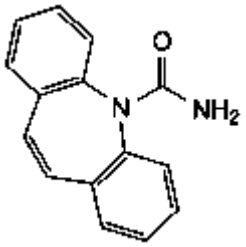
Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{15}H_{12}N_2O_2$ taking into account the assigned content of *oxcarbazepine CRS*.

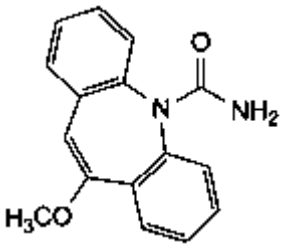
IMPURITIES

Specified impurities *B, I, K, L.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, F, G, H, M.*



A. 5*H*-dibenzo[*b,f*]azepine-5-carboxamide (carbamazepine),



B. 10-methoxy-5*H*-dibenzo[*b,f*]azepine-5-carboxamide (10-methoxycarbamazepine),

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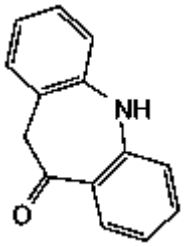
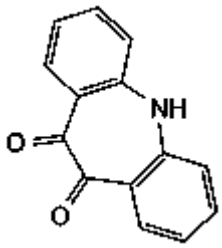
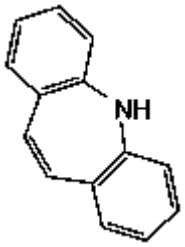


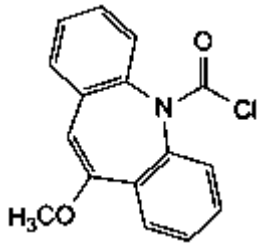
C. 5,11-dihydro-10*H*-dibenzo[*b,f*]azepin-10-one,



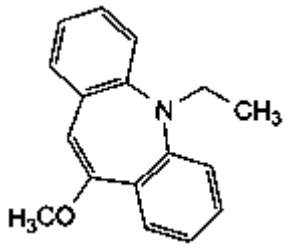
D. 5*H*-dibenzo[*b,f*]azepine-10,11-dione,



E. 5*H*-dibenzo[*b,f*]azepine,



F. 10-methoxy-5*H*-dibenzo[*b,f*]azepine-5-carbonyl chloride,



G. 5-ethyl-10-methoxy-5*H*-dibenzo[*b,f*]azepine,

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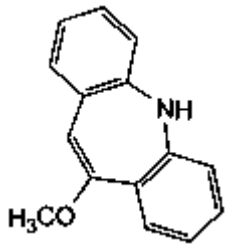
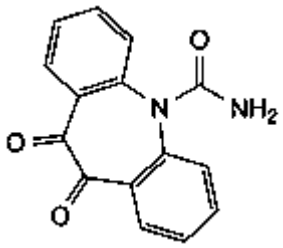
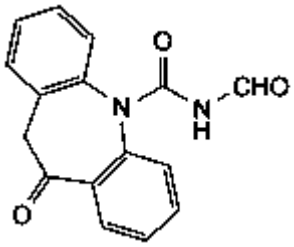


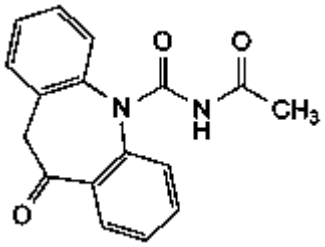
H. 10-methoxy-5*H*-dibenzo[*b,f*]azepine,



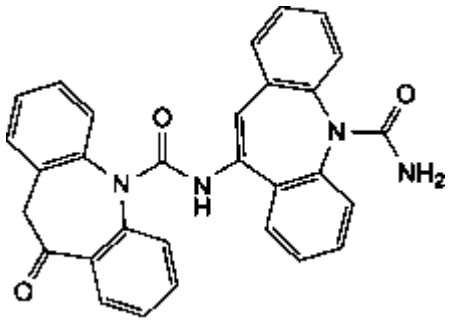
I. 10,11-dioxo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide,



K. *N*-formyl-10-oxo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide,



L. *N*-acetyl-10-oxo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide,



M. 10-[[(10-oxo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)carbonyl]amino]-5*H*-dibenzo[*b,f*]azepine-5-carboxamide.

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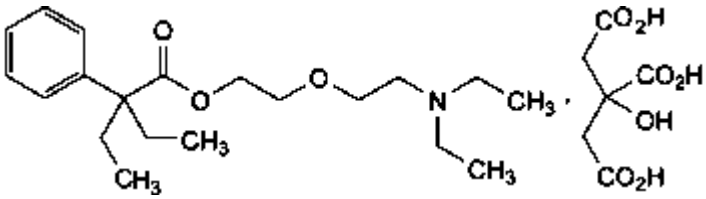
Oxeladin Hydrogen Citrate

General Notices

(Ph. Eur. monograph 1761)



$C_{26}H_{41}NO_{10}$ 527.6 *52432-72-1*

Action and use

Cough suppressant.

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DEFINITION

2-[2-(Diethylamino)ethoxy]ethyl 2-ethyl-2-phenylbutanoate dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble or very slightly soluble in ethyl acetate.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *oxeladin hydrogen citrate CRS*.

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If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 10.0 mL with the same solvent.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure. *Prepare the solutions immediately before use.*

Test solution Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 50 mL with the same solvent. Add 1 mL of a 10.3 g/L solution of *hydrochloric acid R* and shake with 3 quantities, each of 10 mL, of *methylene chloride R*. Combine the lower layers. Add 5 mL of *concentrated ammonia R* to the aqueous layer and shake with 3 quantities, each of 10 mL, of *methylene chloride R*. Combine the lower layers with the lower layers obtained previously, add *anhydrous sodium sulfate R*, shake, filter and evaporate the filtrate by suitable means at a temperature not exceeding 30 °C. Take up the residue with *methylene chloride R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *oxeladin impurity D CRS* in 10 mL of *water R*, add 0.5 mL of *concentrated ammonia R* and shake with 3 quantities, each of 2 mL, of *methylene chloride R*. To the combined lower layers, add 0.2 mL of the test solution and dilute to 10.0 mL with *methylene chloride R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 20.0 mL with *methylene chloride R*.

Reference solution (c) Dissolve 5 mg of *oxeladin impurity C CRS* in 10 mL of *water R*, add 0.5 mL of *concentrated ammonia R* and shake with 3 quantities, each of 2 mL, of *methylene chloride R*. Combine the lower layers and dilute to 10 mL with *methylene chloride R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.4 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.0 mL/min; adjust the flow rate if necessary to obtain a retention time of about 13 min for oxeladin.

Split ratio 1:15.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 4	160
	4 - 12	160 → 240
	12 - 21	240
	21 - 30	240 → 160
Injection port		280
Detector		280

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to oxeladin (retention time = about 13 min): impurity A = about 0.2; impurity B = about 0.4; impurity C = about 0.8; impurity D = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 10 between the peaks due to impurity D and oxeladin.

Limits:

— *impurity C*: maximum 0.2 per cent;

— *impurity D*: maximum 0.3 per cent;

— *any other impurity*: for each impurity, maximum 0.1 per cent;

— *total*: maximum 1.0 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

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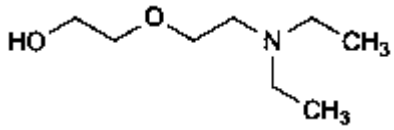
1 mL of *0.1 M perchloric acid* is equivalent to 52.76 mg of $C_{26}H_{41}NO_{10}$.

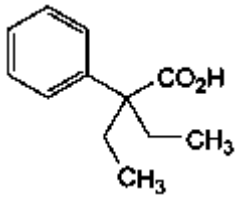
IMPURITIES

Specified impurities C, D.

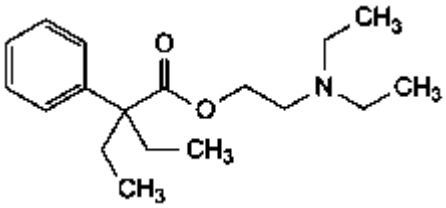
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



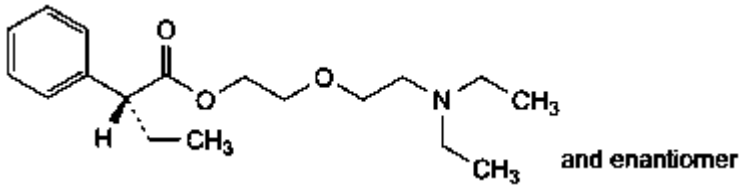
A. 2-[2-(diethylamino)ethoxy]ethanol,



B. 2-ethyl-2-phenylbutanoic acid,



C. 2-(diethylamino)ethyl 2-ethyl-2-phenylbutanoate,



D. 2-[2-(diethylamino)ethoxy]ethyl (2*RS*)-2-phenylbutanoate.

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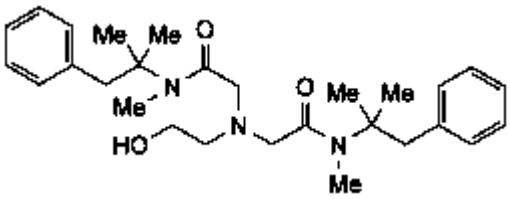
Oxetacaine

General Notices



$C_{28}H_{41}N_3O_3$ 467.6 *126-27-6*

Action and use

Local anaesthetic.

DEFINITION

Oxetacaine is 2,2′-(2-hydroxyethylimino)bis[*N*-(α,α-dimethylphenethyl)-*N*-methylacetamide]. It contains not less than 99.0% and not more than 100.5% of $C_{28}H_{41}N_3O_3$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder.

Practically insoluble in water; freely soluble in methanol; soluble in ethyl acetate.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of oxetacaine *(RS 254)*.

TESTS

Melting point

100°C to 104°C, Appendix V A.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethyl acetate*.

(1) 10.0% w/v of the substance being examined.

(2) Dilute 1 volume of solution (1) to 200 volumes.

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(3) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel 60 precoated plate (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air and spray liberally with a solution containing 6% w/v of *ammonium thiocyanate* and 2% w/v of *cobalt(II) chloride*. Carefully remove excess solution by applying filter paper to the plate and allow the plate to dry in air for 10 minutes or until spots appear.

MOBILE PHASE

1 volume of 18M *ammonia*, 20 volumes of *absolute ethanol* and 79 volumes of *toluene*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%);

not more than one *secondary spot* is more intense than the spot in the chromatogram obtained with solution (3) (0.1%).

Loss on drying

When dried at 60°C at a pressure not exceeding 0.7 kPa for 4 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 1 g in 50 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end-point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 46.76 mg of $C_{28}H_{41}N_3O_3$.

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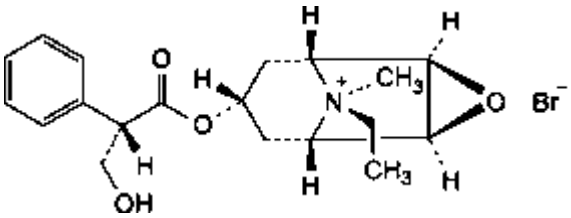
Oxitropium Bromide

General Notices

(Ph. Eur. monograph 2170)



$C_{19}H_{26}BrNO_4$ 412.3 *30286-75-0*

Action and use

Anticholinergic; treatment of reversible airways obstruction.

Ph Eur

DEFINITION

(1*R*,2*R*,4*S*,5*S*,7*s*,9*s*)-9-Ethyl-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide (ethylhyoscine).

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *oxitropium bromide CRS*.

If the spectra obtained in the solid state show differences at about 1700 cm^{-1} and about 3300 cm^{-1}, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Specific optical rotation (*2.2.7*)

-26 to -24 (dried substance).

Dissolve 1.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 75.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 7.5 mg of *oxitropium bromide impurity B CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Mix 5.0 mL of the test solution and 5.0 mL of reference solution (a).

Reference solution (d) Dilute 15.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (e) Dilute 5.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 350 m^2/g and a pore size of 6 nm.

Mobile phase *acetonitrile for chromatography R*, 7.8 g/L solution of *sodium dihydrogen phosphate R* (10:100 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

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Injection 50 µL of the test solution and reference solutions (b), (c), (d) and (e).

Relative retention With reference to oxitropium (retention time = about 6 min): impurity A = about 0.8; impurity B = about 0.9; impurity C = about 1.3.

System suitability Reference solution (c):

— *resolution*: minimum 1.6 between the peaks due to impurity B and oxitropium.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (1.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.10 per cent);

— *sum of unspecified impurities*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (e) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.05 per cent).

Impurity D

Liquid chromatography (2.2.29).

Test solution Dissolve 75.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 6.0 mg of *oxitropium bromide impurity D CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 200.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) To 5.0 mL of the test solution add 5.0 mL of reference solution (a).

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, 7.8 g/L solution of *sodium dihydrogen phosphate R* (18.5:100 *V/V*).

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Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurity D and oxitropium.

Limit:

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

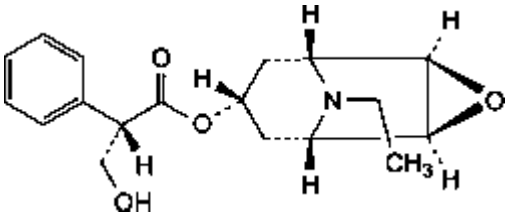
ASSAY

Dissolve 0.350 g in 100 mL of *water R* and add 5.0 mL of *dilute nitric acid R*. Titrate with *0.1 M silver nitrate*. Determine the end-point potentiometrically (2.2.20) using a silver indicator electrode and a silver-silver chloride reference electrode.

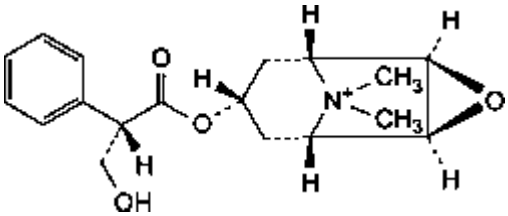
1 mL of *0.1 M silver nitrate* is equivalent to 41.23 mg of $C_{19}H_{26}BrNO_4$.

IMPURITIES

Specified impurities *A, B, C, D.*



A. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-ethyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (*N*-ethylnorhyoscine),



B. (1*R*,2*R*,4*S*,5*S*,7*s*)-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (methylhyoscine),

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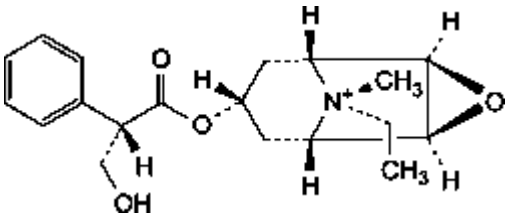
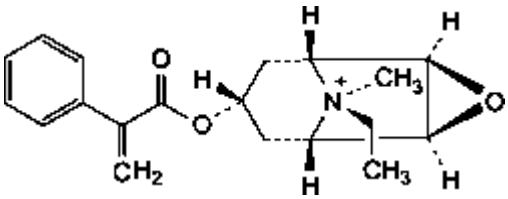


C. (1*R*,2*R*,4*S*,5*S*,7*s*,9*r*)-9-ethyl-7-[[(2*S*)-3-hydroxy-2-phenylpropanoyl]oxy]-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (pseudo-isomer),



D. (1*R*,2*R*,4*S*,5*S*,7*s*,9*s*)-9-ethyl-9-methyl-7-[(2-phenylacryloyl)oxy]-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane (apo-*N*-ethylhyoscine).

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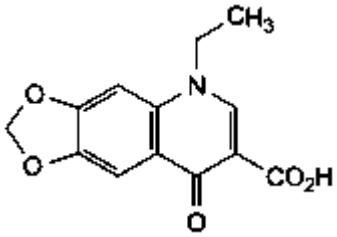
Oxolinic Acid

General Notices

(Ph. Eur. monograph 1353)



$C_{13}H_{11}NO_5$ 261.2 *14698-29-4*

Action and use

Antibacterial.

Ph Eur

DEFINITION

5-Ethyl-8-oxo-5,8-dihydro-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Almost white or pale yellow, crystalline powder.

Solubility

Practically insoluble in water, very slightly soluble in methylene chloride, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

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Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25.0 mg in 5 mL of *0.1 M sodium hydroxide*, heating on a water-bath. Allow to cool and dilute to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 100.0 mL with *0.1 M hydrochloric acid*.

Spectral range 220-350 nm.

Absorption maxima At 260 nm, 322 nm and 336 nm.

Absorbance ratio A_{260}/A_{336} = 4.9 to 5.2.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *oxolinic acid CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 3 mL of *dilute sodium hydroxide solution R* and dilute to 20 mL with *ethanol (96 per cent) R*.

Reference solution (a) Dissolve 10 mg of *oxolinic acid CRS* in 3 mL of *dilute sodium hydroxide solution R* and dilute to 20 mL with *ethanol (96 per cent) R*.

Reference solution (b) Dissolve 5 mg of *ciprofloxacin hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 2 mL with reference solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *acetonitrile R*, *concentrated ammonia R*, *methanol R*, *methylene chloride R* (10:20:40:40 *V/V/V/V*).

Application 10 µL.

Development At the bottom of a chromatographic tank, place an evaporating dish containing 50 mL of *concentrated ammonia R* and expose the plate to the ammonia vapour for 15 min in the closed tank; withdraw the plate, transfer to a second chromatographic tank and proceed with development over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

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TESTS

Solution S

Dissolve 0.6 g in 20 mL of a 40 g/L solution of *sodium hydroxide R*.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Related substances

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.10 g of the substance to be examined in 3 mL of *dilute sodium hydroxide solution R* and dilute to 10 mL with *ethanol (96 per cent) R*.

Reference solution (a) Dilute 1 mL of the test solution to 50.0 mL with *ethanol (96 per cent) R*. Dilute 1.0 mL of this solution to 5.0 mL with *ethanol (96 per cent) R*.

Reference solution (b) Dissolve 2 mg of *oxolinic acid impurity B CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent. Dilute 1.0 mL of this solution to 10 mL with *ethanol (96 per cent) R*.

Reference solution (c) Dissolve 5 mg of the substance to be examined and 5 mg of *oxolinic acid impurity A CRS* in 2 mL of *dilute sodium hydroxide solution R* and dilute to 40 mL with *ethanol (96 per cent) R*.

Plate *cellulose for chromatography R* as the coating substance.

Mobile phase *ammonia R*, *water R*, *propanol R* (15:30:55 *V/V/V*).

Application 5 µL, in sufficiently small portions to obtain small spots.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated principal spots.

Limits:

— *impurity B*: any spot due to impurity B is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.2 per cent);

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— *impurities A, C*: any spot due to impurities A or C is not more intense than the principal spot in the chromatogram obtained with reference solution (a) (0.4 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by heating in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

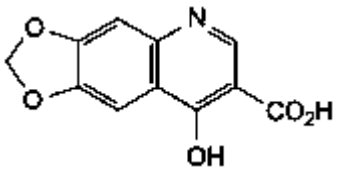
Dissolve 0.200 g in 150 mL of *dimethylformamide R*. Titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (2.2.20). Use a glass indicator electrode and a suitable reference electrode.

1 mL of *0.1 M tetrabutylammonium hydroxide* is equivalent to 26.12 mg of $C_{13}H_{11}NO_5$.

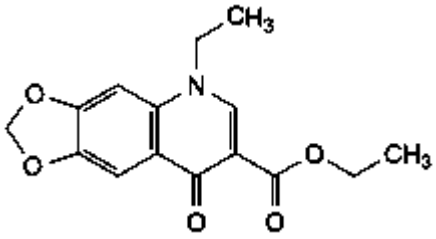
STORAGE

Protected from light.

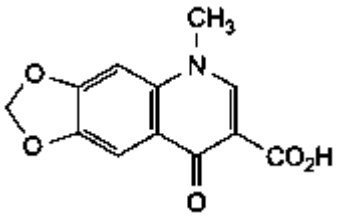
IMPURITIES



A. 8-hydroxy-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid,



B. ethyl 5-ethyl-8-oxo-5,8-dihydro-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylate,



C. 5-methyl-8-oxo-5,8-dihydro-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid.

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Oxybuprocaine Eye Drops

General Notices

Action and use

Local anaesthetic.

DEFINITION

Oxybuprocaine Eye Drops are a sterile solution of Oxybuprocaine Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of oxybuprocaine hydrochloride, $C_{17}H_{28}N_2O_3,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the eye drops containing 0.4% w/v of Oxybuprocaine Hydrochloride add 0.5 mL of 2M *hydrochloric acid* and 0.5 mL of a 10% w/v solution of *sodium nitrite* and mix. Add a solution prepared by dissolving 0.2 g of *2-naphthol* in the minimum volume of 18M *ammonia*; a red precipitate is produced.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Yield reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 3.5 to 4.3, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the eye drops with sufficient of the mobile phase to produce a solution containing 0.016% w/v of Oxybuprocaine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Mix 1 volume of solution (1) with 1 volume of a 4% w/v solution of *sodium hydroxide* and allow to stand for 20 minutes. Add 1 volume of 2M *orthophosphoric acid*, dilute to 100 volumes with the mobile phase and dilute 1 volume of the final solution to 4 volumes with the mobile phase (generation of 4-amino-3-butoxybenzoic acid).

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the eye drops with sufficient of the mobile phase to produce a solution containing 0.016% w/v of Oxybuprocaine Hydrochloride.

(2) 0.016% w/v of *oxybuprocaine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *acetonitrile* containing 0.1% v/v of *diethylamine* and 60 volumes of a 0.75% w/v solution of *ammonium acetate* which has been adjusted to pH 5.0 with *glacial acetic acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{28}N_2O_3$,HCl in the eye drops using the declared content of $C_{17}H_{28}N_2O_3$,HCl in *oxybuprocaine hydrochloride BPCRS*.

STORAGE

Oxybuprocaine Eye Drops should be protected from light. They should not be allowed to freeze.

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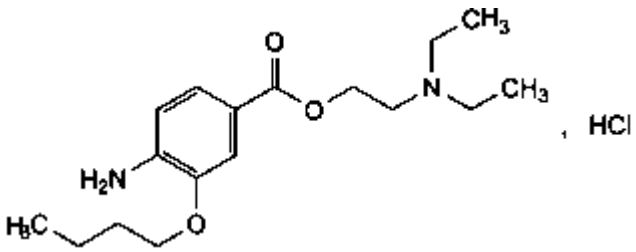
Oxybuprocaine Hydrochloride

General Notices

(Ph. Eur. monograph 1251)



$C_{17}H_{29}ClN_2O_3$ 344.9 *5987-82-6*

Action and use

Local anaesthetic.

Preparation

Oxybuprocaine Eye Drops

Ph Eur

DEFINITION

2-(Diethylamino)ethyl 4-amino-3-butoxybenzoate hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

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IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 158 °C to 162 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *oxybuprocaine hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 40 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 40 mg of *oxybuprocaine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *procaine hydrochloride R* in reference solution (a) and dilute to 5 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *methanol R*, *water R*, *ethyl acetate R* (10:15:15:60 *V/V/V/V*).

Application 5 µL.

Development Over a path of 10 cm.

Drying In a current of warm air for 10 min.

Detection Spray with *dimethylaminobenzaldehyde solution R7* and examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dilute 0.2 mL of solution S (see Tests) to 2 mL with *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

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Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution pH 2.5 Add 6 mL of *perchloric acid solution R* and 12 mL of *dilute phosphoric acid R* to 950 mL of *water R*. Adjust to pH 2.5 with a 40 g/L solution of *sodium hydroxide R* and dilute to 1000.0 mL with *water R*.

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Mix 1.0 mL of the test solution with 1 mL of a 40 g/L solution of *sodium hydroxide R* and allow to stand for 20 min. Add 1 mL of *dilute phosphoric acid R* and dilute to 100.0 mL with the mobile phase. Dilute 25 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent;

— *temperature*: 35 °C.

Mobile phase *acetonitrile R*, buffer solution pH 2.5 (25:75 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 309 nm.

Injection 20 µL.

Run time 4 times the retention time of oxybuprocaine.

Retention time Oxybuprocaine = about 9 min.

System suitability Reference solution (b):

— *resolution*: minimum 12 between the peaks due to oxybuprocaine and impurity B (hydrolysis product).

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Limits:

— *any impurity*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.0125 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

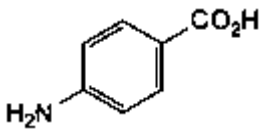
Dissolve 0.300 g in a mixture of 20 mL of *anhydrous acetic acid R* and 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 34.49 mg of $C_{17}H_{29}ClN_2O_3$.

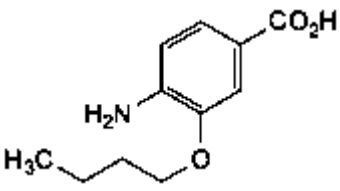
STORAGE

Protected from light.

IMPURITIES



A. 4-aminobenzoic acid,



B. 4-amino-3-butoxybenzoic acid,

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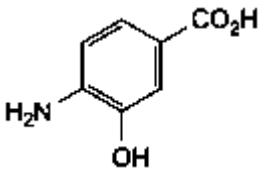

C. 4-amino-3-hydroxybenzoic acid.

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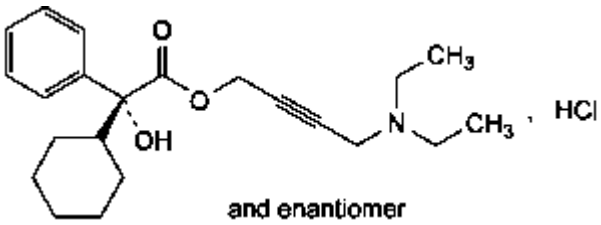
Oxybutynin Hydrochloride

General Notices

(Ph. Eur. monograph 1354)



$C_{22}H_{32}ClNO_3$ 394.0 *1508-65-2*

Action and use

Anticholinergic.

Preparations

Oxybutynin Oral Solution

Oxybutynin Tablets

Oxybutynin Prolonged-release Tablets

Ph Eur

DEFINITION

4-(Diethylamino)but-2-yn-1-yl (*RS*)-cyclohexyl(hydroxy)phenylacetate hydrochloride.

Content

99.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), soluble in acetone, practically insoluble in cyclohexane.

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IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 124 °C to 129 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison oxybutynin hydrochloride CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in ethanol (96 per cent) R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of oxybutynin hydrochloride CRS in ethanol (96 per cent) R and dilute to 2 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase methanol R.

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour for 30 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.00 g in water R and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Related substances

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Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of oxybutynin hydrochloride CRS and 5.0 mg of oxybutynin impurity A CRS in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of oxybutynin hydrochloride for system suitability CRS (containing impurities C, D and F) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 49 volumes of a solution containing 3.4 g/L of potassium dihydrogen phosphate R and 4.36 g/L of dipotassium hydrogen phosphate R and 51 volumes of acetonitrile R1.

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Run time Twice the retention time of oxybutynin.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with oxybutynin hydrochloride for system suitability CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D and F.

Relative retention With reference to oxybutynin (retention time = about 15 min): impurity D = about 0.08; impurity F = about 0.7; impurity C = about 0.8; impurity A = about 1.6.

System suitability Reference solution (c):

— resolution: minimum 2.0 between the peaks due to impurities F and C.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 0.6;

— for impurity A, use the concentration of impurity A in reference solution (a);

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— for impurities other than A, use the concentration of oxybutynin hydrochloride in reference solution (b).

Limits:

— *impurity A*: maximum 1.5 per cent;

— *impurities C, D, F*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than A*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 39.40 mg of $C_{22}H_{32}ClNO_3$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, C, D, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, E.*

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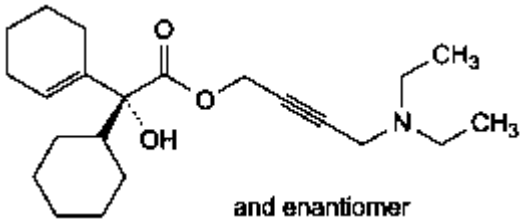
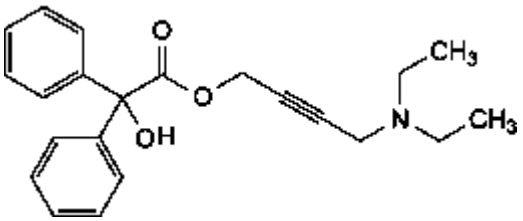
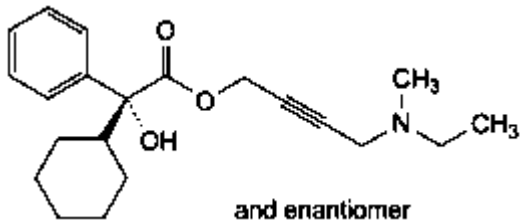


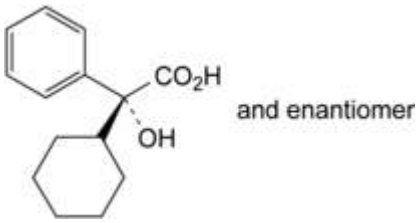
A. 4-(diethylamino)but-2-yn-1-yl (*RS*)-(cyclohex-1-en-1-yl)(cyclohexyl)hydroxyacetate,



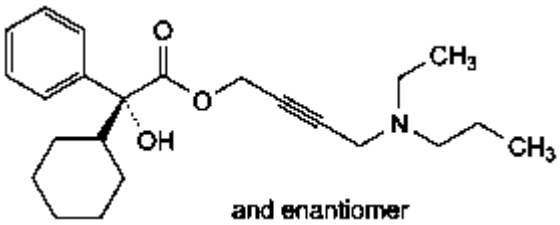
B. 4-(diethylamino)but-2-yn-1-yl hydroxy(diphenyl)acetate (diphenyl analogue of oxybutynin),



C. 4-[ethyl(methyl)amino]but-2-yn-1-yl (*RS*)-cyclohexyl(hydroxy)phenylacetate (methylethyl analogue of oxybutynin),



D. (*RS*)-cyclohexyl(hydroxy)phenylacetic acid (cyclohexylphenylglycolic acid),



E. 4-[ethyl(propyl)amino]but-2-yn-1-yl (*RS*)-cyclohexyl(hydroxy)phenylacetate (ethylpropyl analogue of oxybutynin),

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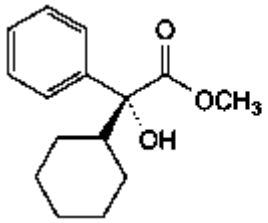

and enantiomer

F. methyl (*RS*)-cyclohexyl(hydroxy)phenylacetate.

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Oxybutynin Oral Solution

General Notices

Action and use

Anticholinergic.

DEFINITION

Oxybutynin Oral Solution contains Oxybutynin Hydrochloride in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements

Content of oxybutynin hydrochloride, $C_{22}H_{31}NO_3$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the oral solution containing 25 mg of Oxybutynin Hydrochloride add sufficient 2M *sodium hydroxide* to adjust to pH 12.0 and extract with four 20-mL quantities of *hexane*. Filter the collected hexane layers through *anhydrous sodium sulfate* (Whatman GF/C is suitable). Evaporate the filtrate to dryness under a current of nitrogen, to yield a clear, sticky liquid residue. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of oxybutynin *(RS 442)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the oral solution containing 25 mg of Oxybutynin Hydrochloride with 40 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 100 mL, mix and filter.

(2) 0.000375% w/v of *oxybutynin impurity A EPCRS* in 0.01M *hydrochloric acid*.

(3) 0.00025% w/v of *phenylcyclohexylglycolic acid BPCRS* in 0.01M *hydrochloric acid*.

(4) Dilute 1 volume of solution (1) to 200 volumes with 0.01M *hydrochloric acid*.

(5) 0.0000125% w/v of *oxybutynin impurity A EPCRS* in solution (4).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography R1* (5 µm) (Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phases described below.

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(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

(g) When the chromatograms are recorded under the prescribed conditions the retention times are about 31 minutes for oxybutynin hydrochloride and about 47 minutes for oxybutynin impurity A.

MOBILE PHASE

Mobile phase A 0.34% w/v of *potassium dihydrogen orthophosphate* and 0.436% w/v of *dipotassium hydrogen orthophosphate*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	70	30	isocratic
5-6	70→45	30→55	linear gradient
6-50	45	55	isocratic
50-51	45→70	55→30	linear gradient
51-60	70	30	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between the peaks due to oxybutynin hydrochloride and oxybutynin impurity A is at least 10.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to oxybutynin impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to phenylcyclohexylglycolic acid is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any such s*econdary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the oral solution containing 25 mg of Oxybutynin Hydrochloride with 400 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 500 mL, mix and filter.

(2) 0.005% w/v of *oxybutynin hydrochloride BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *nitrile silica gel for chromatography R1* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 200 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

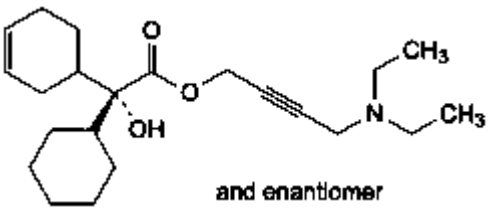
300 volumes of *acetonitrile R1* and 700 volumes of a 0.48% w/v solution of *anhydrous potassium dihydrogen orthophosphate* previously adjusted to pH 3.0 to 3.5 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

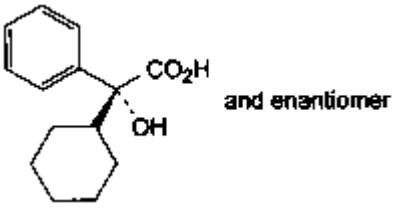
Calculate the content of $C_{22}H_{31}NO_3$,HCl in the oral slution using the declared content of $C_{22}H_{31}NO_3$,HCl in *oxybutynin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include:



1. 4-(diethylamino)but-2-ynyl (*RS*)-2-(cyclohex-3-enyl)-2-cyclohexyl-2-hydroxyacetate (European Pharmacopoeia impurity A),



2. (*RS*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (phenylcyclohexylglycolic acid) (European Pharmacopoeia impurity D).

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Oxybutynin Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Oxybutynin Tablets contain Oxybutynin Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of oxybutynin hydrochloride, $C_{22}H_{31}NO_3$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 25 mg of Oxybutynin Hydrochloride add sufficient 2M *sodium hydroxide* to adjust to pH 12.0 and extract with four 20-mL quantities of *hexane*. Filter the collected hexane layers through *anhydrous sodium sulfate* (Whatman GF/C is suitable). Evaporate the filtrate to dryness under a current of nitrogen, to yield a clear, sticky liquid residue. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of oxybutynin *(RS442)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of 20 mL of the medium, filter through a 0.45-µm membrane filter and discard the first 10 mL of filtrate. Use the filtered dissolution medium diluted, if necessary, to produce a solution containing 0.0005% w/v of Oxybutynin Hydrochloride

(2) 0.0005% w/v of *oxybutynin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Assay may be used.

DETERMINATION OF CONTENT

Calculate the total content of Oxybutynin Hydrochloride, $C_{22}H_{31}NO_3$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{22}H_{31}NO_3$,HCl in *oxybutynin hydrochloride BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 50 mg of Oxybutynin Hydrochloride with 40 mL of 0.01M *hydrochloric acid* with the aid of ultrasound for 15 minutes, add sufficient 0.01M *hydrochloric acid* to produce 50 mL, mix and filter (Whatman GF/A filters are suitable).

(2) 0.0015% w/v of *oxybutynin impurity A EPCRS* in 0.01M *hydrochloric acid*.

(3) 0.001% w/v of *phenylcyclohexylglycolic acid BPCRS* in 0.01M *hydrochloric acid*.

(4) Dilute 1 volume of solution (1) to 200 volumes with 0.01M *hydrochloric acid*.

(5) 0.001% w/v of *oxybutynin impurity A EPCRS* in solution (4).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography R1* (5 µm) (Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

(g) When the chromatograms are recorded under the prescribed conditions the retention times are about 31 minutes for oxybutynin hydrochloride and about 47 minutes for oxybutynin impurity A.

MOBILE PHASE

Mobile phase A 0.34% w/v of *potassium dihydrogen orthophosphate* and 0.436% w/v of *dipotassium hydrogen orthophosphate*.

Mobile phase B *acetonitrile R1*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	70	30	isocratic
5-6	70→45	30→55	linear gradient
6-50	45	55	isocratic
50-51	45→70	55→30	linear gradient
51-60	70	30	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between the peaks due to oxybutynin hydrochloride and oxybutynin impurity A is at least 10.0.

LIMITS

In the chromatogram obtained with solution (1);

the area of any peak corresponding to oxybutynin impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to phenylcyclohexylglycolic acid is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any such s*econdary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix 10 whole tablets with 400 mL of 0.01M *hydrochloric acid* for 20 minutes with the aid of ultrasound, cool, add sufficient 0.01M *hydrochloric acid* to produce 500 mL, mix and filter (Whatman GF/A filters are suitable). Dilute a volume of this solution with sufficient 0.01M *hydrochloric acid* to produce a solution containing 0.005% w/v of Oxybutynin Hydrochloride.

(2) 0.005% w/v of *oxybutynin hydrochloride BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *nitrile silica gel for chromatography R1* (5 µm) (Spherisorb nitrile is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature 40°.

(e) Use a detection wavelength of 200 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

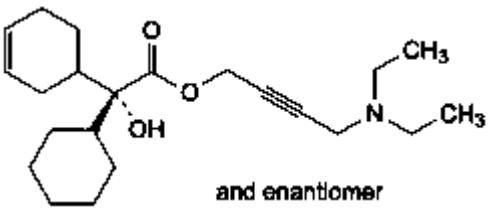
300 volumes of *acetonitrile R1* and 700 volumes of a 0.48% w/v solution of *anhydrous potassium dihydrogen orthophosphate* previously adjusted to pH 3.0 to 3.5 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

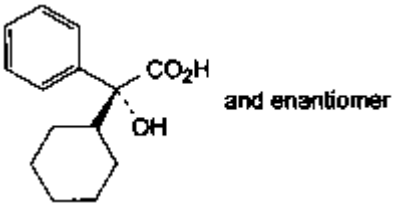
Calculate the content of $C_{22}H_{31}NO_3$,HCl in the tablets using the declared content of $C_{22}H_{31}NO_3$,HCl in *oxybutynin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include:



1. 4-(diethylamino)but-2-ynyl (*RS*)-2-(cyclohex-3-enyl)-2-cyclohexyl-2-hydroxyacetate (European Pharmacopoeia impurity A),



2. (*RS*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (phenylcyclohexylglycolic acid) (European Pharmacopoeia impurity D).

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Oxycodone Capsules

General Notices

Oxycodone Hydrochloride Capsules

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Oxycodone Capsules contain Oxycodone Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the capsule contents containing 50 mg of Oxycodone Hydrochloride with 10 mL of *water*, filter and make the filtrate alkaline with *dilute ammonia R1*. Allow the solution to stand until a precipitate is formed. Filter and wash the precipitate with 10 mL of cold *water*. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of oxycodone hydrochloride *(RS 457)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *0.1M hydrochloric acid* if necessary, expected to contain 0.0005% w/v of Oxycodone Hydrochloride.

(2) 0.0005% w/v of *oxycodone hydrochloride BPCRS* in *0.1M hydrochloric acid*.

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(3) 0.0002% w/v of *oxycodone impurity standard BPCRS* in 0.02M *acetic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-5C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

(g) For solution (3) allow the chromatography to proceed for 4 times the retention time of the peak due to oxycodone.

MOBILE PHASE

100 volumes of *acetonitrile*, 200 volumes of *methanol* and 700 volumes of a solution containing 0.11% w/v of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to oxycodone and 14-hydroxycodeinone is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$, HCl, in the medium from the chromatograms obtained and using the declared content of $C_{18}H_{21}NO_4$,HCl in *oxycodone hydrochloride BPCRS*.

LIMITS

The amount of oxycodone hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.02M *acetic acid*.

(1) Shake, with the aid of ultrasound, a quantity of the capsule contents containing 20 mg of Oxycodone Hydrochloride with 40 mL of 0.02 M *acetic acid*, add sufficient 0.02M *acetic acid* to produce 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 2 volumes of solution (2) to 10 volumes.

(4) 0.0002% w/v of *oxycodone impurity standard BPCRS*.

(5) Dilute 1 volume of solution (3) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1.5 mL per minute.

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(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 70 volumes of *acetonitrile*, 100 volumes of *methanol* and 830 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

Mobile phase B 150 volumes of *acetonitrile*, 250 volumes of *methanol* and 600 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-60	100→50	0→50	linear gradient
60-62	50→100	50→0	linear gradient
62-70	100	0	isocratic

When the chromatograms are recorded using the prescribed conditions the retention time of oxycodone is about 24 minutes. The retention times relative to oxycodone are: impurity D, about 1.18; impurity E, about 1.18 and impurity F, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to oxycodone and 14-hydroxycodeinone is at least 3.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to thebaine and multiply the area of this peak by 0.5.

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to 14-hydroxycodeinone and hydrocodone is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.02M *acetic acid*.

(1) Shake, with the aid of ultrasound, a quantity of the capsule contents containing 25 mg of Oxycodone Hydrochloride with 40 mL of 0.02 M *acetic acid*, add sufficient 0.02M *acetic acid* to produce 50 mL and filter. Dilute 1 volume of the filtrate to 100 volumes with 0.02M *acetic acid*.

(2) 0.0005% w/v of *oxycodone hydrochloride BPCRS*.

(3) 0.0002% w/v of *oxycodone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to oxycodone and 14-hydroxycodeinone is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$,HCl, in the capsules using the declared content of $C_{18}H_{21}NO_4$,HCl in *oxycodone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of the monograph include:

D. 7,8-didehydro-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (14-hydroxycodeinone);

E. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (hydrocodone);

F. 6,7,8,14-tetradehydro-4,5α-epoxy-3-6-dimethoxy-17-methylmorphinan (thebaine).

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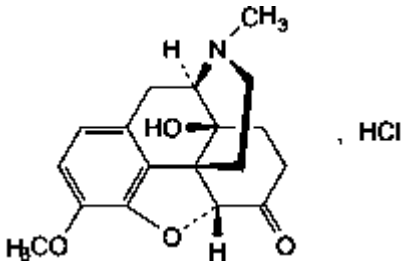
Oxycodone Hydrochloride

General Notices

(Ph. Eur. monograph 1793)



$C_{18}H_{22}ClNO_4$ 351.9 *124-90-3*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Oxycodone Capsules

Oxycodone Injection

Oxycodone Oral Solution

Oxycodone Prolonged-release Tablets

Ph Eur

DEFINITION

4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

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Solubility

Freely soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in toluene.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Dissolve 50 mg in *water R* and dilute to 5 mL with the same solvent. Render the solution alkaline with *dilute ammonia R1*. Allow the mixture to stand until a precipitate is formed. Filter, wash the precipitate with 10 mL of cold *water R*, and dry for 1 h at 105 °C. Examine the precipitate.

Comparison Repeat the operations using 50 mg of *oxycodone hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 0.2 mL of *0.02 M sodium hydroxide* or *0.02 M hydrochloric acid* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*)

-140 to -148 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions protected from light.*

Test solution Dissolve 0.100 g of the substance to be examined in a 1 per cent *V/V* solution of *dilute acetic acid R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 20.0 mg of *oxycodone impurity D CRS* in a 1 per cent *V/V* solution of *dilute acetic acid R* and dilute to 10.0 mL with the same solution.

Reference solution (b) To 1.0 mL of the test solution, add 1.0 mL of reference solution (a) and dilute to 100.0 mL with a 1 per cent *V/V* solution of *dilute acetic acid R*. Dilute 1.0 mL of the solution to 10.0 mL with a 1 per cent *V/V* solution of *dilute acetic acid R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 830 mL of a 1.1 g/L solution of *sodium heptanesulfonate monohydrate R* previously adjusted to pH 2.0 with a mixture of equal volumes of *phosphoric acid R* and *water R*, with 70 mL of *acetonitrile R* and 100 mL of *methanol R*;

— *mobile phase B*: mix 600 mL of a 1.1 g/L solution of *sodium heptanesulfonate monohydrate R* previously adjusted to pH 2.0 with a mixture of equal volumes of *phosphoric acid R* and *water R*, with 150 mL of *acetonitrile R* and 250 mL of *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	100 → 50	0 → 50

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to oxycodone (retention time = about 24 min): impurity A = about 0.4; impurity B = about 0.7; impurity C = about 1.14; impurity D = about 1.18; impurity E = about 1.18; impurity F = about 2.4.

System suitability Reference solution (b):

— *resolution*: minimum 3 between the peaks due to oxycodone and impurity D.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 0.5;

— *sum of impurities D and E*: not more than 10 times the area of the peak due to oxycodone in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurities A, B, C, F*: for each impurity, not more than the area of the peak due to oxycodone in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the peak due to oxycodone in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *total*: not more than 15 times the area of the peak due to oxycodone in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the peak due to oxycodone in the chromatogram obtained with reference solution (b) (0.05 per cent).

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Ethanol (*2.4.24, System A*)

Maximum 1.0 per cent.

Water (*2.5.12*)

Maximum 7.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 60 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M ethanolic sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Measure the volume used between the 2 inflexion points.

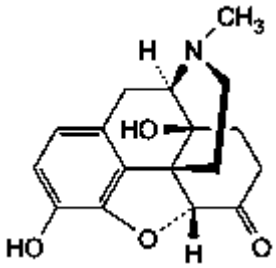
1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 35.19 mg of $C_{18}H_{22}ClNO_4$.

STORAGE

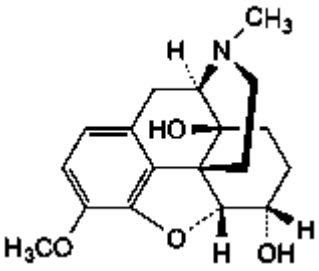
In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*



A. 4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one (oxymorphone),



B. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6α,14-diol (7,8-dihydro-14-hydroxycodeine),

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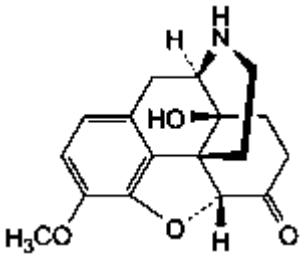
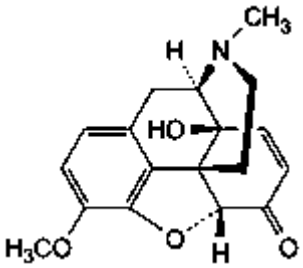
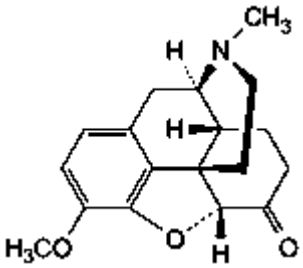


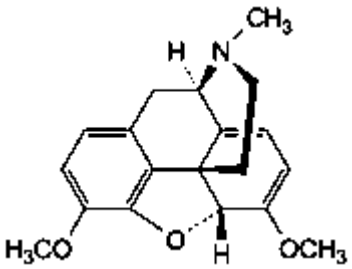
C. 4,5α-epoxy-14-hydroxy-3-methoxymorphinan-6-one (noroxycodone),



D. 7,8-didehydro-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (14-hydroxycodeinone),



E. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (hydrocodone),



F. 6,7,8,14-tetradehydro-4,5α-epoxy-3-6-dimethoxy-17-methylmorphinan (thebain).

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Oxycodone Injection

General Notices

Oxycodone Hydrochloride Injection

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Oxycodone Injection is a sterile solution containing Oxycodone Hydrochloride.

The injection complies with the requirements under Parenteral Preparations and with the following requirements.

Content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the injection containing 50 mg of Oxycodone Hydrochloride with 10 mL of *water*, filter and make the filtrate alkaline with *dilute ammonia R1*. Allow the solution to stand until a precipitate is formed. Filter the solution and wash the precipitate with 10 mL of cold water. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the reference spectrum of oxycodone hydrochloride *(RS 457)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.02M *acetic acid*.

(1) To a quantity of the injection containing 20 mg of Oxycodone Hydrochloride add sufficient 0.02M *acetic acid* to produce 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 2 volume of solution (2) to 10 volumes.

(4) 0.0002% w/v of *oxycodone impurity standard BPCRS*.

(5) Dilute 1 volume of solution (3) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 70 volumes of *acetonitrile*, 100 volumes of *methanol* and 830 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

Mobile phase B 150 volumes of *acetonitrile*, 250 volumes of *methanol* and 600 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-60	100→50	0→50	linear gradient
60-62	50→100	50→0	linear gradient
62-70	100	0	isocratic

When the chromatograms are recorded using the prescribed conditions, the retention time of oxycodone is about 24 minutes. The retention times relative to oxycodone are: impurity D, about 1.18; impurity E, about 1.18 and impurity F, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to oxycodone and 14-hydroxycodeinone is at least 3.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to thebaine and multiply the area of this peak by 0.5.

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to 14-hydroxycodeinone and hydrocodone is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.02M *acetic acid*.

(1) To a quantity of the injection containing 25 mg of Oxycodone Hydrochloride add sufficient 0.02M *acetic acid* to produce 50 mL and filter.Dilute 1 volume of the filtrate to 100 volumes with 0.02M *acetic acid*.

(2) 0.0005% w/v of *oxycodone hydrochloride BPCRS*.

(3) 0.0002% w/v of *oxycodone impurity standard BPCRS* in 0.02M *acetic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

(g) For solution (3) allow the chromatography to proceed for 4 times the retention time of the peak due to oxycodone.

MOBILE PHASE

100 volumes of *acetonitrile*, 200 volumes of *methanol* and 700 volumes of a solution containing 0.11% w/v of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to oxycodone and 14-hydroxycodeinone is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$,HCl, in the injection using the declared content of $C_{18}H_{21}NO_4$,HCl in *oxycodone hydrochloride BPCRS*.

IMPURITIES

D. 7,8-didehydro-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (14-hydroxycodeinone);

E. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (hydrocodone);

F. 6,7,8,14-tetradehydro-4,5α-epoxy-3-6-dimethoxy-17-methylmorphinan (thebaine).

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Oxycodone Oral Solution

General Notices

Oxycodone Hydrochloride Oral Solution

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Oxycodone Oral Solution contains Oxycodone Hydrochloride in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Adjust the pH of a quantity of the oral solution containing 15 mg of Oxycodone Hydrochloride to pH 9.5 with 6M *ammonia*. Transfer the solution to a separating funnel and extract with two 5-mL quantities of *dichloromethane*. Combine the dichloromethane extracts and evaporate 2 mL of the extract to dryness. Dissolve the residue obtained in 1 mL of *dichloromethane*.

(2) Transfer 15 mL of a 0.1% w/v solution of *oxycodone hydrochloride BPCRS,* adjusted to pH 9.5 with 6M *ammonia*, to a separating funnel and extract with two 5-mL quantities of *dichloromethane*. Combine the dichloromethane extracts and evaporate 2 mL of the extract to dryness. Dissolve the residue obtained in 1 mL of *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating substance *silica gel F_{254}* (Merck TLC silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) Dry the plate in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of 13.5M *ammonia*, 10 volumes of *diethyl ether*, 40 volumes of *toluene* and 60 volumes of *acetone*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.5 to 3.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.02M *acetic acid*.

(1) Shake, with the aid of ultrasound, a quantity of the oral solution containing 20 mg of Oxycodone Hydrochloride with 40 mL of 0.02M *acetic acid*, add sufficient 0.02M *acetic acid* to produce 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 2 volumes of solution (2) to 10 volumes.

(4) 0.0002% w/v of oxycodone impurity standard BPCRS.

(5) Dilute 1 volume of solution (3) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 70 volumes of *acetonitrile*, 100 volumes of *methanol* and 830 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

Mobile phase B 150 volumes of *acetonitrile*, 250 volumes of *methanol* and 600 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-60	100→50	0→50	linear gradient
60-62	50→100	50→0	linear gradient
62-70	100	0	isocratic

When the chromatograms are recorded using the prescribed conditions, the retention time of oxycodone is about 24 minutes. The retention times relative to oxycodone are: impurity D, about 1.18; impurity E, about 1.18 and impurity F, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to oxycodone and 14-hydroxycodeinone is at least 3.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to thebaine and multiply the area of this peak by 0.5.

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to 14-hydroxycodeinone and hydrocodone is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.02M *acetic acid*.

(1) To a quantity of the oral solution containing 25 mg of Oxycodone Hydrochloride add sufficient 0.02M *acetic acid* to produce 50 mL and filter.Dilute 1 volume of this solution to 100 volumes with 0.02M *acetic acid*.

(2) 0.0005% w/v of *oxycodone hydrochloride BPCRS*.

(3) 0.0002% w/v of *oxycodone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

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(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

(g) For solution (3) allow the chromatography to proceed for 4 times the retention time of the peak due to oxycodone.

MOBILE PHASE

100 volumes of *acetonitrile*, 200 volumes of *methanol* and 700 volumes of a solution containing 0.11% w/v of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to oxycodone and 14-hydroxycodeinone is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$,HCl, in the oral solution from the chromatograms obtained and using the declared content of $C_{18}H_{21}NO_4$,HCl in *oxycodone hydrochloride BPCRS*.

IMPURITIES

D. 7,8-didehydro-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (14-hydroxycodeinone);

E. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (hydrocodone);

F. 6,7,8,14-tetradehydro-4,5α-epoxy-3-6-dimethoxy-17-methylmorphinan (thebaine).

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Oxycodone Prolonged-release Tablets

General Notices

Prolonged-release Oxycodone Tablets

Oxycodone Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Oxycodone Prolonged-release Tablets that have a tamper-resistant formulation, whilst complying with the requirements of the monograph, may require different methods of sample preparation where justified and authorised.

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Oxycodone Prolonged-release Tablets contain Oxycodone Hydrochloride.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of oxycodone. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of oxycodone hydrochloride, $C_{18}H_{21}NO_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the powdered tablets containing 50 mg of Oxycodone Hydrochloride with 25 mL of *water*, filter and add sufficient *dilute ammonia R1* to make the solution alkaline. Allow the mixture to stand until a precipitate is formed. Filter and wash the precipitate with 10 mL of cold *water*. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of oxycodone hydrochloride *(RS 457)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light using the following solutions in 0.02M *acetic acid*.

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(1) Shake with the aid of ultrasound a quantity of the powdered tablets containing 20 mg of Oxycodone Hydrochloride with 40 mL of 0.02M *acetic acid*, add sufficient 0.02M *acetic acid* to produce 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volumes of solution (2) to 5 volumes.

(4) 0.0002% w/v of *oxycodone impurity standard BPCRS*.

(5) Dilute 1 volume of solution (3) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 70 volumes of *acetonitrile*, 100 volumes of *methanol* and 830 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

Mobile phase B 150 volumes of *acetonitrile*, 250 volumes of *methanol* and 600 volumes of a 0.11% w/v solution of *sodium heptanesulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-60	100→50	0→50	linear gradient
06-62	50→100	50→0	linear gradient
62-70	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the retention time of oxycodone is about 24 minutes. The retention times relative to oxycodone are: impurity D, about 1.18; impurity E, about 1.18 and impurity F, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to oxycodone and impurity D is at least 3.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity F and multiply the area of this peak by 0.5.

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any peaks due to impurity D and impurity E is not more than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.02M *acetic acid*.

(1) To a quantity of the powdered tablets containing 25 mg of Oxycodone Hydrochloride add sufficient 0.02M *acetic acid* to produce 50 mL and filter. Dilute 1 volume of the filtrate to 100 volumes with 0.02M *acetic acid*.
(2) 0.0005% w/v of *oxycodone hydrochloride BPCRS*.
(3) 0.0005% w/v of *oxycodone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 100 µL of each solution.
(g) For solution (3) allow the chromatography to proceed for 4 times the retention time of oxycodone hydrochloride (retention time, about 6 minutes).

MOBILE PHASE

100 volumes of *acetonitrile*, 200 volumes of *methanol* and 700 volumes of a solution containing 0.11% w/v of *sodium heptane sulfonate monohydrate* previously adjusted to pH 2.0 with 8M *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to oxycodone hydrochloride and 14-hydroxycodeinone is at least 2.0.

DETERMINATION OF CONTENT

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Calculate the total content of $C_{18}H_{21}NO_4$,HCl in the tablets using the declared content of $C_{18}H_{21}NO_4$,HCl in *oxycodone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities D, E and F listed under Oxycodone Hydrochloride.

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Oxygen

General Notices

(Ph. Eur. monograph 0417)

Oxygen should be kept in approved metal cylinders, the shoulders of which are painted white and the remainder black. The cylinder should carry a label stating 'Oxygen'. In addition, 'Oxygen' or the symbol 'O2' should be stencilled in paint on the shoulder of the cylinder.

When Oxygen is intended for use in a room in which magnetic resonance imaging (MRI) is being performed, the cylinder and fittings should be made from suitable non-ferromagnetic materials and labelled accordingly.

O_2 32.00 *7782-44-7*

Ph Eur

DEFINITION

Content

Minimum 99.5 per cent *V/V* of O_2.

This monograph applies to oxygen for medicinal use.

CHARACTERS

Appearance

Colourless gas.

Solubility

At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 32 volumes of water.

PRODUCTION

Oxygen is produced by a purification process followed by cryodistillation of the ambient air.

Carbon dioxide

Maximum 300 ppm *V/V*, determined using an infrared analyser (*2.5.24*).

Gas to be examined Filter the substance to be examined to avoid stray light phenomena.

Reference gas (a) *Oxygen R*.

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Reference gas (b) Mixture containing 300 ppm *V/V* of *carbon dioxide R1* in *nitrogen R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon dioxide in the gas to be examined.

Carbon monoxide

Maximum 5 ppm *V/V*, determined using an infrared analyser (*2.5.25*).

Gas to be examined Filter the substance to be examined to avoid stray light phenomena.

Reference gas (a) *Oxygen R*.

Reference gas (b) Mixture containing 5 ppm *V/V* of *carbon monoxide R* in *nitrogen R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

Water

Maximum 67 ppm *V/V*, determined using an electrolytic hygrometer (*2.5.28*).

Assay

Determine the concentration of oxygen using a paramagnetic analyser (*2.5.27*).

IDENTIFICATION

It complies with the limits of the assay.

TESTS

Carbon dioxide

Maximum 300 ppm *V/V*, determined using a carbon dioxide detector tube (*2.1.6*).

Carbon monoxide

Maximum 5 ppm *V/V*, determined using a carbon monoxide detector tube (*2.1.6*).

Water vapour

Maximum 67 ppm *V/V*, determined using a water vapour detector tube (*2.1.6*).

STORAGE

As a compressed gas or liquid in appropriate containers, complying with the legal regulations. Oils and grease are not to be used unless they are oxygen-compatible.

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IMPURITIES

Specified impurities *A, B, C.*

A. CO_2: carbon dioxide,

B. CO: carbon monoxide,

C. H_2O: water.

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Oxygen (93 per cent)

General Notices

(Ph. Eur. monograph 2455)

O_2 32.00

Ph Eur

DEFINITION

Content

90.0 per cent *V/V* to 96.0 per cent *V/V* of O_2, the remainder mainly consisting of argon and nitrogen.

This monograph applies to oxygen (93 per cent) for medicinal use. It does not apply to gas produced using individual concentrators for domiciliary use.

PRODUCTION

Oxygen (93 per cent) is produced in single-stage concentrators by adsorption purification of ambient air using zeolites. During production, the oxygen content is continuously monitored by means of a paramagnetic analyser (2.5.27). Following the design and installation of the concentrator, and after any modification or significant intervention, the gas produced complies with the following requirements.

Carbon dioxide

Maximum 300 ppm *V/V*, determined using an infrared analyser (2.5.24).

Gas to be examined The substance to be examined. It must be filtered to avoid stray light phenomena.

Reference gas (a) *Oxygen R*.

Reference gas (b) A mixture of 7 per cent *V/V* of *nitrogen R1* and 93 per cent *V/V* of *oxygen R*, containing 300 ppm *V/V* of *carbon dioxide R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon dioxide in the gas to be examined.

Carbon monoxide

Maximum 5 ppm *V/V*, determined using an infrared analyser (2.5.25).

Gas to be examined The substance to be examined. It must be filtered to avoid stray light phenomena.

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Reference gas (a) Oxygen R.

Reference gas (b) A mixture containing 5 ppm *V/V* of carbon monoxide R in nitrogen R1.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V* in total, determined using a chemiluminescence analyser (2.5.26).

Gas to be examined The substance to be examined.

Reference gas (a) A mixture of 21 per cent *V/V* of oxygen R and 79 per cent *V/V* of nitrogen R1, containing less than 0.05 ppm *V/V* of nitrogen monoxide and nitrogen dioxide.

Reference gas (b) A mixture containing 2 ppm *V/V* of nitrogen dioxide R in nitrogen R1.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of nitrogen monoxide and nitrogen dioxide in the gas to be examined.

Sulfur dioxide

Maximum 1 ppm *V/V*, determined using an ultraviolet fluorescence analyser (Figure 2455.-1.).

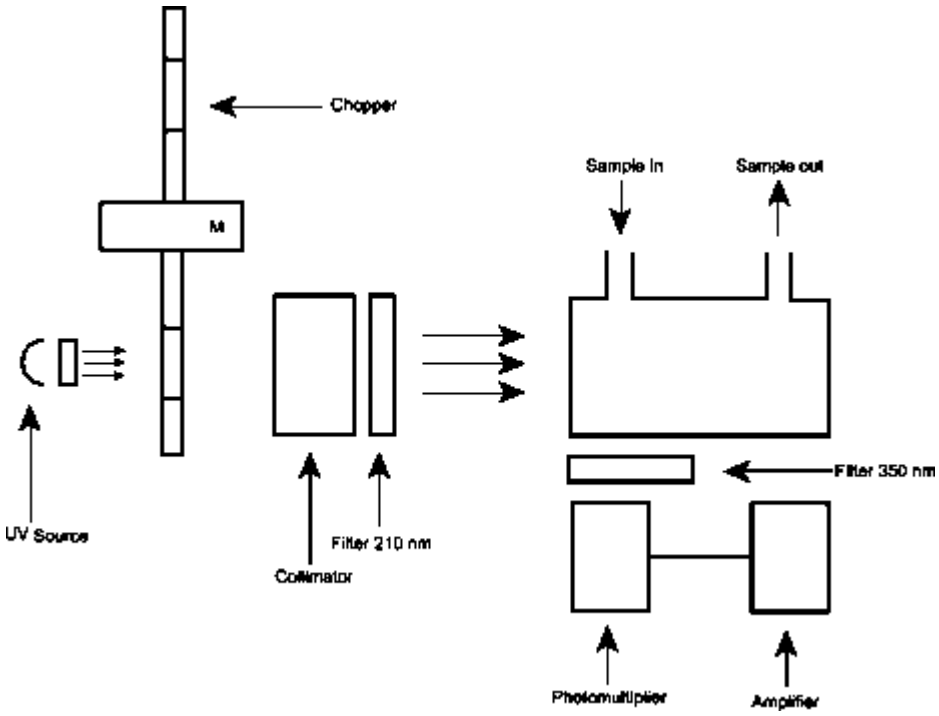

Figure 2455.-1. – *UV fluorescence analyser*

The apparatus consists of the following:

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— a system generating ultraviolet radiation with a wavelength of 210 nm, made up of an ultraviolet lamp, a collimator, and a selective filter; the beam is blocked periodically by a chopper rotating at high speeds;

— a reaction chamber, through which flows the gas to be examined;

— a system that detects radiation emitted at a wavelength of 350 nm, made up of a selective filter, a photomultiplier tube and an amplifier.

Gas to be examined The substance to be examined. It must be filtered.

Reference gas (a) A mixture of 7 per cent *V/V* of *nitrogen R1* and 93 per cent *V/V* of *oxygen R*.

Reference gas (b) A mixture of 7 per cent *V/V* of *nitrogen R1* and 93 per cent *V/V* of *oxygen R*, containing 0.5 ppm *V/V* to 2 ppm *V/V* of *sulfur dioxide R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of sulfur dioxide in the gas to be examined.

Oil

Maximum 0.1 mg/m^3, determined using an oil detector tube (2.1.6).

Water

Maximum 67 ppm *V/V*, determined using an electrolytic hygrometer (2.5.28).

Assay

Determine the concentration of oxygen using a paramagnetic analyser (2.5.27).

CHARACTERS

Appearance

Colourless gas.

IDENTIFICATION

It complies with the limits of the assay.

TESTS

Carbon dioxide

Maximum 300 ppm *V/V*, determined using a carbon dioxide detector tube (2.1.6).

Carbon monoxide

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Maximum 5 ppm *V/V*, determined using a carbon monoxide detector tube (*2.1.6*).

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V* in total, determined using a nitrogen monoxide and nitrogen dioxide detector tube (*2.1.6*).

Sulfur dioxide

Maximum 1 ppm *V/V*, determined using a sulfur dioxide detector tube (*2.1.6*).

Oil

Maximum 0.1 mg/m^3, determined using an oil detector tube (*2.1.6*).

Water vapour

Maximum 67 ppm *V/V*, determined using a water vapour detector tube (*2.1.6*).

ASSAY

Determine the content of oxygen using a paramagnetic analyser (*2.5.27*).

STORAGE

Oxygen 93 per cent obtained from an oxygen concentrator is normally used on the site where it is produced. It is fed directly into a medicinal gas pipeline or administration system. Where authorised by the competent authority, it may be stored in suitable containers complying with the legal regulations. Oils and grease are not to be used unless they are oxygen-compatible.

IMPURITIES

A. CO_2: carbon dioxide,

B. CO: carbon monoxide,

C. SO_2: sulfur dioxide,

D. NO and NO_2: nitrogen monoxide and nitrogen dioxide,

E. oil,

F. H_2O: water.

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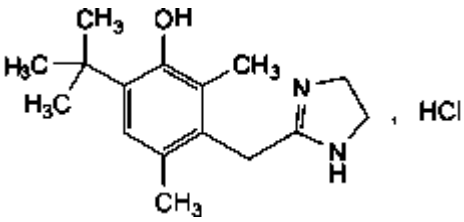
Oxymetazoline Hydrochloride

General Notices

(Ph. Eur. monograph 0943)



$C_{16}H_{25}ClN_2O$ 296.8 *2315-02-8*

Action and use

Alpha-adrenoceptor agonist; decongestant.

Ph Eur

DEFINITION

3-[(4,5-Dihydro-1*H*-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethylphenol hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison oxymetazoline hydrochloride CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in a mixture of equal volumes of ethyl acetate R and methanol R and dilute to 5 mL with the same mixture of solvents.

Reference solution Dissolve 20 mg of oxymetazoline hydrochloride CRS in a mixture of equal volumes of ethyl acetate R and methanol R and dilute to 5 mL with the same mixture of solvents.

Plate TLC silica gel G plate R.

Mobile phase diethylamine R, cyclohexane R, anhydrous ethanol R (6:15:79 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air for 5 min, then allow to cool.

Detection Spray with a freshly prepared 5.0 g/L solution of potassium ferricyanide R in ferric chloride solution R2; examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve about 2 mg in 1 mL of water R, then add 0.2 mL of a 50 g/L solution of sodium nitroprusside R and 0.2 mL of dilute sodium hydroxide solution R. Allow to stand for 10 min. Add 2 mL of sodium hydrogen carbonate solution R. A violet colour develops.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, Method II).

Dissolve 2.5 g in water R and dilute to 50 mL with the same solvent.

Acidity or alkalinity

Dissolve 0.25 g in carbon dioxide-free water R and dilute to 25 mL with the same solvent. Add 0.1 mL of methyl red solution R and 0.2 mL of 0.01 M hydrochloric acid. The solution is red. Not more than 0.4 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

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Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with *water R*. Dilute 2.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 5.0 mg of *oxymetazoline impurity A CRS* and 5 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent. Dilute 10.0 mL of the solution to 50.0 mL with *water R*.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 20.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.36 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	70	30
5 - 20	70 → 15	30 → 85
20 - 35	15	85

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Relative retention With reference to oxymetazoline (retention time = about 5.0 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity A and oxymetazoline.

Limits:

— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

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— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water

(2.5.32): maximum 0.3 per cent, determined on 1.00 g .

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

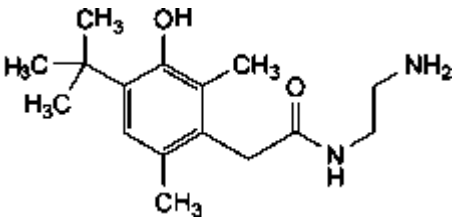
Dissolve 0.200 g in a mixture of 20 mL of *acetic anhydride R* and 20 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 29.68 mg of $C_{16}H_{25}ClN_2O$.

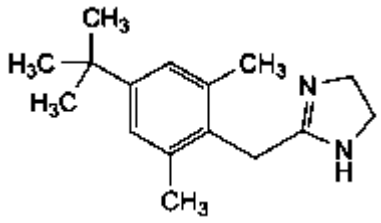
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E.



A. *N*-(2-aminoethyl)-2-[4-(1,1-dimethylethyl)-3-hydroxy-2,6-dimethylphenyl]acetamide,



B. 2-[[4-(1,1-dimethylethyl)-2,6-dimethylphenyl]methyl]-4,5-dihydro-1*H*-imidazole (xylometazoline),

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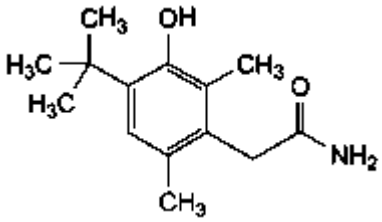
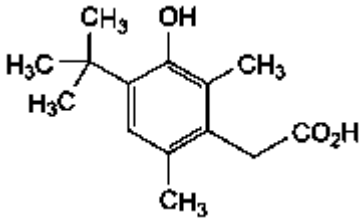
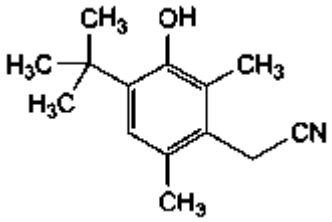


C. 2-[4-(1,1-dimethylethyl)-3-hydroxy-2,6-dimethylphenyl]acetamide,



D. 2-[4-(1,1-dimethylethyl)-3-hydroxy-2,6-dimethylphenyl]acetic acid,



E. 2-[4-(1,1-dimethylethyl)-3-hydroxy-2,6-dimethylphenyl]acetonitrile.

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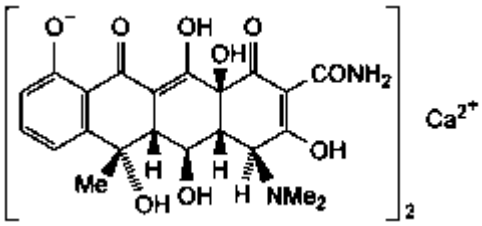
Oxytetracycline Calcium

General Notices



$(C_{22}H_{23}N_2O_9)_2Ca$ 958.9 *15251-48-6*

Action and use

Tetracycline antibacterial.

DEFINITION

Oxytetracycline Calcium is the calcium salt of (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide, a substance produced by the growth of certain strains of *Streptomyces rimosus* or obtained by any other means. It contains not less than 94.5% and not more than 102.0% of $(C_{22}H_{23}N_2O_9)_2Ca$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A pale yellow to greenish fawn, crystalline powder.

Practically insoluble in *water*; soluble in dilute acids. It dissolves slowly in 5M *ammonia*.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in 0.01M *methanolic hydrochloric acid*.

(1) 0.05% w/v of the substance being examined.

(2) 0.05% w/v of *oxytetracycline BPCRS*.

(3) 0.05% w/v of each of *oxytetracycline BPCRS* and *demeclocycline hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* precoated plate (Merck silica gel 60 plates are suitable). Adjust the pH of a 10% w/v solution of *disodium edetate* to 7.0 with 10M *sodium hydroxide* and spray the solution evenly onto the plate (about 10 mL for a plate 100 mm × 200 mm). Allow the plate to dry in a horizontal position for at least 1 hour. Before use, dry the plate at 110° for 1 hour.

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(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. To 2 mg add 5 mL of *sulfuric acid*; a deep red colour is produced. Add the solution to 2.5 mL of *water*; the colour changes to yellow.

C. Yields reaction B characteristic of *calcium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a 2.5% w/v suspension, 6.0 to 7.5, Appendix V L.

Light absorption

Absorbance of a 0.002% w/v solution in *0.1M chloride buffer pH 2.0* at the maximum at 353 nm, 0.56 to 0.61, calculated with reference to the anhydrous substance, Appendix II B.

Specific optical rotation

In a 1% w/v solution in *0.1M hydrochloric acid*, -194 to -210, calculated with reference to the anhydrous substance, Appendix V F. Allow the solution to stand protected from light for 30 minutes before measurement.

Light-absorbing impurities

A. Dissolve 0.2 g in 6 mL of 1M *hydrochloric acid* and add sufficient *methanol* to produce 100 mL. The *absorbance* at 430 nm, when measured within 1 hour of preparing the solution, is not more than 0.30, calculated with reference to the anhydrous substance, Appendix II B.

B. Dissolve 1 g in 6 mL of 1M *hydrochloric acid* and add sufficient *methanol* to produce 100 mL. The *absorbance* at 490 nm, when measured within 1 hour of preparing the solution, is not more than 0.20, calculated with reference to the anhydrous substance, Appendix II B.

Calcium

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3.90 to 4.30%, calculated with reference to the anhydrous substance, when determined by the following method. Transfer about 1 g, accurately weighed, to a Kjeldahl flask, cautiously add 10 mL of *nitric acid* and mix. Allow to stand for 5 minutes, add a glass bead and heat on a water bath for 5 minutes. Remove from the water bath, cautiously add 5 mL of 9M *perchloric acid* and heat, adding further 5 mL quantities of the perchloric acid at intervals until the liquid is almost colourless. Add 0.1 mL of *nitric acid* and allow any further reaction to subside. Do not allow the volume of the liquid in the flask to be reduced below 3 mL at any stage in the oxidation. Wash the walls of the flask with 40 mL of *water*, collecting the washings in the flask, and boil for 3 to 4 minutes to expel chlorine. Cool, transfer the contents of the flask to a conical flask with the aid of *water* and dilute to about 200 mL with *water*. Adjust to pH 9 with 5M *sodium hydroxide* and then add 100 mL of *water* followed by 12 mL of 10M *sodium hydroxide* and mix. Add about 15 mg of *calconcarboxylic acid triturate* and titrate with 0.05M *disodium edetate VS* until the colour changes from violet to full blue. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.004 mg of Ca.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.01M oxalic acid (solvent A). *Prepare the solutions immediately before use.*

(1) 0.008% w/v of the substance being examined.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.08% w/v of *oxytetracycline for system suitability A EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Intertsil C8 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05% v/v *trifluoroacetic acid*.

Mobile phase B 5 volumes of *tetrahydrofuran*, 15 volumes of *methanol* and 80 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	90	10	isocratic
5-20	90→65	10→35	linear gradient
20-21	65→90	35→10	linear gradient
21-27	90	10	re-equilibration

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When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to oxytetracycline (retention time about 7 minutes) are: impurity A, about 0.9; impurity B, about 1.2; impurity C, about 1.3; impurity D, about 1.4; impurity E, about 2.2; impurity F, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where *Hp* is the height above the baseline of the peak due to impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

LIMITS

Identify any peak corresponding to impurities A, B, C, D, E and F in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3). Multiply the areas of the peaks due to Impurity D and E by a correction factor of 0.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the*secondary peaks* is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.10%).

Water

Not more than 15.0% w/w, Appendix IX C. Use 0.15 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.01M *oxalic acid* (solvent A). Prepare the solutions immediately before use.

(1) 0.008% w/v of the substance being examined.

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(2) 0.008% w/v of *oxytetracycline BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions stated under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $(C_{22}H_{23}N_2O_9)_2Ca$ using the declared content of $C_{22}H_{24}N_2O_9$ in *oxytetracycline BPCRS*. Each mg of $C_{22}H_{24}N_2O_9$ is equivalent to 1.041 mg of $(C_{22}H_{23}N_2O_9)_2Ca$.

STORAGE

Oxytetracycline Calcium should be protected from light and stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Oxytetracycline Dihydrate.

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Oxytetracycline Capsules

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Oxytetracycline Capsules contain Oxytetracycline Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of oxytetracycline hydrochloride, $C_{22}H_{24}N_2O_9,HCl$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the contents of the capsules containing 10 mg of Oxytetracycline Hydrochloride with 20 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) Dissolve 5 mg of *oxytetracycline hydrochloride BPCRS* in sufficient *methanol* to produce 10 mL.

(3) Dissolve 5 mg of *oxytetracycline hydrochloride BPCRS* and 5 mg of *demeclocycline hydrochloride BPCRS* in sufficient *methanol* to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable). Adjust the pH of a 10% w/v solution of *disodium edetate* to 7.0 with 10M *sodium hydroxide* and spray the solution evenly onto the plate (about 10 mL for a plate 100 mm × 200 mm). Allow the plate to dry in a horizontal position for at least 1 hour. Before use, dry the plate at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. To 0.5 mg of the contents of the capsules add 2 mL of *sulfuric acid*; a deep crimson colour is produced. Add 1 mL of *water*; the colour changes to yellow.

C. The contents of the capsules yield the reactions characteristic *of chlorides*, Appendix VI.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 353 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of oxytetracycline hydrochloride, $C_{22}H_{24}N_2O_9$,HCl, in the medium taking 282 as the value of A(1%, 1 cm) at the maximum at 353 nm.

LIMITS

The amount of oxytetracycline hydrochloride released is not less than 75% (Q) of the stated amount.

Light-absorbing impurities

Dissolve a portion of the mixed contents of five capsules as completely as possible in sufficient of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *methanol* to produce two solutions of Oxytetracycline Hydrochloride containing (1) 0.20% w/v and (2) 1.0% w/v, and filter each solution.

The *absorbance* of the filtrate obtained from solution (1) at 430 nm is not more than 0.75, Appendix II B, calculated with reference to the dried capsule contents. The *absorbance* of the filtrate obtained from solution (2) at 490 nm is not more than 0.40, calculated with reference to the dried capsule contents.

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, the contents of the capsules lose not more than 5.0% of their weight. Use 1 g.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.01M *oxalic acid* (solvent A). Prepare the solutions immediately before use.

(1) Shake a quantity of the mixed contents of the capsules containing 0.16 g of Oxytetracycline Hydrochloride in 150 mL of solvent A and dilute to 200 mL. Filter the resulting solution (Whatman GF/C filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.08% w/v of *oxytetracycline for system suitability A EPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Intertsil C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05% v/v *trifluoroacetic acid*.

Mobile phase B 5 volumes of *tetrahydrofuran*, 15 volumes of *methanol* and 80 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	90	10	isocratic
5-20	90→65	10→35	linear gradient
20-21	65→90	35→10	linear gradient
21-27	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to oxytetracycline (retention time about 6.5 minutes) are: impurity A, about 0.9; impurity B, about 1.2; impurity C, about 1.3; impurity D, about 1.4; impurity E, about 2.2; impurity F, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where *Hp* is the height above the baseline of the peak due to impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

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LIMITS

Identify any peak corresponding to impurities A, B, C, D, E and F in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3). Multiply the areas of any peaks due to impurity D and E by a correction factor of 0.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.01M *oxalic acid* (solvent A). Prepare the solutions immediately before use.

(1) Shake, with the aid of ultrasound, a quantity of the mixed capsule contents containing 0.16 mg of Oxytetracycline Hydrochloride with 150 mL of solvent A. Dilute to 200 mL and filter (Whatman GF/C filter is suitable). Dilute 1 volume of the filtrate to 10 volumes.
(2) 0.0074% w/v of *oxytetracycline BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions stated under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{24}N_2O_9$,HCl in the capsules using the declared content of $C_{22}H_{24}N_2O_9$ in *oxytetracycline BPCRS*. Each mg of $C_{22}H_{24}N_2O_9$ is equivalent to 1.079 mg of $C_{22}H_{24}N_2O_9$,HCl.

STORAGE

Oxytetracycline Capsules should be protected from light.

IMPURITIES

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The impurities limited by the requirements of this monograph include those listed under Oxytetracycline Hydrochloride.

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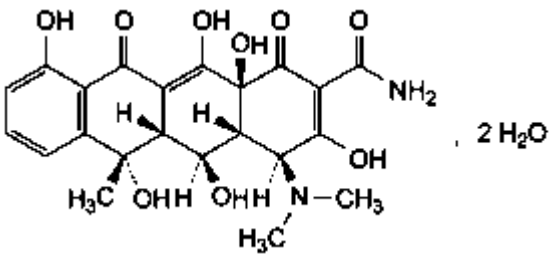
Oxytetracycline Dihydrate

General Notices

(Ph. Eur. monograph 0199)



$C_{22}H_{24}N_2O_9,2H_2O$ 496.4 *6153-64-6*

Action and use

Tetracycline antibacterial.

Preparation

Oxytetracycline Tablets

Ph Eur

DEFINITION

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(Dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide dihydrate.

Substance produced by the growth of certain strains of *Streptomyces rimosus*.

Content

94.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow, crystalline powder, slightly hygroscopic.

Solubility

Very slightly soluble in water. It dissolves in dilute acid and alkaline solutions.

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IDENTIFICATION

First identification: B, C, D.

Second identification: A, C, D.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *oxytetracycline CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *oxytetracycline CRS*, 5 mg of *tetracycline hydrochloride R* and 5 mg of *minocycline hydrochloride R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. To about 2 mg add 5 mL of *sulfuric acid R*. A deep red colour develops. Add the solution to 2.5 mL of *water R*. The colour becomes yellow.

D. Water (see Tests).

TESTS

pH (2.2.3)

4.5 to 7.5.

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Suspend 0.1 g in 10 mL of *carbon dioxide-free water R*.

Light-absorbing impurities

Carry out the measurements within 1 h of preparing the solutions.

Dissolve 20.0 mg in a mixture of 1 volume of a 103 g/L solution of *hydrochloric acid R* and 99 volumes of *methanol R* and dilute to 10.0 mL with the same mixture of solvents. The absorbance (*2.2.25*) determined at 430 nm has a maximum of 0.25 (anhydrous substance).

Dissolve 0.100 g in a mixture of 1 volume of a 103 g/L solution of *hydrochloric acid R* and 99 volumes of *methanol R* and dilute to 10.0 mL with the same mixture of solvents. The absorbance (*2.2.25*) determined at 490 nm has a maximum of 0.20 (anhydrous substance).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 20.0 mg of the substance to be examined in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Reference solution (a) Dissolve 20.0 mg of *oxytetracycline CRS* in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same acid. Dilute 5.0 mL of the solution to 50.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Reference solution (c) Dissolve 4.0 mg of *oxytetracycline for system suitability A CRS* (containing impurities A, B, C, D and E) in a 1 g/L solution of *hydrochloric acid R* and dilute to 5.0 mL with the same solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: 0.05 per cent *V/V* solution of *trifluoroacetic acid R*;

— *mobile phase B*: *tetrahydrofuran for chromatography R*, *methanol R1*, *acetonitrile R1* (5:15:80 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 20	90 → 65	10 → 35

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Flow rate 1.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *oxytetracycline for system suitability A CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to oxytetracycline (retention time = about 6.5 min): impurity A = about 0.9; impurity B = about 1.2; impurity C = about 1.3; impurity D = about 1.4; impurity E = about 2.2.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline; minimum 3.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.4; impurity E = 0.4;

— for each impurity, use the concentration of oxytetracycline dihydrate in reference solution (b).

Limits:

— *impurity C*: maximum 2.0 per cent;

— *impurity B*: maximum 1.0 per cent;

— *impurity A*: maximum 0.7 per cent;

— *impurities D, E*: for each impurity, maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.1 per cent;

— *total*: maximum 3.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

6.0 per cent to 9.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{22}H_{24}N_2O_9$ taking into account the assigned content of *oxytetracycline CRS*.

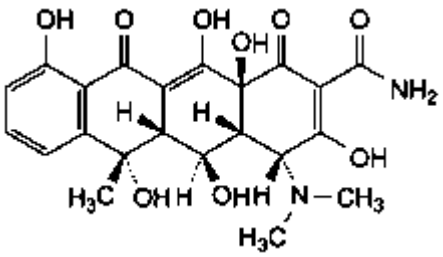
STORAGE

In an airtight container, protected from light.

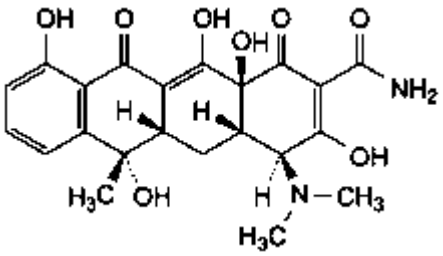
IMPURITIES

Specified impurities *A, B, C, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F.*



A. (4*R*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epioxytetracycline),



B. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (tetracycline),

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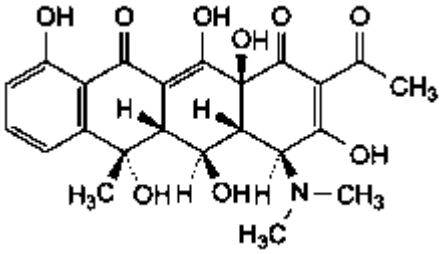
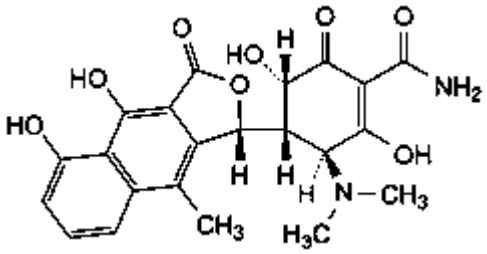
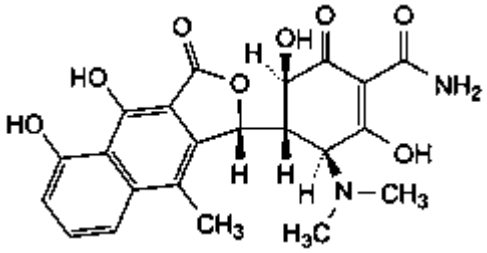


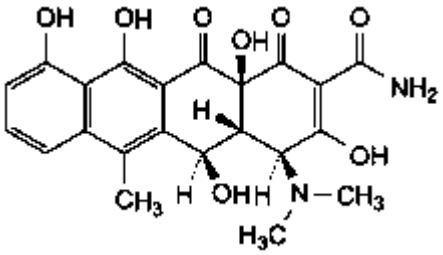
C. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-2-acetyl-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarbamoyloxytetracycline),



D. (3*S*,4*S*,5*S*)-4-[(1*R*)-4,5-dihydroxy-9-methyl-3-oxo-1,3-dihydronaphtho[2,3-*c*]furan-1-yl]-3-(dimethylamino)-2,5-dihydroxy-6-oxocyclohex-1-ene-1-carboxamide,



E. (3*S*,4*S*,5*R*)-4-[(1*R*)-4,5-dihydroxy-9-methyl-3-oxo-1,3-dihydronaphtho[2,3-*c*]furan-1-yl]-3-(dimethylamino)-2,5-dihydroxy-6-oxocyclohex-1-ene-1-carboxamide,



F. (4*S*,4a*R*,5*R*,12a*S*)-4-(dimethylamino)-3,5,10,11,12a-pentahydroxy-6-methyl-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (anhydro-oxytetracycline).

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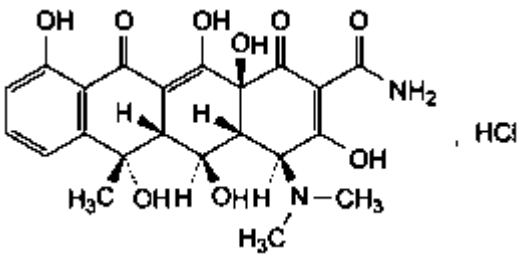
Oxytetracycline Hydrochloride

General Notices

(Ph. Eur. monograph 0198)



$C_{22}H_{25}ClN_2O_9$ 496.9 *2058-46-0*

Action and use

Tetracycline antibacterial.

Preparations

Oxytetracycline Capsules

Oxytetracycline Cutaneous Spray

Ph Eur

DEFINITION

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(Dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride.

Substance produced by the growth of certain strains of *Streptomyces rimosus*.

Content

94.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow, hygroscopic, crystalline powder.

Solubility

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Freely soluble in water, sparingly soluble in ethanol (96 per cent). Solutions in water become turbid on standing, owing to the precipitation of oxytetracycline.

IDENTIFICATION

First identification: B, C, D.

Second identification: A, C, D.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of oxytetracycline hydrochloride CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of oxytetracycline hydrochloride CRS, 5 mg of tetracycline hydrochloride R and 5 mg of minocycline hydrochloride R in methanol R and dilute to 10 mL with the same solvent.

Plate TLC octadecylsilyl silica gel F_{254} plate R.

Mobile phase Mix 20 volumes of acetonitrile R, 20 volumes of methanol R and 60 volumes of a 63 g/L solution of oxalic acid R previously adjusted to pH 2 with concentrated ammonia R.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. To about 2 mg add 5 mL of sulfuric acid R. A deep red colour develops. Add the solution to 2.5 mL of water R. The colour becomes yellow.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

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2.3 to 2.9.

Dissolve 0.1 g in 10 mL of *carbon dioxide-free water R*.

Light-absorbing impurities

Carry out the measurements within 1 h of preparing the solutions.

Dissolve 20.0 mg in a mixture of 1 volume of a 103 g/L solution of *hydrochloric acid R* and 99 volumes of *methanol R* and dilute to 10.0 mL with the same mixture of solvents. The absorbance (*2.2.25*) of the solution determined at 430 nm is not greater than 0.50 (anhydrous substance).

Dissolve 0.100 g in a mixture of 1 volume of a 103 g/L solution of *hydrochloric acid R* and 99 volumes of *methanol R* and dilute to 10.0 mL with the same mixture of solvents. The absorbance (*2.2.25*) of the solution determined at 490 nm is not greater than 0.20 (anhydrous substance).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture Mix 20 volumes of *acetonitrile R* and 80 volumes of a 1.26 g/L solution of *oxalic acid R* previously adjusted to pH 2.0 with *dilute hydrochloric acid R1*.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution. Dilute 5.0 mL of the solution to 50.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Reference solution (a) Dissolve 20.0 mg of *oxytetracycline CRS* in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution. Dilute 5.0 mL of the solution to 50.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 4 mg of *oxytetracycline for system suitability A CRS* (containing impurities A, B, C, D, E and F) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: 0.05 per cent *V/V* solution of *trifluoroacetic acid R*;

— *mobile phase B*: *tetrahydrofuran for chromatography R*, *methanol R*, *acetonitrile R* (5:15:80 *V/V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 20	90 → 65	10 → 35

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *oxytetracycline for system suitability A CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention With reference to oxytetracycline (retention time = about 6.5 min): impurity A = about 0.9; impurity B = about 1.2; impurity C = about 1.3; impurity D = about 1.4; impurity E = about 2.2; impurity F = about 2.3.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline; minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.4; impurity E = 0.4;

— for each impurity, use the concentration of oxytetracycline hydrochloride in reference solution (b).

Limits:

— *impurity C*: maximum 2.0 per cent;

— *impurity B*: maximum 1.0 per cent;

— *sum of impurities D, E and F*: maximum 1.0 per cent;

— *impurity A*: maximum 0.5 per cent;

— *impurities D, E*: for each impurity, maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.1 per cent;

— *total*: maximum 3.5 per cent;

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— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

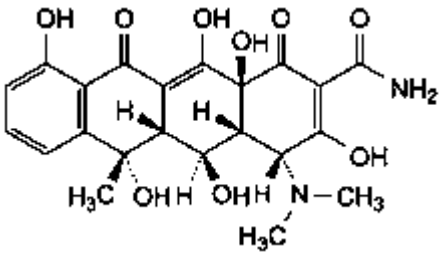
Calculate the percentage content of $C_{22}H_{25}ClN_2O_9$ taking into account the assigned content of *oxytetracycline CRS* and a conversion factor of 1.079.

STORAGE

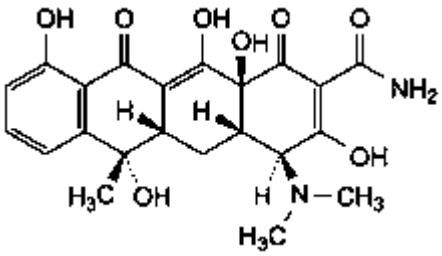
In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*



A. (4*R*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-*epi*-oxytetracycline),



B. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (tetracycline),

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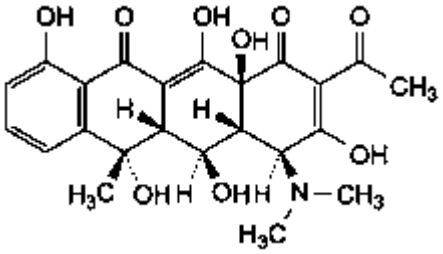
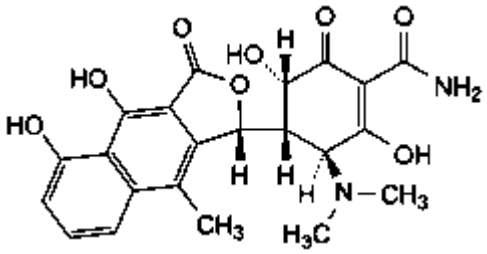
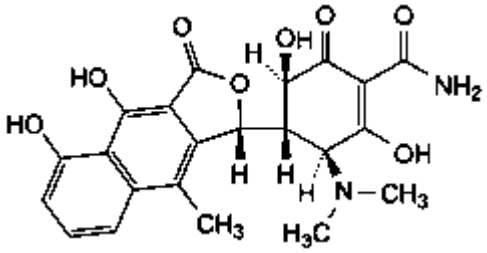


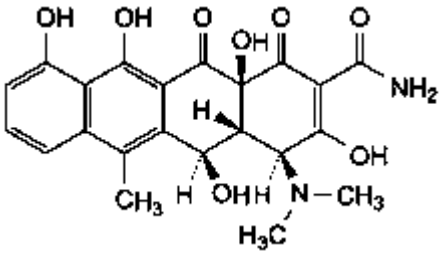
C. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-2-acetyl-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarbamoyloxytetracycline),



D. (3*S*,4*S*,5*S*)-4-[(1*R*)-4,5-dihydroxy-9-methyl-3-oxo-1,3-dihydronaphtho[2,3-*c*]furan-1-yl]-3-(dimethylamino)-2,5-dihydroxy-6-oxocyclohex-1-ene-1-carboxamide,



E. (3*S*,4*S*,5*R*)-4-[(1*R*)-4,5-dihydroxy-9-methyl-3-oxo-1,3-dihydronaphtho[2,3-*c*]furan-1-yl]-3-(dimethylamino)-2,5-dihydroxy-6-oxocyclohex-1-ene-1-carboxamide,



F. (4*S*,4a*R*,5*R*,12a*S*)-4-(dimethylamino)-3,5,10,11,12a-pentahydroxy-6-methyl-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (anhydro-oxytetracycline).

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Oxytetracycline Tablets

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Oxytetracycline Tablets contain Oxytetracycline Dihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of oxytetracycline dihydrate, $C_{22}H_{24}N_2O_9,2H_2O$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 10 mg of Oxytetracycline Dihydrate with 20 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) Dissolve 5 mg of *oxytetracycline hydrochloride BPCRS* in sufficient *methanol* to produce 10 mL.

(3) Dissolve 5 mg of *oxytetracycline hydrochloride BPCRS* and 5 mg of *demeclocycline hydrochloride BPCRS* in sufficient *methanol* to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable). Adjust the pH of a 10% w/v solution of *disodium edetate* to 7.0 with 10M *sodium hydroxide* and spray the solution evenly onto the plate (about 10 mL for a plate 100 mm × 200 mm). Allow the plate to dry in a horizontal position for at least 1 hour. Before use, dry the plate at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. To 2 mg of the powdered tablets add 2 mL of *sulfuric acid*; a deep crimson colour is produced. Add 1 mL of *water*; the colour changes to yellow.

C. Shake 4 mg of the powdered tablets with 5 mL of a 1% w/v solution of *sodium carbonate* and add 2 mL of *diazobenzenesulfonic acid solution*. A light brown colour is produced.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 30 minutes withdraw a 10-mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 353 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of oxytetracycline dihydrate, $C_{22}H_{24}N_2O_9,2H_2O$, in the medium taking 282 as the value of A(1%, 1 cm) at the maximum at 353 nm.

LIMITS

The amount of oxytetracycline dihydrate released is not less than 75% (Q) of the stated amount.

Light-absorbing impurities

Wash five tablets with *water* or *chloroform* until any coloured coating is removed, dry with filter paper and powder. Dissolve portions of the powder as completely as possible in sufficient of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *methanol* to produce two solutions of Oxytetracycline Dihydrate containing (1) 0.20% w/v and (2) 1.0% w/v, and filter each solution.

The *absorbance* of the filtrate obtained from solution (1) at 430 nm is not more than 0.50 and the *absorbance* of the filtrate obtained from solution (2) at 490 nm is not more than 0.40, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.01M oxalic acid (solvent A). Prepare the solutions immediately before use.

(1) Shake a quantity of the powdered tablets containing 0.16 g of Oxytetracycline Dihydrate in 150 mL of solvent A and dilute to 200 mL. Filter the resulting solution (Whatman GF/C filter is suitable).

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(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.08% w/v of *oxytetracycline for system suitability A EPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Intertsil C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05% v/v *trifluoroacetic acid*.

Mobile phase B 5 volumes of *tetrahydrofuran*, 15 volumes of *methanol* and 80 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	90	10	isocratic
5-20	90→65	10→35	linear gradient
20-21	65→90	35→10	linear gradient
21-27	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to oxytetracycline (retention time about 7 minutes) are: impurity A, about 0.9; impurity B, about 1.2; impurity C, about 1.3; impurity D, about 1.4; impurity E, about 2.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where *Hp* is the height above the baseline of the peak due to impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytetracycline.

LIMITS

Identify any peak corresponding to impurities A, B, C, D and E in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3). Multiply the areas of the peaks due to Impurity D and E by a correction factor of 0.4.

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity A is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile* and 80 volumes of 0.01M *oxalic acid* (solvent A). *Prepare the solutions immediately before use.*

(1) Shake, with the aid of ultrasound, a quantity of the powdered tablets containing 0.16 g of Oxytetracycline Dihydrate with 150 mL of solvent A. Dilute to 200 mL and filter (Whatman GF/C filter is suitable). Dilute 1 volume of the filtrate to 10 volumes.
(2) 0.0074% w/v of *oxytetracycline BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions stated under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{24}N_2O_9,2H_2O$ in the tablets using the declared content of $C_{22}H_{24}N_2O_9$ in *oxytetracycline BPCRS*. Each mg of $C_{22}H_{24}N_2O_9$ is equivalent to 1.078 mg of $C_{22}H_{24}N_2O_9,2H_2O$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Oxytetracycline Dihydrate.

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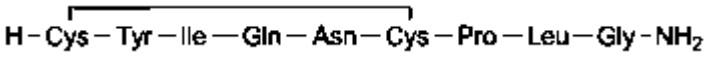
Oxytocin

General Notices

(Ph. Eur. monograph 0780)



$C_{43}H_{66}N_{12}O_{12}S_2$ 1007 *50-56-6*

Action and use

Oxytocic.

Preparations

Ergometrine and Oxytocin Injection

Oxytocin Injection

Ph Eur

DEFINITION

L-*S*$^{3.1}$,*S*$^{3.6}$-Cyclo(L-cysteinyl-LL-tyrosyl-LL-isoleucyl-LL-glutaminyl-LL-asparaginyl-LL-cysteinyl-LL-prolyl-LL-leucylglycinamide).

Synthetic cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary gland that stimulates contraction of the uterus and milk ejection in receptive mammals. It is available in the freeze-dried form as an acetate.

Content

93.0 per cent to 102.0 per cent (anhydrous and acetic acid-free substance).

By convention, for the purpose of labelling oxytocin preparations, 1 mg of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600 IU of biological activity.

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

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Solubility

Very soluble in water. It dissolves in dilute solutions of acetic acid and of ethanol (96 per cent).

IDENTIFICATION

Carry out either tests A, B or tests A, C.

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

B. Nuclear magnetic resonance spectrometry (2.2.64).

Preparation 5 mg/mL solution in *0.2 M deuterated sodium phosphate buffer solution pH 5.0 R* containing 20 µg/mL of *deuterated sodium trimethylsilylpropionate R*.

Comparison Dissolve the contents of a vial of *oxytocin for NMR identification CRS* in *0.2 M deuterated sodium phosphate buffer solution pH 5.0 R* containing 20 µg/mL of *deuterated sodium trimethylsilylpropionate R* to obtain a concentration of 5 mg/mL.

Operating conditions:

— *field strength*: minimum 300 MHz;

— *temperature*: 25 °C.

Results Examine the ^{1}H NMR spectrum from 0 to 8 ppm. The ^{1}H NMR spectrum obtained is qualitatively similar to the ^{1}H NMR spectrum obtained with *oxytocin for NMR identification CRS*.

C. Amino acid analysis (2.2.56). For hydrolysis use Method 1 and for analysis use Method 1.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids, taking 1/6 of the sum of the number of moles of aspartic acid, glutamic acid, proline, glycine, isoleucine and leucine as equal to 1. The values fall within the following limits: aspartic acid: 0.90 to 1.10; glutamic acid: 0.90 to 1.10; proline: 0.90 to 1.10; glycine: 0.90 to 1.10; leucine: 0.90 to 1.10; isoleucine: 0.90 to 1.10; tyrosine: 0.7 to 1.05; half-cystine: 1.4 to 2.1. Not more than traces of other amino acids are present.

TESTS

pH (2.2.3)

3.0 to 6.0.

Dissolve 0.200 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

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Test solution Prepare a 0.25 mg/mL solution of the substance to be examined in a 15.6 g/L solution of *sodium dihydrogen phosphate R*.

Reference solution (a) Dissolve the contents of a vial of *oxytocin for peak identification CRS* (containing impurities B, D, E and I) in 1 mL of a 15.6 g/L solution of *sodium dihydrogen phosphate R*.

Reference solution (b) Dissolve the contents of a vial of *oxytocin impurity F CRS* in 1 mL of a 15.6 g/L solution of *sodium dihydrogen phosphate R*.

Reference solution (c) Dissolve the contents of a vial of *oxytocin CRS* in a 15.6 g/L solution of *sodium dihydrogen phosphate R* to obtain a concentration of 0.25 mg/mL.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 15.6 g/L solution of *sodium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile for chromatography R*, *water for chromatography R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	70 → 40	30 → 60
30 - 30.1	40 → 70	60 → 30
30.1 - 45	70	30

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *oxytocin for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, D, E and I; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity F.

Relative retention With reference to oxytocin (retention time = about 10 min): impurity I = about 0.9; impurity D = about 0.95; impurities E and F = about 1.4; impurity B = about 1.7.

System suitability Reference solution (a):

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— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to oxytocin.

Limits:

— *sum of impurities E and F*: maximum 1.5 per cent;

— *impurity B*: maximum 1.0 per cent;

— *impurity I*: maximum 1.0 per cent;

— *any other impurity*: maximum 1.0 per cent;

— *total*: maximum 5.0 per cent;

— *disregard limit*: 0.1 per cent.

The thresholds indicated under Related substances (Table 2034.-2) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Acetic acid (*2.5.34*)

6.0 per cent to 10.0 per cent.

Test solution Dissolve 15.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on at least 50.0 mg.

Bacterial endotoxins (*2.6.14*)

Less than 300 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection 25 µL of the test solution and reference solution (c).

Calculate the percentage content of oxytocin ($C_{43}H_{66}N_{12}O_{12}S_2$) taking into account the assigned content of $C_{43}H_{66}N_{12}O_{12}S_2$ in *oxytocin CRS*.

STORAGE

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In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states:

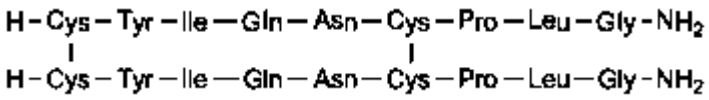
— the oxytocin peptide content ($C_{43}H_{66}N_{12}O_{12}S_2$);

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

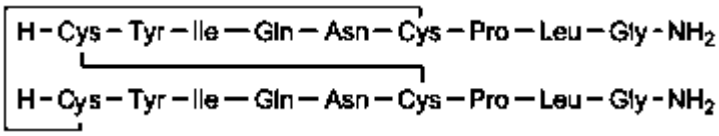
IMPURITIES

Specified impurities *B, E, F, I.*

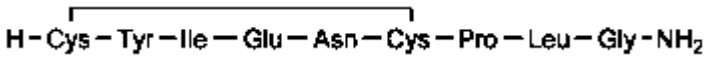
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D.*



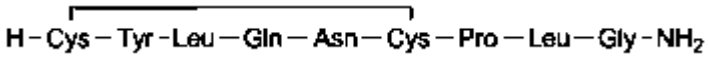
A. $S^{3.1}$,$S^{3.1'}$:$S^{3.6}$,$S^{3.6'}$-cyclo[bis(L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide)] (oxytocin parallel dimer),



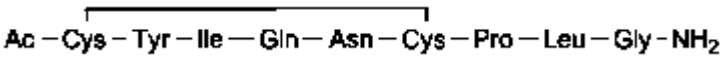
B. $S^{3.1}$,$S^{3.6'}$:$S^{3.6}$,$S^{3.1'}$-cyclo[bis(L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide)] (oxytocin antiparallel dimer),



C. [4-glutamic acid]oxytocin,



D. [3-leucine]oxytocin,



E. $N^{2.1}$-acetyloxytocin,

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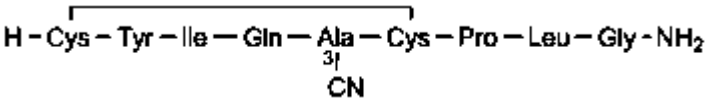
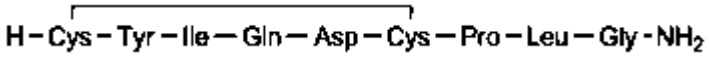


F. [5-(3-cyanoalanine)]oxytocin,



I. [5-aspartic acid]oxytocin.

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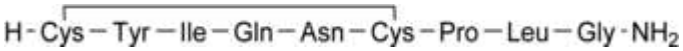
Oxytocin Concentrated Solution

General Notices

Oxytocin Bulk Solution

(Ph. Eur. monograph 0779)



$C_{43}H_{66}N_{12}O_{12}S_2$ 1007

Action and use

Oxytocic.

Preparations

Ergometrine and Oxytocin Injection

Oxytocin Injection

Ph Eur

DEFINITION

L-Cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide.

Solution of oxytocin, a synthetic cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary gland that stimulates contraction of the uterus and milk ejection in receptive mammals. It is available as a solution with a stated concentration of not less than 0.25 mg of oxytocin per millilitre, in a solvent that may contain an appropriate antimicrobial preservative.

Content

95.0 per cent to 105.0 per cent of the amount of the peptide stated per millilitre.

By convention, for the purpose of labelling oxytocin preparations, 1 mg of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600 IU of biological activity.

CHARACTERS

Appearance

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Clear, colourless liquid.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

B. Amino acid analysis (2.2.56). For hydrolysis use Method 1 and for analysis use Method 1.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids taking 1/6 of the sum of the number of moles of aspartic acid, glutamic acid, proline, glycine, isoleucine and leucine as equal to 1. The values fall within the following limits: aspartic acid: 0.90 to 1.10; glutamic acid: 0.90 to 1.10; proline: 0.90 to 1.10; glycine: 0.90 to 1.10; leucine: 0.90 to 1.10; isoleucine: 0.90 to 1.10; tyrosine: 0.7 to 1.05; half -cystine: 1.4 to 2.1. Not more than traces of other amino acids are present.

TESTS

pH (2.2.3)

3.0 to 5.0.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution The preparation to be examined.

Resolution solution Dissolve the contents of a vial of *oxytocin/desmopressin validation mixture CRS* in 1 mL of a 15.6 g/L solution of *sodium dihydrogen phosphate R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 15.6 g/L solution of *sodium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile for chromatography R*, *water R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	70 → 40	30 → 60
30 - 30.1	40 → 70	60 → 30

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
30.1 - 45	70	30

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL.

Retention time Oxytocin = about 7.5 min; desmopressin = about 10 min.

System suitability Resolution solution:

— *resolution*: minimum 5.0 between the peaks due to desmopressin and oxytocin.

Limits:

— *any impurity*: maximum 1.5 per cent;

— *total*: maximum 5 per cent;

— *disregard limit*: 0.1 per cent.

Bacterial endotoxins (*2.6.14*)

Less than 300 IU in the volume that contains 1 mg of oxytocin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Reference solution Dissolve the contents of a vial of *oxytocin CRS* in a 15.6 g/L solution of *sodium dihydrogen phosphate R* to obtain a concentration of 0.25 mg/mL.

Injection 25 µL.

Calculate the content of oxytocin ($C_{43}H_{66}N_{12}O_{12}S_2$) from the declared content of $C_{43}H_{66}N_{12}O_{12}S_2$ in *oxytocin CRS*.

STORAGE

At a temperature of 2 °C to 8 °C, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states the oxytocin peptide content in milligrams of $C_{43}H_{66}N_{12}O_{12}S_2$ per millilitre.

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Oxytocin Injection

General Notices

Action and use

Oxytocic.

DEFINITION

Oxytocin Injection is a sterile solution of Oxytocin or a sterile dilution of Oxytocin Concentrated Solution in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of oxytocin, $C_{43}H_{66}N_{12}O_{12}S_2$

90.0 to 110.0% of the stated amount.

For the purpose of labelling oxytocin preparations, 1 mg of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600 IU of biological activity.

CHARACTERISTICS

A clear, colourless liquid.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a high performance *silica gel* precoated plate (Merck Silica gel 60 plates are suitable) and a mixture of 1 volume of *glacial acetic acid*, 6 volumes of *water*, 30 volumes of *methanol* and 70 volumes of *dichloromethane* as the mobile phase but allowing the solvent front to ascend 8 cm above the line of application. Prepare a solution containing 17 µg per mL of *oxytocin EPCRS* by dissolving the contents of one vial in the requisite volume of a 1.56% w/v solution of *sodium dihydrogen orthophosphate* (solution A). For solution (1) evaporate 5 mL of the injection on a rotary evaporator at 30° and dissolve the residue in 0.5 mL of *water*.
For injections containing 0.00167% w/v prepare solution (2) by evaporating 5 mL of solution A on a rotary evaporator at 30° and dissolving the residue in 0.5 mL of *water*. Apply separately to the plate 1 µL of solutions (1) and (2), dry in a stream of cold air and develop immediately.

For injections containing 0.00083% w/v prepare solution (2) by evaporating 2.5 mL of solution A on a rotary evaporator at 30° and dissolving the residue in 0.5 mL of *water*. Apply separately to the plate 2 µL of solutions (1) and (2), dry in a stream of cold air and develop immediately.

After removal of the plate, allow it to dry in a stream of cold air for 10 minutes and develop again in a tank, previously equilibrated for 30 minutes with fresh mobile phase. After removal of the plate, allow it to dry in a stream of warm air for 10 minutes, cool and spray with *phosphomolybdotungstic reagent* until the plate appears translucent. Immediately place the plate in a tank, previously equilibrated for 30

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minutes with 13.5M *ammonia*, for 5 minutes, remove and dry in a stream of warm air. The principal spot in the chromatogram obtained with solution (1) corresponds in position, size and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a volume of the injection, if necessary, to produce a solution containing the equivalent of 0.00083% w/v of Oxytocin.
(2) Dilute 1 volume of solution (1) to 50 volumes.
(3) 0.16% w/v solution of *oxytocin/desmopressin validation mixture EPCRS*.
(4) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 1.56% w/v of *sodium dihydrogen orthophosphate* in *water*, filtered through a membrane filter with a pore size of 0.22 µm.

Mobile phase B Equal volumes of *Acetonitrile R1* and *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	70→40	30→60	linear gradient
30-30.1	40→70	60→30	linear gradient
30.1-45	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to oxytocin (retention time about 10 min) are: impurity 1, about 0.9; impurity 2, about 1.5; impurity 3, about 1.55; impurity 4, about 1.65.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to oxytocin and desmopressin is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than 3 times the area of the principal peak in the chromatogram obtained with solution (4) (0.3%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in water.

(1) Dilute a volume of the injection, if necessary, to produce a solution containing the equivalent of 0.00083% w/v of Oxytocin.
(2) 0.0008% w/v of *oxytocin EPCRS*.
(3) 0.16% w/v solution of *oxytocin/desmopressin validation mixture EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to oxytocin and desmopressin is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of oxytocin, $C_{43}H_{66}N_{12}O_{12}S_2$, in the injection from the chromatograms obtained and using the declared content of $C_{43}H_{66}N_{12}O_{12}S_2$, in *oxytocin EPCRS*.

LABELLING

The strength is stated as the number of IU (Units) per mL. The label also states the equivalent number of micrograms of oxytocin per mL.

IMPURITIES

The impurities limited by the requirements of this monograph include:

IMPURITIES

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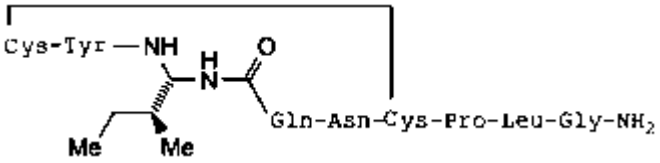
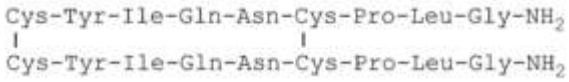
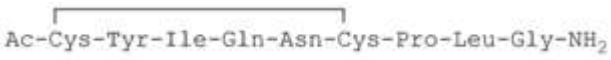


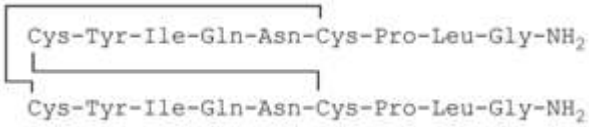
1. Carbamido-oxytocin



2. α-Oxytocin dimer



3. Acetyloxytocin



4. β-Oxytocin dimer

STORAGE

Oxytocin Injection should be protected from light and stored at a temperature of 2° to 8°.

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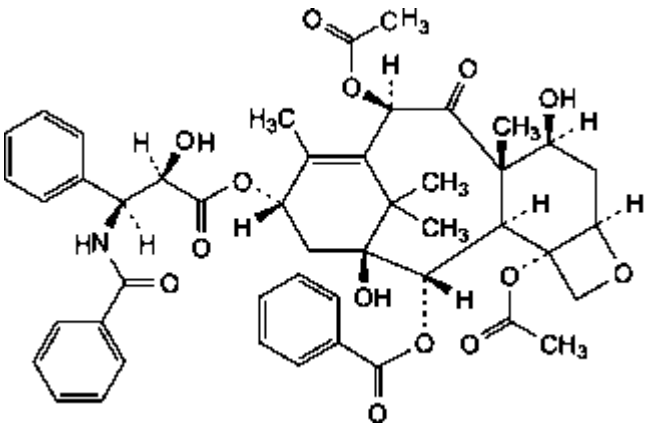
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Paclitaxel

General Notices

(Ph. Eur. monograph 1794)



$C_{47}H_{51}NO_{14}$ 854 *33069-62-4*

Action and use

Taxane cytotoxic.

Ph Eur

DEFINITION

4,10β-Bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β-dihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate.

It is isolated from natural sources or produced by fermentation or by a semi-synthetic process.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Practically insoluble in water, soluble in methanol and freely soluble in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *paclitaxel CRS*.

If the spectra obtained in the solid state show differences, dissolve 10 mg of the substance to be examined and the reference substance separately in 0.4 mL of *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.1 g in 10 mL of *methanol R*.

Specific optical rotation (2.2.7)

-55.0 to -49.0 (anhydrous substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

A. Paclitaxel isolated from natural sources or produced by fermentation.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in *acetonitrile R1* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with *acetonitrile R1*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 10.0 mL with *acetonitrile R1*. Dilute 1.0 mL of this solution to 100.0 mL with *acetonitrile R1*.

Reference solution (b) Dissolve 5.0 mg of *paclitaxel CRS* in *acetonitrile R1* and dilute to 5.0 mL with the same solvent. Dilute 2.0 mL of this solution to 20.0 mL with *acetonitrile R1*.

Reference solution (c) Dissolve 2.0 mg of *paclitaxel impurity C CRS* in *acetonitrile R1* and dilute to 20.0 mL with the same solvent.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 50.0 mL with *acetonitrile R1*.

Reference solution (e) To 1 mL of reference solution (b) add 1 mL of reference solution (c).

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Reference solution (f) Dissolve 5 mg of *paclitaxel natural for peak identification CRS* (containing impurities A, B, C, D, E, F, H, O, P, Q and R) in *acetonitrile R1* and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *diisopropylcyanosilyl silica gel for chromatography R* (5 µm) with a specific surface area of 180 m^2/g and a pore size of 8 nm;

— *temperature*: 20 ± 1 °C.

Mobile phase:

— *mobile phase A*: *methanol R1*, *water for chromatography R* (20:80 *V/V*);

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	85 → 56	15 → 44
60 - 61	56 → 85	44 → 15
61 - 75	85	15

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 227 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (d), (e) and (f).

Identification of impurities Use the chromatogram supplied with *paclitaxel natural for peak identification CRS* and the chromatogram obtained with reference solution (f) to identify the peaks due to impurities A, B, C, D, E, F, H, O, P, Q and R.

Relative retention With reference to paclitaxel (retention time = about 50 min): impurities A and B = about 0.90; impurity R = about 0.93; impurity H = about 0.96; impurities Q and P = about 1.02; impurity C = about 1.05; impurity D = about 1.07; impurities O and E = about 1.15; impurity F = about 1.20.

System suitability Reference solution (e):

— *resolution*: minimum 3.5 between the peaks due to paclitaxel and impurity C.

Limits:

— *sum of impurities E and O*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

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— *impurity R*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *sum of impurities A and B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurity C*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of impurities P and Q*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

B. Paclitaxel produced by a semi-synthetic process.

Test solution Dissolve 10.0 mg of the substance to be examined in *acetonitrile R1* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *acetonitrile R1*. Dilute 1.0 mL of this solution to 100.0 mL with *acetonitrile R1*.

Reference solution (b) Dissolve 5.0 mg of *paclitaxel CRS* in *acetonitrile R1* and dilute to 5.0 mL with the same solvent.

Reference solution (c) Dissolve 5 mg of *paclitaxel semi-synthetic for peak identification CRS* (containing impurities A, G, I and L) in *acetonitrile R1* and dilute to 5 mL with the same solvent.

Reference solution (d) Dissolve the contents of a vial of *paclitaxel semi-synthetic for system suitability CRS* (containing impurities E, H and N) in 1 mL of *acetonitrile R1*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm) with a specific surface area of 300 m^2/g and a pore size of 12 nm;

— temperature: 35 °C.

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Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, *water for chromatography R* (40:60 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 60	100 → 10	0 → 90
60 - 62	10 → 100	90 → 0
62 - 70	100	0

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 227 nm.

Injection 15 µL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram supplied with *paclitaxel semi-synthetic for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, G, I and L; use the chromatogram supplied with *paclitaxel semi-synthetic for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities E, H and N.

Relative retention With reference to paclitaxel (retention time = about 23 min): impurity N = about 0.2; impurity G = about 0.5; impurity A = about 0.8; impurities M, J and H = about 0.9; impurity E = about 1.3; impurity I = about 1.4; impurity L = about 1.5; impurity K = about 2.2.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity H and paclitaxel.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity N by 1.29;

— *impurity A*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *impurity L*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities E, I*: for each impurity, not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

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— *sum of impurities H, J and M*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurities G, K, N*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 12 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.32*)

Maximum 3.0 per cent, determined on 0.050 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Bacterial endotoxins (*2.6.14*)

Less than 0.4 IU/mg.

ASSAY

A. Paclitaxel isolated from natural sources or produced by fermentation.

Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modification.

Injection Test solution (b) and reference solution (b).

Calculate the percentage content of $C_{47}H_{51}NO_{14}$ from the declared content of *paclitaxel CRS*.

B. Paclitaxel produced by a semi-synthetic process.

Liquid chromatography (*2.2.29*) as described in test B for related substances with the following modification.

Injection 10 µL of the test solution and reference solution (b).

Calculate the percentage content of $C_{47}H_{51}NO_{14}$ from the declared content of *paclitaxel CRS*.

STORAGE

In an airtight container, protected from light.

LABELLING

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The label states the origin of the substance:

— isolated from natural sources;

— produced by fermentation;

— produced by a semi-synthetic process.

IMPURITIES

Test A for related substances

A, B, C, D, E, F, H, O, P, Q, R.

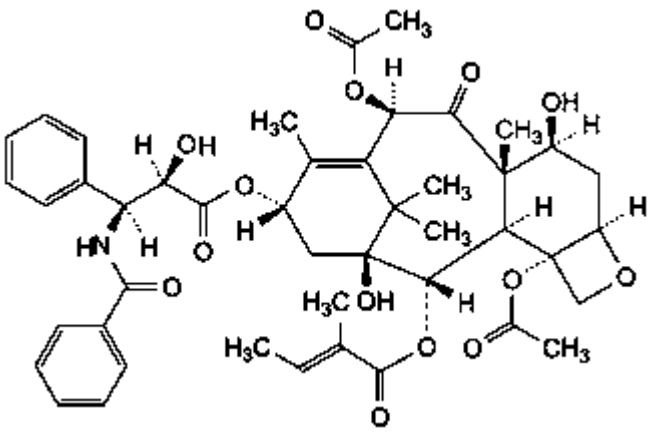
Specified impurities *A, B, C, D, E, F, O, P, Q, R.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H.*

Test B for related substances

A, E, G, H, I, J, K, L, M, N.

Specified impurities *A, E, G, H, I, J, K, L, M, N.*



A. 4,10β-bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β-dihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl (2*E*)-2-methylbut-2-enoate (2-*O*-debenzoyl-2-*O*-tigloylpaclitaxel),

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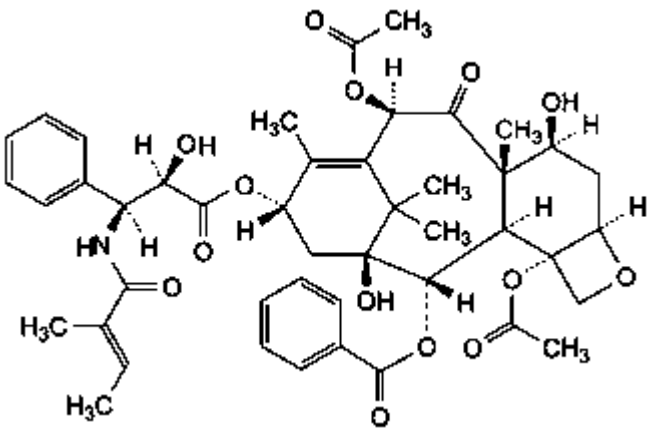
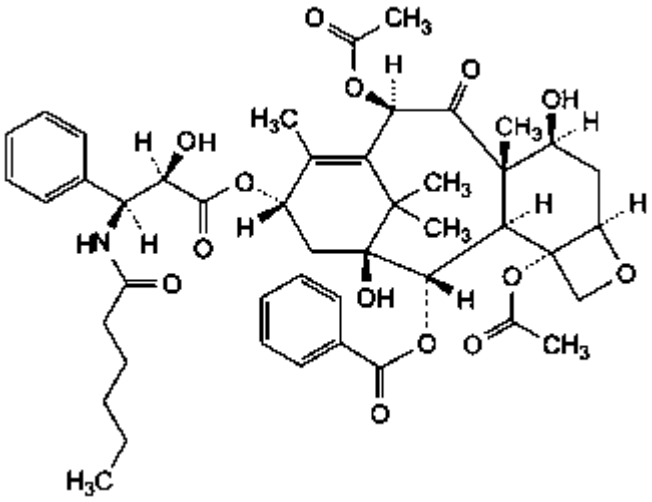
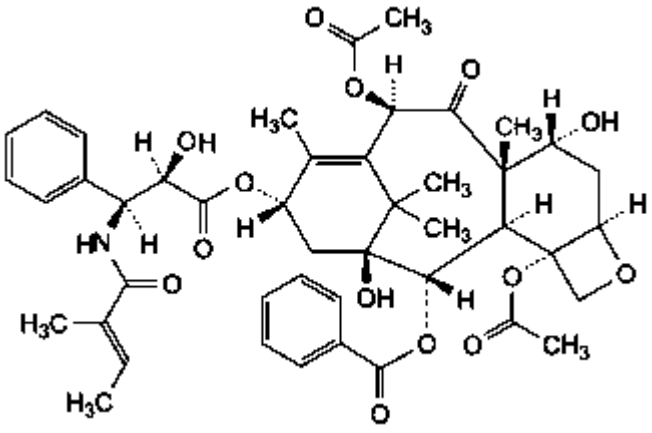


B. 4,10β-bis(acetyloxy)-1,7β-dihydroxy-13α-[[(2*R*,3*S*)-2-hydroxy-3-[[(2*E*)-2-methylbut-2-enoyl]amino]-3-phenylpropanoyl]oxy]-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-debenzoyl-*N*-tigloylpaclitaxel; cephalomannine),



C. 4,10β-bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-(hexanoylamino)-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β-dihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-debenzoyl-*N*-hexanoylpaclitaxel; paclitaxel C),



D. 4,10β-bis(acetyloxy)-1,7α-dihydroxy-13α-[[(2*R*,3*S*)-2-hydroxy-3-[[(2*E*)-2-methylbut-2-enoyl]amino]-3-phenylpropanoyl]oxy]-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-debenzoyl-*N*-tigloyl-7-*epi*-paclitaxel; 7-*epi*-cephalomannine),

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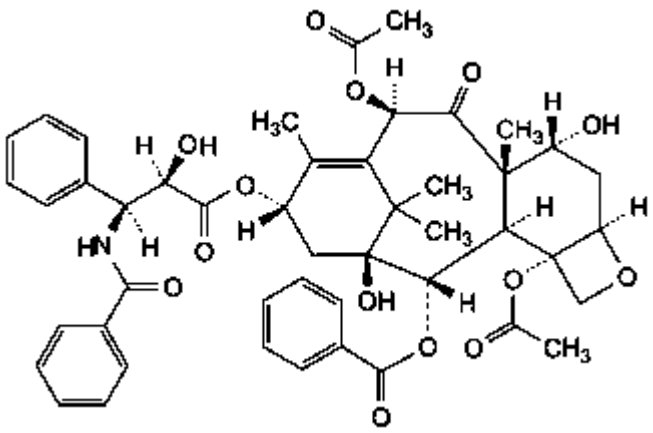
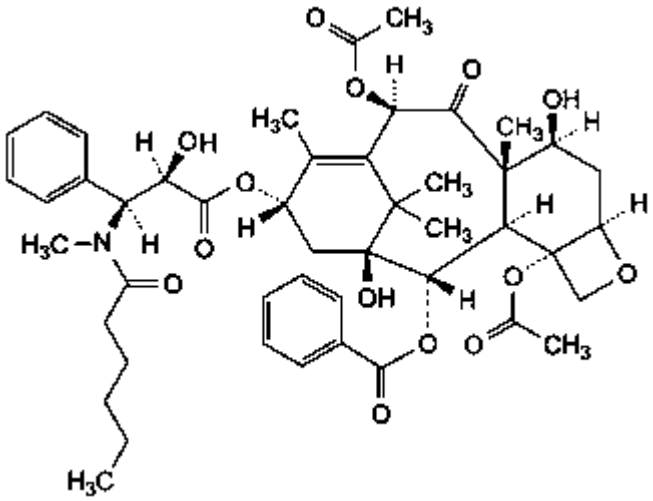
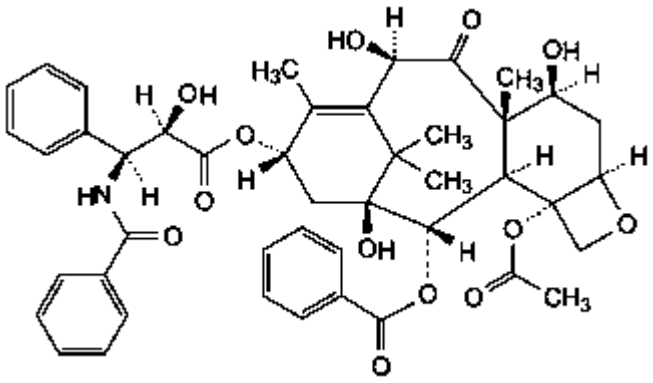


E. 4,10β-bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,7α-dihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (7-*epi*-paclitaxel),



F. 4,10β-bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-[hexanoyl(methyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β-dihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-debenzoyl-*N*-hexanoyl-*N*-methylpaclitaxel; *N*-methylpaclitaxel C),



G. 4-(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (10-*O*-deacetylpaclitaxel),

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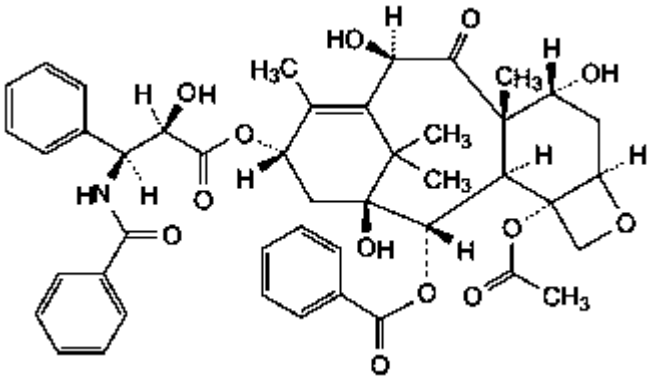
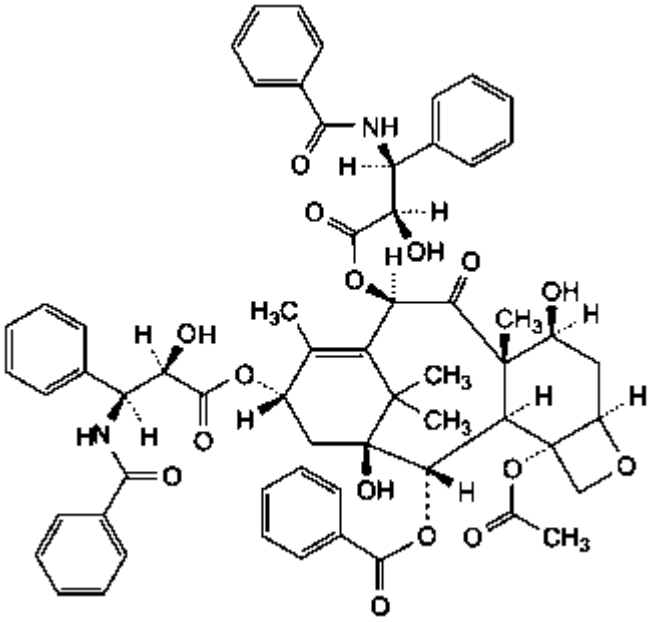
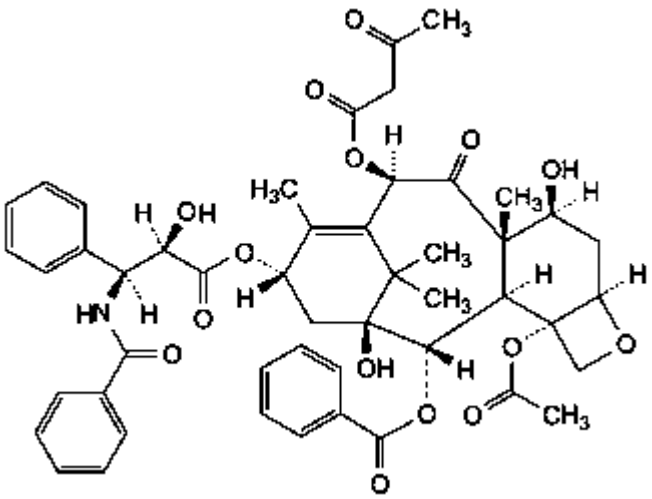


H. 4-(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,7α,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (10-*O*-deacetyl-7-*epi*-paclitaxel),



I. 4-(acetyloxy)-10β,13α-bis[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β-dihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (10-*O*-[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]-10-*O*-deacetylpaclitaxel),



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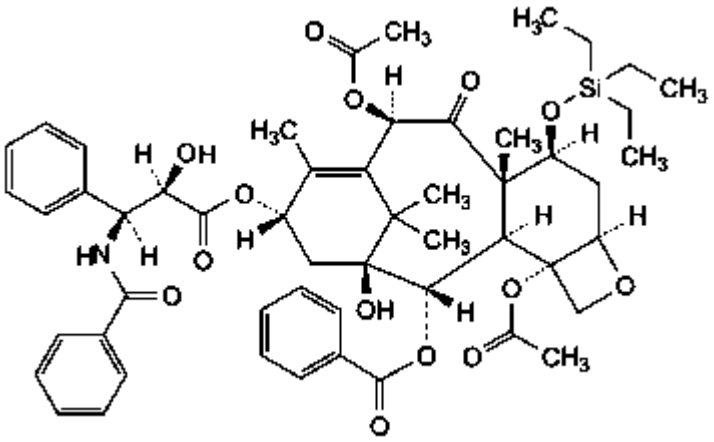
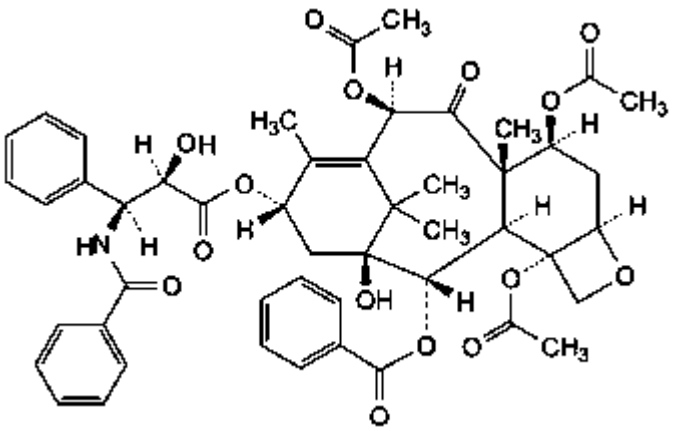
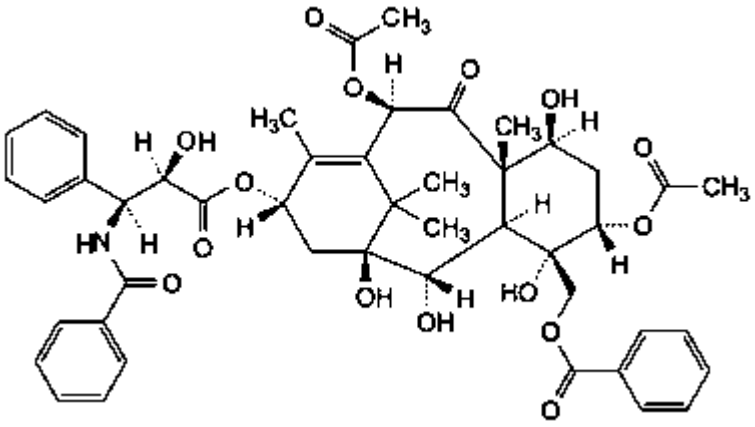
J. 4-(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β-dihydroxy-9-oxo-10β-[(3-oxobutanoyl)oxy]-5β,20-epoxytax-11-en-2α-yl benzoate (10-*O*-deacetyl-10-*O*-(3-oxobutanoyl)paclitaxel),



K. 4,10β-bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-9-oxo-7β-[(triethylsilyl)oxy]-5β,20-epoxytax-11-en-2α-yl benzoate (7-*O*-(triethylsilanyl)paclitaxel),



L. 4,7β,10β-tris(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (7-*O*-acetylpaclitaxel),



M. 5α,10β-bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy]-1,2α,4,7β-tetrahydroxy-9-oxotax-11-en-20-yl benzoate,

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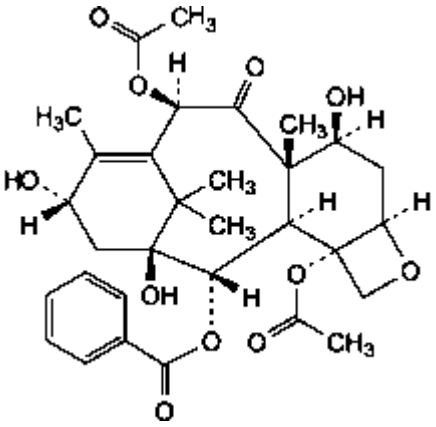
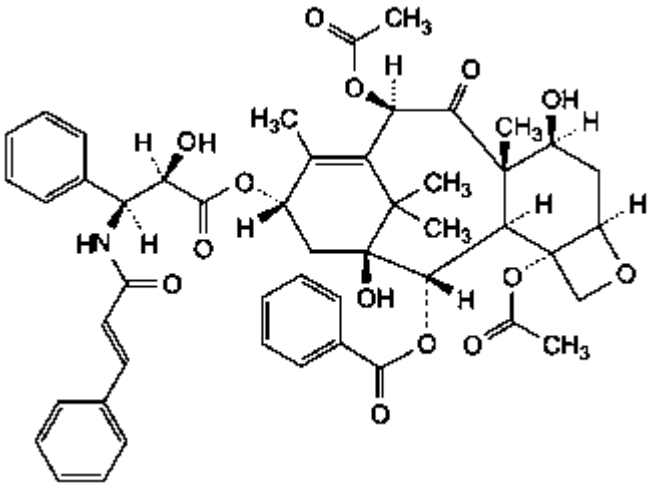
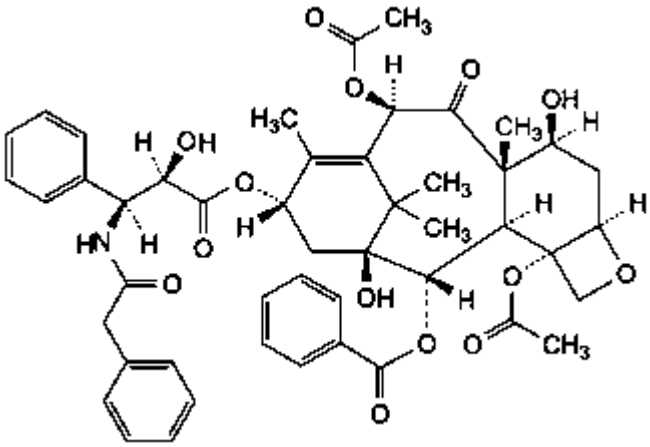


N. 4,10β-bis(acetyloxy)-1,7β,13α-trihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (13-*O*-de[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]paclitaxel; baccatin III),



O. 4,10β-bis(acetyloxy)-1,7β-dihydroxy-13α-[[(2*R*,3*S*)-2-hydroxy-3-phenyl-3-[[(2*E*)-3-phenylprop-2-enoyl]amino]propanoyl]oxy]-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-cinnamoyl-*N*-debenzoylpaclitaxel),



P. 4,10β-bis(acetyloxy)-1,7β-dihydroxy-13α-[[(2*R*,3*S*)-2-hydroxy-3-phenyl-3-(2-phenylacetamido)propanoyl]oxy]-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-debenzoyl-*N*-(phenylacetyl)paclitaxel),

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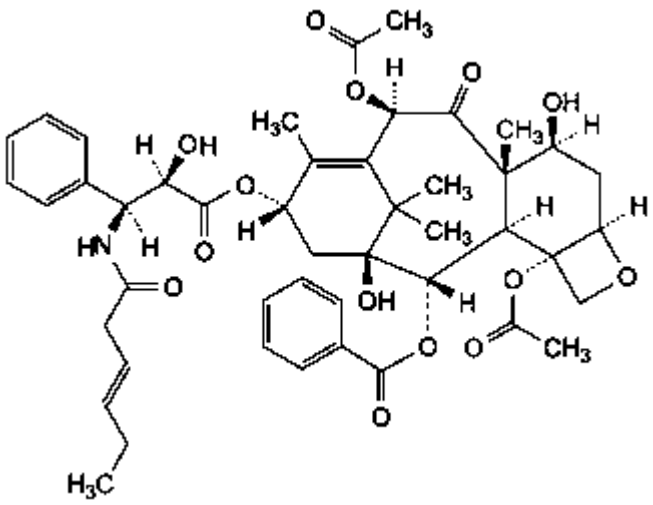
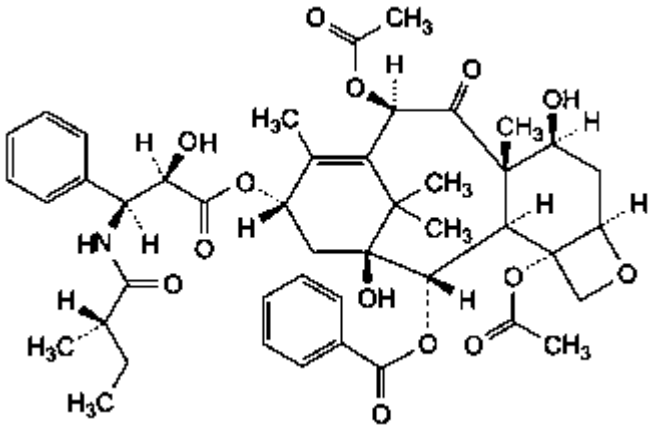


Q. 4,10β-bis(acetyloxy)-13α-[[(2*R*,3*S*)-3-[[(3*E*)-hex-3-enoyl]amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β-dihydroxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-debenzoyl-*N*-[(3*E*)-hex-3-enoyl]paclitaxel),



R. 4,10β-bis(acetyloxy)-1,7β-dihydroxy-13α-[[(2*R*,3*S*)-2-hydroxy-3-[[(2*S*)-2-methylbutanoyl]amino]-3-phenylpropanoyl]oxy]-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate (*N*-debenzoyl-*N*-[(2*S*)-2-methylbutanoyl]paclitaxel).

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Paediatric Alimemazine Oral Solution

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Paediatric Alimemazine Oral Solution is a solution containing 0.15% w/v of Alimemazine Tartrate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of alimemazine tartrate, $C_{36}H_{44}N_4S_2,C_4H_6O_6$

0.135 to 0.165% w/v.

IDENTIFICATION

Dilute 50 mL of the oral solution with 175 mL of *water* and add 7 mL of 1M *sodium hydroxide*. Extract with 100 mL of *ether*, wash the ether layer with 15 mL of *water* and dry over *anhydrous sodium sulfate* (solution A). Evaporate 30 mL of solution A to dryness and dissolve the residue in 0.2 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of alimemazine *(RS 005)*.

TESTS

Related substances

Complies with the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and the following freshly prepared solutions. For solution (1) dilute 15 mL with an equal volume of *water*, add 2 mL of 1M *sodium hydroxide* and extract with two 15-mL quantities of *chloroform*. Dry the chloroform extracts with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. Dissolve the residue as completely as possible in 1 mL of a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine*. For solution (2) dilute 1 volume of solution (1) to 50 volumes with the same solvent mixture.

ASSAY

Carry out the following procedure protected from light. To a weighed quantity containing 15 mg of Alimemazine Tartrate add 25 mL of *water* and 5 mL of a 5% w/v solution of *sodium hydroxide*. Extract the mixture with two 50 mL quantities of *chloroform*, shaking vigorously for 1 minute each time, evaporate the combined extracts to dryness at about 30° at a pressure of 2 kPa and dissolve the residue in sufficient *0.1 M hydrochloric acid* to produce 50 mL (solution B). Dilute 10 mL of solution B to 50 mL with *water* (solution C). To a further 10 mL of solution B add 5 mL of *peroxyacetic acid solution*, allow to stand for 10 minutes and add sufficient *water* to produce 50 mL (solution D). Measure the

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absorbance of solution D at the maximum at 342 nm, Appendix II B, using solution C in the reference cell and measure the *absorbance* of solution C at the same wavelength using *water* in the reference cell. Repeat the procedure using a 0.03% w/v solution of *alimemazine tartrate BPCRS* in *0.1M hydrochloric acid* in place of solution B and beginning at the words 'Dilute 10 mL of ...'. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{36}H_{44}N_4S_2,C_4H_6O_6$, weight in volume, using the declared content of $C_{36}H_{44}N_4S_2,C_4H_6O_6$ in *alimemazine tartrate BPCRS*. The result is not valid if the absorbance of solution C is more than 0.10.

STORAGE

Paediatric Alimemazine Oral Solution should be protected from light.

Paediatric Alimemazine Oral Solution contains 7.5 mg of Alimemazine Tartrate in 5 mL.

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Paediatric Co-trimoxazole Oral Suspension

General Notices

Paediatric Trimethoprim and Sulfamethoxazole Oral Suspension

Action and use

Dihydrofolate reductase inhibitor + sulfonamide antibacterial.

DEFINITION

Paediatric Co-trimoxazole Oral Suspension is a suspension containing 0.8% w/v of Trimethoprim and 4% w/v of Sulfamethoxazole in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of trimethoprim, $C_{14}H_{18}N_4O_3$

0.72 to 0.88% w/v.

Content of sulfamethoxazole, $C_{10}H_{11}N_3O_3S$

3.60 to 4.40% w/v.

IDENTIFICATION

Complies with the tests described under Co-trimoxazole Oral Suspension but in test B for solution (2) use a 1.0% w/v solution of *sulfamethoxazole BPCRS* in *methanol* and for solution (3) use a 0.20% w/v solution of *trimethoprim BPCRS* in *methanol*. Apply to the plate 10 µL of each of the three solutions.

Acidity

pH, 5.0 to 6.5, Appendix V L.

ASSAY

Carry out the Assays for trimethoprim and sulfamethoxazole described under Co-trimoxazole Oral Suspension but using 8 g of the oral suspension.

STORAGE

Paediatric Co-trimoxazole Oral Suspension should be protected from light and stored at a temperature not exceeding 30°.

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Paediatric Co-trimoxazole Oral Suspension contains, in 5 mL, 40 mg of Trimethoprim and 200 mg of Sulfamethoxazole.

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Paediatric Co-trimoxazole Tablets

General Notices

Paediatric Trimethoprim and Sulfamethoxazole Tablets

Action and use

Dihydrofolate reductase inhibitor + sulfonamide antibacterial.

DEFINITION

Paediatric Co-trimoxazole Tablets contain, in each, 20 mg of Trimethoprim and 100 mg of Sulfamethoxazole.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of trimethoprim, $C_{14}H_{18}N_4O_3$

0.0185 to 0.0215 g.

Content of sulfamethoxazole, $C_{10}H_{11}N_3O_3S$

0.0925 to 0.1075 g.

IDENTIFICATION

Comply with the tests described under Co-trimoxazole Tablets.

ASSAY

Carry out the Assays for trimethoprim and for sulfamethoxazole described under Co-trimoxazole Tablets.

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Paediatric Digoxin Injection

General Notices

Action and use

Na/K-ATPase inhibitor; cardiac glycoside.

DEFINITION

Digoxin	10 mg
Ethanol (80 per cent)	12.5 mL
Propylene Glycol	40 mL
Citric Acid Monohydrate	75 mg
Disodium Hydrogen Phosphate Dodecahydrate	0.45 g
Water for Injections	Sufficient to produce 100 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Digoxin in the Ethanol (80 per cent) and add the Propylene Glycol, a solution of the Citric Acid Monohydrate and the Disodium Hydrogen Phosphate Dodecahydrate in Water for Injections and add sufficient Water for Injections to produce 100 mL. Sterilise by *heating in an autoclave*.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of digoxin, $C_{41}H_{64}O_{14}$

0.0090 to 0.0110% w/v.

IDENTIFICATION

Evaporate 5 mL to dryness, dissolve the residue in 1 mL of *glacial acetic acid* containing 0.01% w/v of *iron(III) chloride* and cautiously add 1 mL of *sulfuric acid* without mixing. A brown ring, free from red colour, is produced at the interface and, after a short time, an indigo colour is produced in the upper layer.

Acidity or alkalinity

pH, 6.7 to 7.3, Appendix V L.

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ASSAY

Transfer 50 mL to a separating funnel containing 10 mL of *water*. Make alkaline with 5M *ammonia* and extract with four 25-mL quantities of *chloroform*. Wash each extract with the same 10 mL of *water*. Evaporate the combined chloroform extracts to dryness on a water bath, dry the residue at 105° for 15 minutes, cool, dissolve the residue in 5 mL of a mixture of 65 volumes of *chloroform* and 35 volumes of *methanol* and add 20 mL of *glacial acetic acid* (solution A). To 5 mL of a 0.2% w/v solution of *digoxin EPCRS* in *glacial acetic acid* add 10 mL of a mixture of 65 volumes of *chloroform* and 35 volumes of *methanol* and sufficient *glacial acetic acid* to produce 50 mL (solution B). Dilute 5 mL of solution A to 25 mL with *digoxin reagent*, mix, allow to stand for 2 hours and measure the *absorbance* of the resulting solution at 590 nm, Appendix II B, using *water* in the reference cell. Calculate the content of $C_{41}H_{64}O_{14}$ from the *absorbance* obtained by treating 5 mL of solution B at the same time and in the same manner.

STORAGE

Paediatric Digoxin Injection should be protected from light.

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Paediatric Digoxin Oral Solution

General Notices

Action and use

Na/K-ATPase inhibitor; cardiac glycoside.

DEFINITION

Paediatric Digoxin Oral Solution is a solution containing 0.005% w/v of Digoxin in a suitable flavoured vehicle.

Paediatric Digoxin Oral Solution should not be diluted.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of digoxin, $C_{41}H_{64}O_{14}$

0.0045 to 0.0055% w/v.

IDENTIFICATION

Extract 5 mL with four 20 mL quantities of *chloroform*, washing each extract with the same 10 mL of *water*, evaporate the combined extracts to dryness and dissolve the residue in 1 mL of *glacial acetic acid* containing 0.01% w/v of *iron(III) chloride hexahydrate*. Cautiously add 1 mL of *sulfuric acid* without mixing. A brown ring, free from red colour, is produced at the interface and, after a short time, an indigo colour is produced in the upper layer.

Acidity or alkalinity

pH, 6.8 to 7.2, Appendix V L.

ASSAY

Extract 100 mL with four 25 mL quantities of *chloroform*, washing each extract with the same 5 mL of *water*, and evaporate the combined extracts to dryness. To the residue add 3 mL of *absolute ethanol* and carefully evaporate to dryness on a water bath with the aid of a gentle current of air. Repeat the evaporation using a further 3 mL of *absolute ethanol* and cool. Dissolve the residue in 5 mL of a mixture of 65 volumes of *chloroform* and 35 volumes of *methanol*, add 20 mL of *glacial acetic acid* and filter if necessary. Dilute 5 mL of the filtrate to 25 mL with *digoxin reagent*, allow to stand for 2 hours and measure the *absorbance* of the resulting solution at the maximum at 590 nm, Appendix II B. Calculate the content of $C_{41}H_{64}O_{14}$ from the *absorbance* obtained by carrying out the operation at the same time but using a solution prepared by mixing 5 mL of a 0.2% w/v solution of *digoxin EPCRS* in *glacial acetic acid* with 10 mL of a mixture of 65 volumes *chloroform* and 35 volumes of *methanol* and adding sufficient *glacial acetic acid* to produce 50 mL, beginning at the words ‘Dilute 5 mL of the filtrate …’ and using *water* in the reference cell.

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STORAGE

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Paediatric Docusate Oral Solution

General Notices

Action and use

Stimulant laxative; faecal softener.

DEFINITION

Paediatric Docusate Oral Solution contains 0.25% w/v of Docusate Sodium in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of docusate sodium, $C_{20}H_{37}NaO_7S$

0.238 to 0.263% w/v.

IDENTIFICATION

Complies with the tests described under Docusate Oral Solution.

ASSAY

Carry out the Assay described under Docusate Oral Solution but preparing solution (1) in the following manner. For solution (1) pass a weighed quantity of the oral solution containing 5 mg of docusate sodium, with the aid of vacuum, through a solid-phase extraction column of 1 mL capacity and containing 0.1 g of an *octadecyl-bonded silica sorbent* (a Sep-pak C18 column is suitable) previously washed with 2 mL of *methanol*, followed by 5 mL of *water*. Wash the column with 2 mL of *water*, discarding the aqueous eluate. Elute the docusate sodium with 4 mL of *methanol* and dilute to 10 mL with a mixture of equal volumes of *acetonitrile* and *water*.

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Paediatric Ferrous Sulfate Oral Solution

General Notices

Paediatric Ferrous Sulphate Oral Solution

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Paediatric Ferrous Sulfate Oral Solution is a solution containing 1.2% w/v of Ferrous Sulfate Heptahydrate and a suitable antioxidant in a suitable vehicle with an orange flavour. It is intended to be diluted well with water before use.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ferrous sulfate heptahydrate, $FeSO_4,7H_2O$

1.10 to 1.30% w/v.

ASSAY

To 20 mL add 45 mL of *water*, 0.2 mL of *hydrochloric acid* and *dilute potassium permanganate solution* drop wise until a permanent pink colour is produced. Add 10 mL of *hydrochloric acid* and 3 mL of a 10% w/v solution of *ammonium thiocyanate* and titrate with *0.1M titanium(III) chloride VS* maintaining a steady flow of *carbon dioxide* through the flask. Each mL of *0.1M titanium(III) chloride VS* is equivalent to 27.80 mg of $FeSO_4,7H_2O$.

Paediatric Ferrous Sulfate Oral Solution contains in 5 mL about 12 mg of ferrous iron.

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Paediatric Oseltamivir Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Treatment of influenza.

DEFINITION

Paediatric Oseltamivir Oral Solution is a solution of Oseltamivir Phosphate in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of oseltamivir, $C_{16}H_{28}N_2O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the oral solution, if necessary, with sufficient *water* to produce a solution containing the equivalent of 1.14% w/v of oseltamivir (1.5% w/v of Oseltamivir Phosphate).

(2) 1.5% w/v of *oseltamivir phosphate (impurity B-free) EPCRS* in *water*.

(3) 1.5% w/v of *oseltamivir phosphate (impurity B-free) EPCRS* and 0.15% w/v of *aciclovir BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 7 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of 13.5M *ammonia*, 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Yields reaction B characteristic of *phosphates*, Appendix VI.

TESTS

Acidity

pH, 4.0 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution with sufficient of a mixture of 135 volumes of *acetonitrile R1*, 245 volumes of *methanol R2* and 620 volumes of *water for chromatography* (solvent A) to produce a solution containing the equivalent of 0.08% w/v of oseltamivir (0.1% w/v of Oseltamivir Phosphate).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and further dilute 1 volume to 10 volumes with solvent A.

(3) 0.001% w/v of each of *oseltamivir impurity A EPCRS* and *oseltamivir impurity C EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 207 nm.

(f) Inject 15 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for twice the retention time of the peak due to oseltamivir phosphate.

MOBILE PHASE

135 volumes of *acetonitrile R1*, 245 volumes of *methanol R2* and 620 volumes of a 0.68% w/v solution of *potassium dihydrogen orthophosphate* in *water for chromatography*, the pH of which has been adjusted to 6.0 with 1M *potassium hydroxide*.

When the chromatograms are recorded under the prescribed conditions the retention time of oseltamivir is about 17 minutes; the relative retention of impurity A is about 0.16 and the relative retention of impurity C is about 0.17.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity C is at least 1.5.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 0.3 times the area of the peak due to impurity C in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution with sufficient of the mobile phase to produce a solution containing the equivalent of 0.015% w/v of oseltamivir and then dilute 10 volumes of this solution to 100 volumes with the mobile phase.
(2) 0.002% w/v of *oseltamivir phosphate (impurity-B free) EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Varian Pursuit C8 and Waters Symmetry C8 are suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 207 nm.
(f) Inject 15 µL of each solution.

MOBILE PHASE

43.5 volumes of *methanol* and 56.5 volumes of 0.05M *potassium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.0 with 4M *potassium hydroxide*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{16}H_{28}N_2O_4$, weight in volume, using the declared content of $C_{16}H_{28}N_2O_4,H_3PO_4$ in *oseltamivir phosphate (impurity B-free) EPCRS*. Each mg of $C_{16}H_{28}N_2O_4,H_3PO_4$ is equivalent to 0.7612 mg of $C_{16}H_{28}N_2O_4$.

STORAGE

Paediatric Oseltamivir Oral Solution should be stored at a temperature of 2° to 8°.

LABELLING

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The quantity of active ingredient is stated in terms of the equivalent amount of oseltamivir.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C, D, E, F and G listed under Oseltamivir Phosphate.

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Paediatric Paracetamol Oral Solution

General Notices

Action and use

Analgesic; antipyretic.

DEFINITION

Paediatric Paracetamol Oral Solution is a solution containing 2.4% w/v of Paracetamol in a suitable flavoured vehicle.

It should not be diluted.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

2.28 to 2.52% w/v.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the preparation being examined with *methanol* to produce a solution containing 0.24% w/v of Paracetamol and filter if necessary.

(2) 0.24% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}.

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop to 15 cm.

(e) After removal of the plate, dry in a current of warm air, examine under *ultraviolet light (254 nm)* and reveal the spots using *Method 1*.

MOBILE PHASE

0.5 volume of *glacial acetic acid*, 10 volumes of *toluene*, 25 volumes of *acetone* and 65 volumes of *chloroform*.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to paracetamol in the chromatogram obtained with solution (1).

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4-Aminophenol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 5 mL of the preparation being examined with 15 mL of the mobile phase, dilute to 25 mL with the mobile phase and filter if necessary.
(2) 0.0024% w/v of *4-aminophenol* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil ODS is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 272 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium butanesulfonate* in a mixture of 0.4 volumes of *formic acid*, 15 volumes of *methanol* and 85 volumes of *water*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminophenol is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

Peaks with a long retention time may occur due to preservatives in the preparation.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a weighed quantity of the preparation being examined containing 24 mg of Paracetamol with 100 mL of the mobile phase, dilute to 200 mL with the mobile phase and filter, if necessary.
(2) 0.012% w/v of *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure may be carried out using the conditions described in the test for 4-Aminophenol but using a detection wavelength of 243 nm.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the preparation, Appendix V G, and calculate the percentage content of $C_8H_9NO_2$, weight in volume, using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

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STORAGE

Paediatric Paracetamol Oral Solution should be protected from light. It should not be refrigerated.

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Paediatric Paracetamol Oral Suspension

General Notices

Action and use

Analgesic; antipyretic.

DEFINITION

Paediatric Paracetamol Oral Suspension is a suspension containing not more than 5% w/v of Paracetamol in a suitably flavoured vehicle. It should not be diluted.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the preparation being examined with *methanol* and shake to produce a solution containing 0.24% w/v of Paracetamol and filter if necessary.

(2) 0.24% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}.

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop to 15 cm.

(e) After removal of the plate, dry in a current of warm air, examine under *ultraviolet light (254 nm)* and also reveal the spots using *Method 1*.

MOBILE PHASE

0.5 of a volume of *glacial acetic acid*, 10 volumes of *toluene*, 25 volumes of *acetone* and 65 volumes of *dichloromethane*.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to paracetamol in the chromatogram obtained with solution (2).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D. *Prepare the solutions immediately before use and protect from light*.

(1) Shake 5 mL of the preparation being examined with 4 mL of the mobile phase, dilute with the mobile phase to contain 0.12% w/v of Paracetamol and filter if necessary.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(3) 0.00012% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.

(4) Dilute a 0.0012% w/v solution of *4′-chloroacetanilide* in *methanol* with the mobile phase to produce a solution containing 0.0000012% w/v of *4′-chloroacetanilide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 12 times the retention time of the principal peak.

MOBILE PHASE

250 volumes of *methanol* containing 1.15 g of a 40% w/v solution of *tetrabutylammonium hydroxide*, 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (10 ppm);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

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the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.03%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a weighed quantity of the preparation being examined containing 24 mg of Paracetamol with 100 mL of the mobile phase, dilute to 200 mL with the mobile phase and filter if necessary.
(2) 0.012% w/v of *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances test may be used.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the preparation, Appendix V G, and calculate the percentage content of $C_8H_9NO_2$, weight in volume, using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

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Paediatric Phenobarbital Oral Solution

General Notices

Different formulations of Paediatric Phenobarbital Oral Solution may vary in bioavailability. Patients should be monitored to ensure blood levels remain within the required therapeutic range.

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Barbiturate.

DEFINITION

Paediatric Phenobarbital Oral Solution is a solution containing Phenobarbital Sodium in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of phenobarbital, $C_{12}H_{12}N_2O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Acidify 50 mL of the preparation being examined to *litmus paper* with *2M hydrochloric acid* and extract with four 25-mL quantities of *ether*. Wash the combined ether extracts with two 2-mL quantities of *water* and wash the combined aqueous washings with 10 mL of *ether*. Add the ether washings to the combined ether extracts, evaporate the ether and dry the residue to constant weight at 105°. The *infrared absorption spectrum*, Appendix II A, of the dried residue is concordant with the *reference spectrum* of phenobarbital (*RS 270*).

B. Yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Alkalinity

pH, 7.5 to 9.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the oral solution, if necessary, to produce a solution containing the equivalent of 0.1% w/v of phenobarbital.

(2) Dilute 1 volume of solution (1) to 10 volumes; further dilute 1 volume to 50 volumes.

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(3) 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb S5 ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of phenobarbital.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution containing 0.66% w/v *sodium acetate* in *water*, adjusted to pH 4.5 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to phenobarbital (retention time, about 9 minutes) are: impurity A, about 0.4; impurity B, about 0.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution to produce a solution containing the equivalent of 0.01% w/v of phenobarbital.

(2) 0.01% w/v of *phenobarbital BPCRS*.

(3) 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{12}H_{12}N_2O_3$, weight in volume, using the declared content of $C_{12}H_{12}N_2O_3$ in *phenobarbital BPCRS*.

STORAGE

Paediatric Phenobarbital Oral Solution should be protected from light. It should not be refrigerated.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of phenobarbital.

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Paediatric Simple Linctus

General Notices

Paediatric Simple Oral Solution

DEFINITION

Paediatric Simple Linctus is an *oral solution* containing 0.625% w/v of Citric Acid Monohydrate in a suitable vehicle with an anise flavour.

Extemporaneous preparation

It may be prepared extemporaneously by diluting Simple Linctus with a suitable vehicle in accordance with the manufacturer's instructions.

The linctus complies with the requirements stated under Oral Liquids and with the following requirements.

Content of free acid, calculated as citric acid monohydrate, $C_6H_8O_7,H_2O$

0.53 to 0.69% w/v.

IDENTIFICATION

Dilute 20 mL to 50 mL with *water*, add 2 g of *activated charcoal*, mix and filter. To 1 mL of the filtrate add 1 mL of *pyridine*, swirl to mix, add 5 mL of *acetic anhydride* and mix using, for example, a rotary vortex mixer. Immediately place in a water bath at about 30° for 5 minutes. A yellow colour is produced.

ASSAY

Dilute 15 g with 50 mL of *water* and titrate with *0.1M sodium hydroxide VS* using 2 mL of *thymol blue solution* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 7.005 mg of $C_6H_8O_7,H_2O$. Determine the *weight per mL* of the linctus, Appendix V G, and calculate the content of $C_6H_8O_7,H_2O$, weight in volume.

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Paediatric Vitamins A, C and D Oral Drops

General Notices

DEFINITION

Paediatric Vitamins A, C and D Oral Drops are a solution of vitamin A, Ascorbic Acid and Colecalciferol in a suitable, flavoured vehicle.

The oral drops comply with the requirements stated under Oral Liquids and with the following requirements.

Content of vitamin A

5200 to 6200 IU per mL.

Content of ascorbic acid

160 to 175 mg per mL.

Content of colecalciferol

2100 to 2500 IU per mL.

IDENTIFICATION

A. In the Assay for vitamin A, the solution shows a maximum at 325 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the oral drops, if necessary, with *water* to contain the equivalent of 0.5% w/v of ascorbic acid.

(2) 0.5% w/v of *ascorbic acid BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC silica gel F_{254} plate* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *water* and 120 volumes of *ethanol* (*96%*).

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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C. In the Assay for colecalciferol, the chromatogram obtained with solution (1) shows a peak corresponding to the colecalciferol peak in the chromatogram obtained with solution (2).

ASSAY

For Vitamin A

Carry out the test as rapidly as possible, avoiding exposure to actinic light and air, oxidising agents, oxidation catalysts (e.g. copper and iron) and acids.

Examine by *ultraviolet absorption spectrophotometry*, Appendix II B (Method A). If method A is found not to be valid, examine by *liquid chromatography*, Appendix III D (Method B).

Method A

Test solution To a weighed quantity of the oral drops containing 50,000 IU in a round-bottomed flask, add 3 mL of a freshly prepared 50% w/w solution of *potassium hydroxide* and 30 mL of *absolute ethanol*. Boil under a reflux condenser in a current of *nitrogen* for 30 minutes. Cool rapidly and add 30 mL of *water*. Extract with four 50 mL quantities of *ether* discarding the lower layer after complete separation. Wash the combined upper layers with four 50 mL quantities of *water* and evaporate to dryness under a gentle current of *nitrogen* at a temperature not exceeding 30° or in a rotary evaporator at a temperature not exceeding 30° under reduced pressure (water ejector). Dissolve the residue in sufficient *propan-2-ol* to give an expected concentration of vitamin A equivalent to 10 to 15 IU per mL.

Measure the *absorbances*, Appendix II B, of the solution at 300 nm, 310 nm, 325 nm and 334 nm and at the wavelength of maximum absorption with a suitable spectrophotometer in 1 cm matched cells, using *propan-2-ol* as the compensation liquid.

Calculate the content of vitamin A, as *all-trans*-retinol, in IU per gram from the expression:

$$A_{325} \times \frac{1830}{100m} \times V$$

where	A_{325}	=	absorbance at 325 nm
	m	=	weight of the oral drops in grams
	V	=	total volume of solution containing 10 IU to 15 IU of vitamin A per mL
	1830	=	conversion factor for the specific absorbance of *all-trans*-retinol in IU

The above expression can be used only if A_{325} has a value of not greater than $A_{325,\,corr}$ / 0.970 where $A_{325,\,corr}$ is the corrected absorbance at 325 nm and is given by the equation:

$$A_{325,\,corr} = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$$

where A designates the absorbance at the wavelength indicated by the subscript.

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If A_{325} has a value greater than $A_{325,\,corr}$ / 0.970, calculate the content of vitamin A from the expression:

$$A_{325,\,corr} \times \frac{1830}{100m} \times V$$

The assay is not valid unless:

(a) the wavelength of maximum absorption lies between 323 nm and 327 nm and

(b) the absorbance at 300 nm relative to that at 325 nm is at most 0.73.

Method B

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the oral drops containing 50,000 IU in a round-bottomed flask, add 5 mL of a freshly prepared 10% w/v solution of *ascorbic acid* and 10 mL of a freshly prepared 80% w/v solution of *potassium hydroxide* and 100 mL of *ethanol* (*96%*). Boil under a reflux condenser on a water bath for 15 minutes. Add 100 mL of a 1% w/v solution of *sodium chloride* and cool. Transfer the solution to a 500 mL separating funnel rinsing the round-bottomed flask with about 75 mL of a 1% w/v solution of *sodium chloride* and then with 150 mL of a mixture of equal volumes of *petroleum spirit* (*boiling range, 40° to 60°*) and *ether*. Shake for 1 minute. When the layers have separated completely, discard the lower layer and wash the upper layer, first with 50 mL of a 3% w/v solution of *potassium hydroxide* in a 10% v/v solution of *ethanol* (*96%*) and then with three 50 mL quantities of a 1% w/v solution of *sodium chloride*. Filter the upper layer through 5 g of *anhydrous sodium sulfate* on a fast filter paper into a 250 mL flask suitable for a rotary evaporator. Wash the funnel with 10 mL of fresh extraction mixture, filter and combine the upper layers. Distil them at a temperature not exceeding 30° under reduced pressure (water ejector) and fill with *nitrogen* when evaporation is completed. Alternatively evaporate the solvent under a gentle current of *nitrogen* at a temperature not exceeding 30°. Dissolve the residue in *propan-2-ol*, transfer to a 25 mL volumetric flask and dilute to 25 mL with *propan-2-ol*. Gentle heating in an ultrasonic bath may be required.

(2) Prepare a solution of *retinyl acetate EPCRS* in *propan-2-ol R1* so that 1 mL contains about 1000 IU of *all-trans*-retinol.

The exact concentration of solution (2) is assessed by ultraviolet absorption spectrophotometry, Appendix II B. Dilute solution (2) with *propan-2-ol R1* to a presumed concentration of 10 to 15 IU per mL and measure the *absorbance* at 326 nm in matched 1 cm cells using *propan-2-ol R1* as the compensation liquid.

Calculate the content of vitamin A in IU per mL of solution (2) from the following expression, taking into account the assigned content of *retinyl acetate EPCRS*:

$$A_{326} \times \frac{1900 \times V_2}{100 \times V_1}$$

where A_{326} = absorbance at 326 nm

V_2 = volume of the diluted solution

V_1 = volume of solution (2) used

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1900 = conversion factor for the specific absorbance of *retinyl acetate EPCRS* in IU

For solution (3) proceed as described for solution (1) but use 2 mL of solution (2) in place of the oral drops.

The exact concentration of solution (3) is assessed by *ultraviolet absorption spectrophotometry*, Appendix II B. Dilute solution (3) with *propan-2-ol R1* to a presumed concentration of 10 to 15 IU per mL of *all-trans*-retinol and measure the absorbance at 325 nm in matched 1 cm cells using *propan-2-ol R1* as the compensation liquid.

Calculate the content of *all-trans*-retinol in IU per millilitre of solution (3) from the expression:

$$A_{325} \times \frac{1830 \times V_4}{100 \times V_3}$$

where A_{325} = absorbance at 325 nm

V_3 = volume of the diluted solution

V_4 = volume of solution (3) used

1830 = conversion factor for the specific absorbance of *all-trans*-retinol in IU

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm to 10 µm).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 325 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

3 volumes of *water* and 97 volumes of *methanol*.

SYSTEM SUITABILITY

Inject in triplicate solution (1) and solution (3). The retention time of *all-trans*-retinol is 5 ± 1 minutes.

The assay is not valid unless: (a) the chromatogram obtained with solution (1) shows a peak corresponding to that of *all-trans*-retinol in the chromatogram obtained with solution (3); (b) when using the method of standard additions to solution (1) there is greater than 95% recovery of the added *retinyl acetate EPCRS*; (c) the recovery of *all-trans*-retinol in solution (3), as assessed by direct absorption spectrophotometry, is greater than 95%.

DETERMINATION OF CONTENT

Calculate the content of vitamin A using the following expression:

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$$A_1 \times \frac{C \times V}{A_2} \times \frac{1}{m}$$

where A_1 = area of the peak corresponding to *all-trans*-retinol in the chromatogram obtained with solution (1)

A_2 = area of the peak corresponding to *all-trans*-retinol in the chromatogram obtained with solution (3)

C = concentration of *retinyl acetate EPCRS* in solution (2) as assessed prior to the saponification in International Units per mL (= 1000 IU per mL)

V = volume of solution (2) treated

m = weight of the oral drops in solution (1)

For ascorbic acid

To a volume of the oral drops containing the equivalent of 0.14 g of ascorbic acid, add 100 mL of 1% w/v *orthophosphoric acid* in *water* and 1 mL of *starch solution* and titrate with *0.05M iodine VS* until a full blue colour is produced. Each mL of *0.05M iodine VS* is equivalent to 0.0088 g of ascorbic acid.

For colecalciferol

Carry out the assay as rapidly as possible, avoiding exposure to actinic light and air. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the oral drops containing about 4000 IU of colecalciferol, add 10 mL of a 0.001% w/v solution of *ergocalciferol BPCRS* in *absolute ethanol*, 20 mL of *absolute ethanol* and 5 mL of a 60% w/v solution of *potassium hydroxide* in *water*. Pass a stream of nitrogen and boil under a reflux condenser for 20 minutes, cool and transfer the contents to a separating funnel using *ether*, shake and allow the layers to separate; discard the lower layer and wash the ether layer with four 50 mL quantities of *water*, swirling gently for each washing and discard the lower layer. Evaporate to dryness using a rotary evaporator and transfer the residue to a 4 mL vial using small quantities of *methanol* until 4 mL of solution is obtained.

(2) In the same manner as solution (1) but using 10 mL each of 0.001% w/v each of *colecalciferol BPCRS* and *ergocalciferol BPCRS* respectively beginning at the words '20 mL of *absolute ethanol*...'.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with particles of silica the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below. Allow the mobile phase to equilibrate for 30 minutes.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

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7 volumes of *water* and 93 volumes of *methanol*.

SYSTEM SUITABILITY

The assay is not valid unless the chromatogram obtained with solution (2) shows two distinct peaks. If complete resolution is not attained, add 3% v/v of *distilled water* to the mobile phase, allow to equilibrate and repeat the chromatography. If the resolution is still not achieved, use a new column and allow the mobile phase to equilibrate for 30 minutes.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral drops, Appendix V G, and calculate the content of colecalciferol, weight in volume, using the declared content of colecalciferol in *colecalciferol BPCRS*.

STORAGE

Paediatric Vitamins A, C and D Oral Drops should be kept in an airtight container and protected from light.

LABELLING

The label states the number of International Units of Vitamin A and Colecalciferol and the content of vitamin C in terms of the equivalent amount of ascorbic acid.

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Palmitic Acid

General Notices

(Ph. Eur. monograph 1904)

57-10-3

Action and use

Excipient.

Ph Eur

DEFINITION

Hexadecanoic acid ($C_{16}H_{32}O_2$; M_r 256.4), obtained from fats or oils of vegetable or animal origin.

Content

Minimum 92.0 per cent.

CHARACTERS

Appearance

White or almost white, waxy solid.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Freezing point (see Tests).

B. Acid value (*2.5.1*): 216 to 220, determined on 0.1 g.

C. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Appearance

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Heat the substance to be examined to about 75 °C. The resulting liquid is not more intensely coloured than reference solution Y_7 or BY_7 (*2.2.2, Method I*).

Acidity

Melt 5.0 g, stir for 2 min in 10 mL of hot *carbon dioxide-free water R*, cool slowly and filter. To the filtrate add 0.05 mL of *methyl orange solution R*. No red colour develops.

Freezing point (*2.2.18*)

60 °C to 66 °C.

Iodine value (*2.5.4*)

Maximum 1.

Stearic acid

Maximum 6.0 per cent, determined as prescribed in the assay.

ASSAY

Gas chromatography (*2.4.22, Method C*) with the following modifications. Prepare the solutions as described in the method but omitting the initial hydrolysis.

Reference solution Prepare the reference solution in the same manner as the test solution using a mixture of 50 mg of *palmitic acid R* and 50 mg of *stearic acid R* instead of the substance to be examined.

Relative retention With reference to methyl stearate: methyl palmitate = about 0.9.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to methyl stearate and methyl palmitate.

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Pamidronate Disodium Infusion

General Notices

Pamidronate Disodium Intravenous Infusion

Action and use

Bisphosphonate; treatment of osteolytic lesions; Paget's disease; hypercalcaemia of malignancy.

DEFINITION

Pamidronate Disodium Infusion is a sterile solution containing Pamidronate Disodium. It is prepared by diluting Pamidronate Disodium for Infusion in a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of anhydrous pamidronate disodium per mL (solution A). The endotoxin limit concentration of solution A is 30 IU of endotoxin per mL.

STORAGE

Pamidronate Disodium Infusion should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

PAMIDRONATE DISODIUM FOR INFUSION

DEFINITION

Pamidronate Disodium for Infusion is a sterile material prepared from Pamidronate Disodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of anhydrous pamidronate disodium, $C_3H_9NNa_2O_7P_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

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A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of the sealed container in sufficient *water* to produce a solution containing the equivalent of 0.3% w/v of anhydrous pamidronate disodium.

(2) 0.4% w/v of *disodium pamidronate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a precoated cellulose plate (Avicel F1440 precoated 10 cm × 10 cm sheets are suitable). Before use, place the plate in an unlined tank and allow the mobile phase to ascend to the top of the sheet, dry it for 30 minutes in a current of warm air at about 50° and allow it to cool. Use with the flow of mobile phase in the same direction as that used for the prewash and use the same chamber and mobile phase.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in a current of warm air for 30 minutes, spray with a solution prepared by dissolving 1 g of *ammonium molybdate* in 85 mL of *water* and adding 10 mL of *hydrochloric acid* and 5 mL of a 60% v/v solution of *perchloric acid*, heat at 80° for 10 minutes, allow to cool and expose to *ultraviolet light (365 nm)* for 2 minutes; examine the plate in daylight.

MOBILE PHASE

1% w/v of *trichloroacetic acid* in 5 volumes of 13.5M *ammonia*, 40 volumes of *water* and 55 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to pamidronate disodium in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing the equivalent of 0.3% w/v of anhydrous pamidronate disodium. The pH of the solution is 6.0 to 7.0, Appendix V L.

β-Alanine

Carry out the method for *thin-layer chromatography* under subdued light, Appendix III A, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing the equivalent of 0.30% w/v of anhydrous pamidronate disodium.

(2) 0.0015% w/v of *3-aminopropionic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

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(d) Develop the plate to 7 cm.

(e) After removal of the plate, dry in a current of warm air and spray with a 0.01% w/v solution of *fluorescamine* in *acetone*, immerse the plate for 2 seconds in a mixture of 1 volume of *liquid paraffin* and 2 volumes of *n-hexane*, allow to dry in air for 15 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

4 volumes of 13.5M *ammonia*, 8 volumes of *di-isopropyl ether* and 9 volumes of *methanol*.

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to β-alanine (3-aminopropionic acid) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of the 10 containers in *water* and dilute with the same solvent to produce a solution containing the equivalent of 0.20% w/v of anhydrous pamidronate disodium.

(2) 0.20% w/v of *disodium pamidronate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with an anion-exchange stationary phase (7 µm) (Allsep Anion is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a *differential refractometer* (RI) detector.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Add 0.47 mL of *formic acid* to 2500 mL of *water* and adjust the pH to 3.5 with 2M *sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the content of $C_3H_9NNa_2O_7P_2$ in a container of average content weight using the declared content of $C_3H_9NNa_2O_7P_2$ in *disodium pamidronate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous pamidronate disodium.

IMPURITIES

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The impurities limited by the requirements of this monograph include *β-alanine*.

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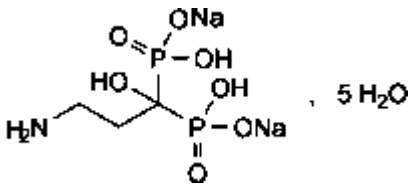
Pamidronate Disodium Pentahydrate

General Notices

Disodium Pamidronate

(Ph. Eur. monograph 1779)



$C_3H_9NNa_2O_7P_2,5H_2O$ 369.1 *109552-15-0*

Action and use

Bisphosphonate; treatment of osteolytic lesions; Paget's disease; hypercalcaemia of malignancy.

Preparation

Pamidronate Disodium Infusion

Ph Eur

DEFINITION

Disodium dihydrogen (3-amino-1-hydroxypropylidene)bisphosphonate pentahydrate.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in methylene chloride. It is sparingly soluble in dilute mineral acids and dissolves in dilute alkaline solutions.

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *pamidronate disodium pentahydrate CRS*.

B. Dissolve 0.5 g in 10 mL of *water R*. The solution gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

pH (2.2.3)

7.8 to 8.8.

Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 15 mg of *3-aminopropionic acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *di-isopropyl ether R*, *methanol R* (4:8:9 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Spray with a *ninhydrin solution R*. Heat at 100-105 °C for 15 min.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Impurities B and C

Liquid chromatography (2.2.29).

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Test solution Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution To 2.0 mL of a 0.3 g/L solution of *phosphoric acid R* add 2.0 mL of a 0.25 g/L solution of *phosphorous acid R* and dilute to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *anion-exchange resin R* (5 µm),

— *temperature*: 35 °C.

Mobile phase To 0.5 mL of *anhydrous formic acid R* add 2500 mL of *water R*; adjust to pH 3.5 with an 80 g/L solution of *sodium hydroxide R*.

Flow rate 1.0 mL/min.

Detection Refractometer.

Injection 100 µL.

Relative retention With reference to pamidronate (retention time = about 13 min): impurity B = about 1.3; impurity C = about 1.6.

System suitability Reference solution:

— *resolution*: minimum 2.5 between the peaks due to impurities B and C.

Limits:

— *impurities B, C*: for each impurity, not more than the area of the corresponding peaks in the chromatogram obtained with the reference solution (0.5 per cent).

Water (*2.5.12*)

23.0 per cent to 27.0 per cent, determined on 0.100 g.

ASSAY

Dissolve 0.250 g in 70 mL of *water R*. Titrate with *0.1 M hydrochloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 27.91 mg of $C_3H_9NNa_2O_7P_2$.

IMPURITIES

Specified impurities *A, B, C.*

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A. 3-aminopropanoic acid (β-alanine),

B. H_3PO_4: phosphoric acid,

C. H_3PO_3: phosphorous acid.

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Pancreatic Extract

General Notices

(Pancreas Powder, Ph. Eur. monograph 0350)

Ph Eur

DEFINITION

Pancreas powder is prepared from the fresh or frozen pancreases of mammals. It contains various enzymes having proteolytic, lipolytic and amylolytic activities.

1 mg of pancreas powder contains not less than 1.0 Ph. Eur. U. of total proteolytic activity, 15 Ph. Eur. U. of lipolytic activity and 12 Ph. Eur. U. of amylolytic activity.

PRODUCTION

The animals from which pancreas powder is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

Appearance

Slightly brown, amorphous powder.

Solubility

Partly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Triturate 0.5 g with 10 mL of *water R* and adjust to pH 8 with *0.1 M sodium hydroxide*, using 0.1 mL of *cresol red solution R* as indicator. Divide the suspension into 2 equal parts (suspension (a) and suspension (b)). Boil suspension (a). To each suspension add 10 mg of *fibrin congo red R*, heat to 38-40 °C and maintain at this temperature for 1 h. Suspension (a) is colourless or slightly pink and suspension (b) is distinctly more red.

B. Triturate 0.25 g with 10 mL of *water R* and adjust to pH 8 with *0.1 M sodium hydroxide*, using 0.1 mL of *cresol red solution R* as indicator. Divide the suspension into 2 equal parts (suspension (a) and suspension (b)). Boil suspension (a). Dissolve 0.1 g of *soluble starch R* in 100 mL of boiling *water R*, boil for 2 min, cool and dilute to 150 mL with *water R*. To 75 mL of the starch solution add suspension (a) and to the remaining 75 mL add suspension (b). Heat each mixture to 38-40 °C and maintain at this temperature for 5 min. To 1 mL of each mixture add 10 mL of *iodine solution R2*. The mixture obtained with suspension (a) has an intense blue-violet colour; the mixture obtained with suspension (b) has the colour of the iodine solution.

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TESTS

Fat content

Maximum 5.0 per cent.

In an extraction apparatus, treat 1.0 g with *light petroleum R1* for 3 h. Evaporate the solvent and dry the residue at 100-105 °C for 2 h. The residue weighs a maximum of 50 mg.

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 0.50 g by drying at 60 °C at a pressure not exceeding 670 Pa for 4 h.

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

ASSAY

Total proteolytic activity

The total proteolytic activity of pancreas powder is determined by comparing the quantity of peptides non-precipitable by a 50 g/L solution of *trichloroacetic acid R* released per minute from a substrate of casein solution with the quantity of such peptides released by *pancreas powder (protease) BRP* from the same substrate in the same conditions.

Casein solution Suspend a quantity of *casein BRP* equivalent to 1.25 g of dried substance in 5 mL of *water R*, add 10 mL of *0.1 M sodium hydroxide* and stir for 1 min. (Determine the water content of *casein BRP* prior to the test by heating at 60 °C *in vacuo* for 4 h.) Add 60 mL of *water R* and stir with a magnetic stirrer until the solution is practically clear. Adjust to pH 8.0 with *0.1 M sodium hydroxide* or *0.1 M hydrochloric acid*. Dilute to 100.0 mL with *water R*. Use the solution on the day of preparation.

Enterokinase solution Dissolve 50 mg of *enterokinase BRP* in *0.02 M calcium chloride solution R* and dilute to 50.0 mL with the same solvent. Use the solution on the day of preparation.

To avoid absorption of water formed by condensation, allow the preparation to be examined and the reference preparation to reach room temperature before opening the containers.

For the test suspension and the reference suspension, prepare the suspension and carry out the dilution at 0-4 °C.

Test suspension Triturate 0.100 g of the substance to be examined for 5 min adding gradually 25 mL of *0.02 M calcium chloride solution R*. Transfer completely to a volumetric flask and dilute to 100.0 mL with *0.02 M calcium chloride solution R*. To 10.0 mL of this

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suspension add 10.0 mL of the enterokinase solution and heat on a water-bath at 35 ± 0.5 °C for 15 min. Cool and dilute with *borate buffer solution pH 7.5 R* at 5 ± 3 °C to a final concentration of about 0.065 Ph. Eur. U. of total proteolytic activity per millilitre calculated on the basis of the stated activity.

Reference suspension Prepare a suspension of *pancreas powder (protease) BRP* as described for the test suspension but without the addition of enterokinase so as to obtain a known final concentration of about 0.065 Ph. Eur. U. per millilitre calculated on the basis of the stated activity.

Designate tubes in duplicate T, T_b, S_1, S_{1b}, S_2, S_{2b}, S_3, S_{3b}; designate a tube B.

Add *borate buffer solution pH 7.5 R* to the tubes as follows:

B: 3.0 mL;

S_1 and S_{1b}: 2.0 mL;

S_2, S_{2b}, T and T_b: 1.0 mL.

Add the reference suspension to the tubes as follows:

S_1 and S_{1b}: 1.0 mL;

S_2 and S_{2b}: 2.0 mL;

S_3 and S_{3b}: 3.0 mL.

Add 2.0 mL of the test suspension to tubes T and T_b.

Add 5.0 mL of a 50 g/L solution of *trichloroacetic acid R* to tubes B, S_{1b}, S_{2b}, S_{3b} and T_b. Mix by shaking.

Place the tubes and the casein solution in a water-bath at 35 ± 0.5 °C. Place a glass rod in each tube. When temperature equilibrium is reached, add 2.0 mL of the casein solution to tubes B, S_{1b}, S_{2b}, S_{3b} and T_b. Mix. At time zero, add 2.0 mL of casein solution successively and at intervals of 30 s to tubes S_1, S_2, S_3 and T. Mix immediately after each addition. Exactly 30 min after addition of the casein solution, taking into account the regular interval adopted, add 5.0 mL of a 50 g/L solution of *trichloroacetic acid R* to tubes S_1, S_2, S_3 and T. Mix. Withdraw the tubes from the water-bath and allow to stand at room temperature for 20 min.

Filter the contents of each tube twice through the same suitable filter paper previously washed with a 50 g/L solution of *trichloroacetic acid R*, then with *water R* and dried.

A suitable filter paper complies with the following test: filter 5 mL of a 50 g/L solution of *trichloroacetic acid R* on a 7 cm disc of white filter paper; the absorbance (*2.2.25*) of the filtrate, measured at 275 nm using unfiltered trichloroacetic acid solution as the compensation liquid, is less than 0.04.

A schematic presentation of the above operations is shown in Table 0350.-1.

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Table 0350.-1

	Tubes								
	S_1	S_{1b}	S_2	S_{2b}	S_3	S_{3b}	T	T_b	B
Buffer solution	2	2	1	1			1	1	3
Reference suspension	1	1	2	2	3	3			
Test suspension							2	2	
Trichloroacetic acid solution		5		5		5		5	5
Mix		+		+		+		+	+
Water-bath 35 °C	+	+	+	+	+	+	+	+	+
Casein solution		2		2		2		2	2
Mix		+		+		+		+	+
Casein solution	2		2		2		2		
Mix	+		+		+		+		
Water-bath 35 °C 30 min	+	+	+	+	+	+	+	+	+
Trichloroacetic acid solution	5		5		5		5		
Mix	+		+		+		+		
Room temperature 20 min	+	+	+	+	+	+	+	+	+
Filter	+	+	+	+	+	+	+	+	+

Measure the absorbance (2.2.25) of the filtrates at 275 nm using the filtrate obtained from tube B as the compensation liquid.

Correct the average absorbance values for the filtrates obtained from tubes S_1, S_2 and S_3 by subtracting the average values obtained for the filtrates from tubes S_{1b}, S_{2b} and S_{3b} respectively. Draw a calibration curve of the corrected values against the volume of reference suspension used.

Determine the activity of the substance to be examined using the corrected absorbance for the test suspension ($T - T_b$) and the calibration curve and taking into account the dilution factors.

The test is not valid unless the corrected absorbance values are between 0.15 and 0.60.

Lipolytic activity

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The lipolytic activity is determined by comparing the rate at which a suspension of pancreas powder hydrolyses a substrate of olive oil emulsion with the rate at which a suspension of *pancreas powder (lipase) BRP* hydrolyses the same substrate under the same conditions. *The test is carried out under nitrogen.*

Olive oil stock emulsion In an 800 mL beaker 9 cm in diameter, place 40 mL of *olive oil R*, 330 mL of *acacia solution R* and 30 mL of *water R*. Place an electric mixer at the bottom of the beaker. Place the beaker in a vessel containing *ethanol (96 per cent) R* and a sufficient quantity of ice as a cooling mixture. Emulsify using the mixer at an average speed of 1000-2000 r/min. Cool to 5-10 °C. Increase the mixing speed to 8000 r/min. Mix for 30 min keeping the temperature below 25 °C by the continuous addition of crushed ice into the cooling mixture. (A mixture of calcium chloride and crushed ice is also suitable). Store the stock emulsion in a refrigerator and use within 14 days. The emulsion must not separate into 2 distinct layers. Check the diameter of the globules of the emulsion under a microscope. At least 90 per cent have a diameter below 3 µm and none has a diameter greater than 10 µm. Shake the emulsion thoroughly before preparing the emulsion substrate.

Olive oil emulsion For 10 determinations, mix the following solutions in the order indicated: 100 mL of the stock emulsion, 80 mL of *tris(hydroxymethyl)aminomethane solution R1*, 20 mL of a freshly prepared 80 g/L of *sodium taurocholate BRP* and 95 mL of *water R*. Use on the day of preparation.

Apparatus Use a reaction vessel of about 50 mL capacity provided with:

— a device that will maintain a temperature of 37 ± 0.5 °C;

— a magnetic stirrer;

— a lid with holes for the insertion of electrodes, the tip of a burette, a tube for the admission of nitrogen and the introduction of reagents.

An automatic or manual titration apparatus may be used. In the latter case, the burette is graduated in 0.005 mL and the pH-meter is provided with a wide reading scale and glass-silver-silver chloride or other suitable electrodes. After each test the reaction vessel is evacuated by suction and washed several times with *water R*, the washings being removed each time by suction.

To avoid absorption of water formed by condensation, allow the preparation to be examined and the reference preparation to reach room temperature before opening the containers.

For the test suspension and the reference suspension, prepare the suspension and carry out the dilution at 0-4 °C.

Test suspension In a small mortar cooled to 0-4 °C, triturate carefully a quantity of the substance to be examined equivalent to about 2500 Ph. Eur. U. of lipolytic activity with 1 mL of maleate buffer solution pH 7.0 R (lipase solvent) until a very fine suspension is obtained. Dilute the suspension with maleate buffer solution pH 7.0 R, transfer quantitatively to a volumetric flask and dilute to 100.0 mL with the buffer solution. Keep the flask containing the test suspension in iced water during the titration.

Reference suspension Prepare a suspension of *pancreas powder (lipase) BRP* as described for the test suspension using a quantity equivalent to about 2500 Ph. Eur. U.

Carry out the titrations immediately after preparation of the test suspension and the reference suspension. Place 29.5 mL of olive oil emulsion in the reaction vessel equilibrated at 37 ± 0.5 °C. Fit the vessel with the electrodes, a stirrer and the burette (the tip being

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immersed in the olive oil emulsion).

Put the lid in place and switch on the apparatus. Carefully add *0.1 M sodium hydroxide* with stirring to adjust to pH 9.2. Using a rapid-flow graduated pipette transfer about 0.5 mL of the previously homogenised reference suspension, start the chronometer and add continuously *0.1 M sodium hydroxide* to maintain the pH at 9.0. After exactly 1 min, note the volume of *0.1 M sodium hydroxide* used. Carry out the measurement a further 4 times. Discard the first reading and determine the average of the 4 others (S_1). Make 2 further determinations (S_2 and S_3). Calculate the average of the values S_1, S_2 and S_3. The average volume of *0.1 M sodium hydroxide* used should be about 0.12 mL per minute with limits of 0.08 mL to 0.16 mL.

Carry out 3 determinations in the same manner for the test suspension (T_1, T_2 and T_3). If the quantity of *0.1 M sodium hydroxide* used is outside the limits of 0.08 mL to 0.16 mL per minute, the assay is repeated with a quantity of test suspension that is more suitable but situated between 0.4 mL and 0.6 mL. Otherwise the quantity of the substance to be examined is adjusted to comply with the conditions of the test. Calculate the average of the values T_1, T_2 and T_3.

Calculate the activity in European Pharmacopoeia Units per milligram using the following expression:

$$\frac{n \times m_1}{n_1 \times m} \times A$$

n	=	average volume of *0.1 M sodium hydroxide* used per minute during the titration of the test suspension, in millilitres;
n_1	=	average volume of *0.1 M sodium hydroxide* used per minute during the titration of the reference suspension, in millilitres;
m	=	mass of the substance to be examined, in milligrams;
m_1	=	mass of the reference preparation, in milligrams;
A	=	activity of *pancreas powder (lipase) BRP*, in European Pharmacopoeia Units per milligram.

Amylolytic activity

The amylolytic activity is determined by comparing the rate at which a suspension of pancreas powder hydrolyses a substrate of starch solution with the rate at which a suspension of *pancreas powder (amylase) BRP* hydrolyses the same substrate under the same conditions.

Starch solution To a quantity of *starch BRP* equivalent to 2.0 g of the dried substance add 10 mL of *water R* and mix. (Determine the water content of *starch BRP* prior to the test by heating at 120 °C for 4 h). Add this suspension, whilst stirring continuously, to 160 mL of boiling *water R*. Wash the container several times with successive quantities, each of 10 mL, of *water R* and add the washings to the hot starch solution. Heat to boiling, stirring continuously. Cool to room temperature and dilute to 200 mL with *water R*. Use the solution on the day of preparation.

To avoid absorption of water formed by condensation, allow the preparation to be examined and the reference preparation to reach room temperature before opening the containers.

For the test suspension and the reference suspension, prepare the suspension and carry out the dilution at 0-4 °C.

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Test suspension Triturate a quantity of the substance to be examined equivalent to about 1500 Ph. Eur. U. of amylolytic activity with 60 mL of phosphate buffer solution pH 6.8 R1 for 15 min. Transfer quantitatively to a volumetric flask and dilute to 100.0 mL with phosphate buffer solution pH 6.8 R1.

Reference suspension Prepare a suspension of *pancreas powder (amylase) BRP* as described for the test suspension, using a quantity equivalent to about 1500 Ph. Eur. U.

In a test-tube 200 mm long and 22 mm in diameter, fitted with a ground-glass stopper, place 25.0 mL of starch solution, 10.0 mL of phosphate buffer solution pH 6.8 R1 and 1.0 mL of an 11.7 g/L solution of *sodium chloride R*. Close the tube, shake and place in a water-bath at 25.0 ± 0.1 °C. When the temperature equilibrium has been reached, add 1.0 mL of the test suspension and start the chronometer. Mix and place the tube in the water-bath. After exactly 10 min, add 2 mL of *1 M hydrochloric acid*. Transfer the mixture quantitatively to a 300 mL conical flask fitted with a ground-glass stopper. Whilst shaking continuously, add 10.0 mL of *0.05 M iodine* immediately followed by 45 mL of *0.1 M sodium hydroxide*. Allow to stand in the dark at a temperature between 15 °C and 25 °C for 15 min. Add 4 mL of a mixture of 1 volume of *sulfuric acid R* and 4 volumes of *water R*. Titrate the excess of iodine with *0.1 M sodium thiosulfate* using a microburette. Carry out a blank titration adding the 2 mL of *1 M hydrochloric acid* before introducing the test suspension. Carry out the titration of the reference suspension in the same manner.

The test is not valid unless both n'-n and n'_1-n_1 are between 1.9 mL and 3.6 mL.

Calculate the amylolytic activity in European Pharmacopoeia Units per milligram using the following expression:

$$\frac{\left(n'-n\right)m_1}{\left(n'_1-n_1\right)m}\times A$$

n	=	volume of *0.1 M sodium thiosulfate* used in the titration of the test suspension, in millilitres;
n_1	=	volume of *0.1 M sodium thiosulfate* used in the titration of the reference suspension, in millilitres;
n'	=	volume of *0.1 M sodium thiosulfate* used in the blank titration of the test suspension, in millilitres;
n'_1	=	volume of *0.1 M sodium thiosulfate* used in the blank titration of the reference suspension, in millilitres;
m	=	mass of the substance to be examined, in milligrams;
m_1	=	mass of the reference preparation, in milligrams;
A	=	activity of *pancreas powder (amylase) BRP*, in European Pharmacopoeia Units per milligram.

STORAGE

In an airtight container.

Ph Eur

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Pancreatin

General Notices

Action and use

Enzyme; treatment of pancreatic exocrine deficiency.

Preparations

Pancreatin Gastro-resistant Capsules

Pancreatin Granules

Pancreatin Gastro-resistant Tablets

DEFINITION

Pancreatin is a preparation of mammalian pancreas containing enzymes having protease, lipase and amylase activity. It may contain Sodium Chloride.

Potency

Pancreatin contains in 1 mg not less than 1.4 Units of free protease activity, not less than 20 Units of lipase activity and not less than 24 Units of amylase activity.

PRODUCTION

Pancreatin is prepared in conditions designed to minimise the degree of microbial contamination.

CHARACTERISTICS

A white or buff amorphous powder.

Soluble or partly soluble in *water* forming a slightly turbid solution; practically insoluble in *ethanol (96%)* and in *ether*.

IDENTIFICATION

A. It demonstrates free protease activity in the Assay for Free protease activity.

B. Triturate 0.25 g with 10 mL of *water* and adjust to pH 8.0 by the addition of 1M *sodium hydroxide* using *cresol red solution* as indicator. Divide the resulting solution into two equal portions. Boil one portion [solution (1)] and leave the other untreated [solution (2)]. Dissolve 0.1 g of *soluble starch* in 100 mL of boiling *water*, boil for 2 minutes, cool and dilute to 150 mL with *water*. Add solution (1) to half the starch mucilage and solution (2) to the remainder and maintain the mixtures at 38° to 40° for 5 minutes. To 1 mL of each mixture add 10 mL of

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iodinated potassium iodide solution. The liquid containing solution (2) retains the colour of the solution of iodine and the liquid containing solution (1) acquires an intense blue colour.

TESTS

Fat

Extract 1 g with *petroleum spirit (boiling range, 40° to 60°)* for 3 hours in an apparatus for the *continuous extraction of drugs*, Appendix XI F, evaporate the extract and dry the residue at 105° for 2 hours. The residue weighs not more than 30 mg.

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 4 hours, loses not more than 5.0% of its weight. Use 0.5 g.

Microbial contamination

1 g is free from *Escherichia coli*; 10 g is free from *Salmonella*, Appendix XVI B1.

ASSAY

Carry out the *Assay of pancreatin,* Appendix XIV I.

STORAGE

Pancreatin should be stored at a temperature not exceeding 15°.

LABELLING

The label states (1) the minimum number of Units of activity of free protease, lipase and amylase per mg; (2) the name of any added substance; (3) the date after which the material is not intended to be used; (4) the conditions under which it should be stored.

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Pancreatin Gastro-resistant Capsules

General Notices

Pancreatin Capsules

Action and use

Enzyme; treatment of pancreatic exocrine deficiency.

DEFINITION

Pancreatin Gastro-resistant Capsules contain Pancreatin. They may be prepared by filling capsules with granules or particles that are covered with a gastro-resistant coating.

PRODUCTION

A validated dissolution test capable of characterising the *in vitro* release of pancreatin, relevant to the dosing schedule recommended by the manufacturer, should be applied to demonstrate batch-to-batch consistency in dissolution characteristics.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of pancreatin

Not less than 90.0% of the stated minimum number of Units of free protease activity, of lipase activity and of amylase activity.

IDENTIFICATION

A. It demonstrates the presence of free protease activity in the Assay for Free protease activity.

B. Triturate a quantity of the contents of the capsules containing 2.5 g of Pancreatin with 100 mL of *water* and adjust to pH 8.0 by the addition of 1M *sodium hydroxide* using *cresol red solution* as indicator. Divide 10 mL of the resulting solution into two equal portions. Boil one portion [solution (1)] and leave the other untreated [solution (2)]. Dissolve 0.1 g of *soluble starch* in 100 mL of boiling *water*, boil for 2 minutes, cool and dilute to 150 mL with *water*. Add solution (1) to half the starch mucilage and solution (2) to the remainder and maintain the mixtures at 38° to 40° for 5 minutes. To 1mL of each mixture add 10 mL of *iodinated potassium iodide solution*. The liquid containing solution (2) retains the colour of the solution of iodine and the liquid containing solution (1) acquires an intense blue colour.

ASSAY

Carry out the *Assay of pancreatin,* Appendix XIV I, for Free protease activity, Lipase activity and Amylase activity.

STORAGE

Pancreatin Gastro-resistant Capsules should be stored at a temperature not exceeding 15°, unless otherwise justified and authorised.

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LABELLING

The label states (1) the minimum number of Units of free protease activity, of lipase activity and of amylase activity per g; (2) where applicable, that the capsules contain gastro-resistant substances.

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Pancreatin Gastro-resistant Tablets

General Notices

Pancreatin Tablets

Gastro-resistant Pancreatin Tablets

Action and use

Enzyme; treatment of pancreatic exocrine deficiency.

DEFINITION

Pancreatin Gastro-resistant Tablets contain Pancreatin. They are made gastro-resistant by enteric-coating or by other means.

PRODUCTION

A validated dissolution test capable of characterising the *in vitro* release of pancreatin, relevant to the dosing schedule recommended by the manufacturer, should be applied to demonstrate batch to batch consistency in dissolution characteristics.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pancreatin

Not less than 90.0% of the stated minimum numbers of Units of free protease activity, of lipase activity and of amylase activity.

IDENTIFICATION

A. The tablets demonstrate free protease activity in the Assay for Free protease activity.

B. Triturate a quantity of powdered tablets containing 2.5 g of Pancreatin with 100 mL of *water* and filter. Adjust 10 mL of the filtrate to pH 8.0 by the addition of 1M *sodium hydroxide* using *cresol red solution* as indicator. Divide the resulting solution into two equal portions. Boil one portion [solution (1)] and leave the other untreated [solution (2)]. Dissolve 0.1 g of *soluble starch* in 100 mL of boiling *water*, boil for 2 minutes, cool and dilute to 150 mL with *water*. Add solution (1) to half the starch mucilage and solution (2) to the remainder and maintain the mixtures at 38° to 40° for 5 minutes. To 1 mL of each mixture add 10 mL of *iodinated potassium iodide solution*. The liquid containing solution (2) retains the colour of the solution of iodine and the liquid containing solution (1) acquires an intense blue colour.

ASSAY

Weigh and powder 20 tablets. Carry out the *Assay of pancreatin,* Appendix XIV I, for Free protease activity, Lipase activity and Amylase activity.

STORAGE

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Pancreatin Gastro-resistant Tablets should be stored at a temperature not exceeding 15°, unless otherwise justified and authorised.

LABELLING

The label states the minimum number of Units of free protease activity, of lipase activity and of amylase activity in each tablet.

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Pancreatin Granules

General Notices

Action and use

Enzyme; treatment of pancreatic exocrine deficiency.

DEFINITION

Pancreatin Granules contain Pancreatin and may also contain suitable gastro-resistant substances.

The granules comply with the requirements stated under Granules and with the following requirements.

Content of pancreatin

Not less than 90.0% of the stated minimum number of Units of free protease activity, of lipase activity and of amylase activity.

IDENTIFICATION

A. The granules demonstrate free protease activity in the Assay for Free protease activity.

B. Triturate a quantity of powdered granules containing 2.5 g of Pancreatin with 100 mL of *water* and filter. Adjust 10 mL of the liquid to pH 8.0 by the addition of 1M *sodium hydroxide* using *cresol red solution* as indicator. Divide the resulting solution into two equal portions. Boil one portion [solution (1)] and leave the other untreated [solution (2)]. Dissolve 0.1 g of *soluble starch* in 100 mL of boiling *water*, boil for 2 minutes, cool and dilute to 150 mL with *water*. Add solution (1) to half the starch mucilage and solution (2) to the remainder and maintain the mixtures at 38° to 40° for 5 minutes. To 1 mL of each mixture add 10 mL of *iodinated potassium iodide solution*. The liquid containing solution (2) retains the colour of the solution of iodine and the liquid containing solution (1) acquires an intense blue colour.

ASSAY

Carry out the *Assay of pancreatin,* Appendix XIV I, using in the determination of each activity a quantity of the powdered granules estimated to contain the number of Units specified in the method.

STORAGE

Pancreatin Granules should be stored at a temperature not exceeding 15°, unless otherwise justified and authorised.

LABELLING

The label states (1) the minimum number of Units of free protease activity, of lipase activity and of amylase activity per g; (2) where applicable, that the granules contain gastro-resistant substances.

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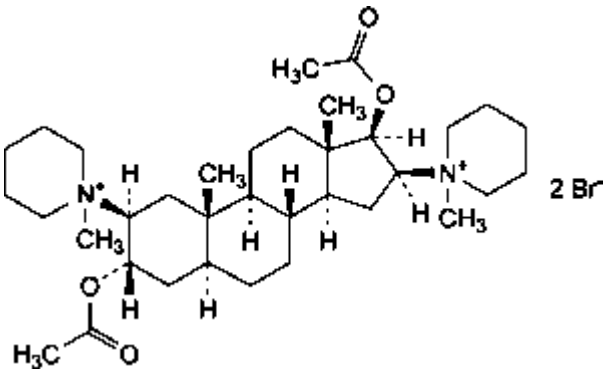
Pancuronium Bromide

General Notices

(Ph. Eur. monograph 0681)



$C_{35}H_{60}Br_2N_2O_4$ 733 *15500-66-0*

Action and use

Non-depolarizing neuromuscular blocker.

Preparation

Pancuronium Injection

Ph Eur

DEFINITION

1,1′-[3α,17β-Bis(acetyloxy)-5α-androstane-2β,16β-diyl]bis(1-methylpiperidinium) dibromide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White, yellowish-white or slightly pink, crystalline powder, hygroscopic.

Solubility

Very soluble or freely soluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 per cent).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *pancuronium bromide CRS*.

B. It gives reaction (a) of bromides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 50 mg in *water R* and dilute to 25 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 38.0 to + 42.0 (anhydrous substance).

Dissolve 0.75 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use.*

Test solution Dissolve 50.0 mg of the substance to be examined in *methylene chloride R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 20.0 mL with *methylene chloride R*.

Reference solution (b) Dissolve 10.0 mg of *pancuronium bromide for system suitability CRS* (containing 1.0 per cent of impurity D) in 1.0 mL of *methylene chloride R*.

Plate *TLC silica gel plate R* (2-10 µm).

Mobile phase 400 g/L solution of *sodium iodide R*, *acetonitrile R*, *2-propanol R* (5:10:85 *V/V/V*).

Application 5 µL.

Development In an unlined and unsaturated tank over a path of 8 cm.

Drying In a current of air at room temperature.

Detection Spray with a 20 g/L solution of *sodium nitrite R* and allow to dry for 5 min. Then spray with *potassium iodobismuthate solution R5*. Cover the plate with a transparent glass cover.

System suitability:

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— the chromatogram obtained with reference solution (b) shows 2 clearly separated spots due to pancuronium bromide (R_F = about 0.5) and impurity D (R_F = about 0.6);

— the chromatogram obtained with reference solution (a) shows a clearly visible spot.

Note Impurity A if present will co-migrate with impurity D.

Limits:

— *impurities A, D*: any spot due to impurities A and/or D is not more intense than the spot due to impurity D in the chromatogram obtained with reference solution (b) (1.0 per cent),

— *unspecified impurities*: any other spot is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.10 per cent).

Water (2.5.12)

Maximum 8.0 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *acetic anhydride R*, heating if necessary. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 36.63 mg of $C_{35}H_{60}Br_2N_2O_4$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, E.*

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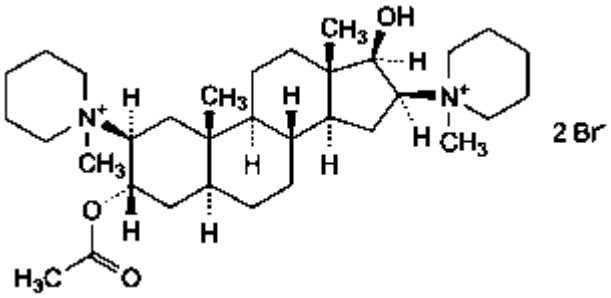
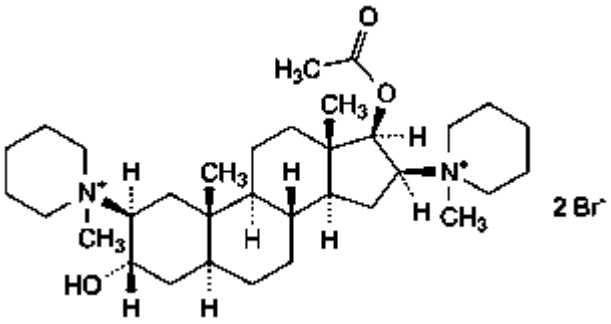
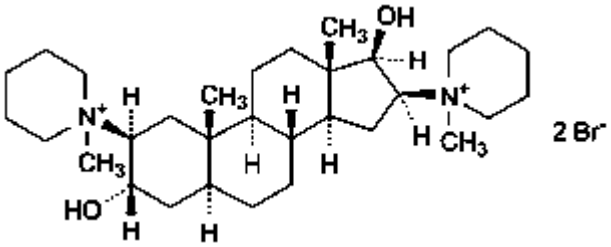


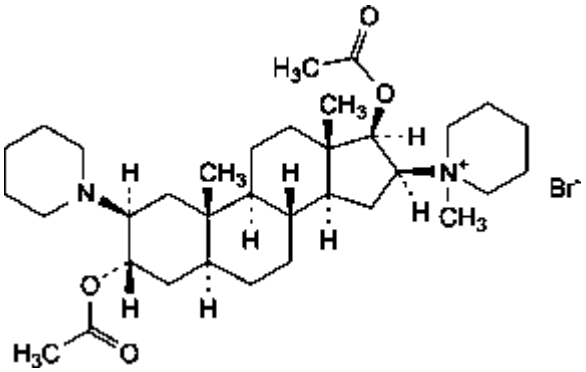
A. 1,1′-[3α-(acetyloxy)-17β-hydroxy-5α-androstane-2β,16β-diyl]bis(1-methylpiperidinium) dibromide (dacuronium bromide),



B. 1,1′-[17β-(acetyloxy)-3α-hydroxy-5α-androstane-2β,16β-diyl]bis(1-methylpiperidinium) dibromide,



C. 1,1′-(3α,17β-dihydroxy-5α-androstane-2β,16β-diyl)bis(1-methylpiperidinium) dibromide,



D. 1-[3α,17β-bis(acetyloxy)-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidinium bromide (vecuronium bromide),

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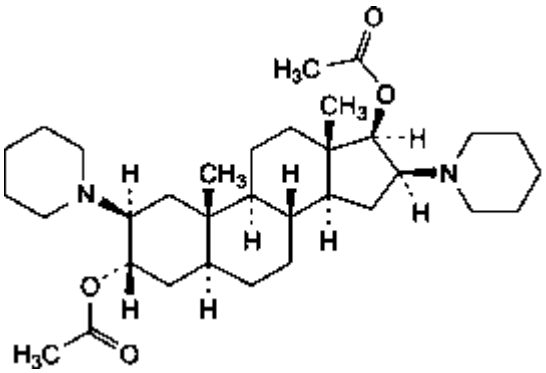

E. 2β,16β-bis(piperidin-1-yl)-5α-androstane-3α,17β-diyl diacetate.

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Pancuronium Injection

General Notices

Action and use

Non-depolarizing neuromuscular blocker.

DEFINITION

Pancuronium Injection is a sterile solution of Pancuronium Bromide in Sodium Chloride Intravenous Infusion.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of pancuronium bromide, $C_{35}H_{60}Br_2N_2O_4$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless liquid.

IDENTIFICATION

A. In the test for Related substances, the principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to the principal spot in the chromatogram obtained with solution (2).

B. To a volume containing 5 mg of Pancuronium Bromide, diluted if necessary to 10 mL with *water*, add 10 mL of *1,2-dichloroethane* followed by 1 mL of *methyl orange solution*. Shake, centrifuge, allow the layers to separate and acidify the organic layer with 1M *sulfuric acid*. A red colour is produced.

C. Yields reaction A characteristic of *bromides*, Appendix VI.

TESTS

Acidity

pH, 3.8 to 4.2, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Evaporate a volume of the injection containing 20 mg of Pancuronium Bromide to dryness in a current of *nitrogen*, add 2 mL of *acetonitrile* to the residue and mix with the aid of ultrasound for 1 minute.

(2) 1.0% w/v of *pancuronium bromide BPCRS* in *acetonitrile*.

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(3) Dilute 1 volume of solution (1) to 50 volumes with *acetonitrile*.

(4) Dilute 1 volume of solution (3) to 2 volumes with *acetonitrile*.

(5) 3% w/v of *pancuronium bromide for system suitability EPCRS* (containing 1.0 per cent of impurity D) in *methylene chloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm in an unsaturated tank.

(e) After removal of the plate, dry it in a current of cold air and spray with a 1% w/v solution of *sodium nitrite* in *methanol*. Allow to stand for 2 minutes, spray the plate with *potassium iodobismuthate solution* and dry in a current of cold air.

MOBILE PHASE

5 volumes of a 20% w/v solution of *sodium iodide*, 10 volumes of *acetonitrile* and 85 volumes of *propan-2-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (5) shows two distinct spots and the Rf value of the spot due to impurity D relative to that due to pancuronium bromide is at least 1.2.

LIMITS

In the chromatogram obtained with solution (1):
any spot corresponding to dacuronium bromide (impurity A) or vecuronium bromide (impurity D) is not more intense than the spot in the chromatogram obtained with solution (5) (3%). Impurity A and impurity D have the same Rf value and if present in the same solution would produce a single spot;

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3) (2%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (4) (1%).

ASSAY

To a volume containing 4 mg of Pancuronium Bromide add 1 mL of a 13.9% w/v solution of *hydroxylamine hydrochloride* followed by 1 mL of a 15% w/v solution of *sodium hydroxide*. Allow to stand for 10 minutes and then add 1 mL of a solution prepared by diluting *hydrochloric acid* with *water* to contain 12.76% w/v of HCl. Add 1 mL of a 10% w/v solution of *iron(III) chloride* in 0.1M *hydrochloric acid*, add sufficient *water* to produce 25 mL, centrifuge and measure the *absorbance* of the clear, supernatant liquid at the maximum at 510 nm, Appendix II B, using in the reference cell a solution prepared by carrying out the operation using an equal volume of *water* in place of the injection. Calculate the content of $C_{35}H_{60}Br_2N_2O_4$ from the *absorbance* obtained by repeating the operation using a suitable quantity of *pancuronium bromide BPCRS* dissolved in *water* and using the declared content of $C_{35}H_{60}Br_2N_2O_4$ in *pancuronium bromide BPCRS*.

STORAGE

Pancuronium Injection should be stored at a temperature of 2° to 8°.

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Pantoprazole for Injection

General Notices

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Pantoprazole for Injection is a sterile material consisting of Pantoprazole Sodium Sesquihydrate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of pantoprazole, $C_{16}H_{15}F_2N_3O_4S$

93.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powder containing the equivalent of 40 mg of pantoprazole with 10 mL of *acetone*, filter (Whatman GF/C is suitable) and evaporate to dryness. Dry the residue at 60° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pantoprazole sodium *(RS 488)*.

TESTS

Alkalinity

pH of a solution containing the equivalent of 0.4% w/v of pantoprazole, 9.0 to 11.5, Appendix V L.

Clarity and colour of solution

A solution containing the equivalent of 0.4% w/v of pantoprazole is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* B_5 or BY_5, Appendix IV B, Method II.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a solution containing equal volumes of *acetonitrile* and 0.001M *sodium hydroxide* (solution A).

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(1) Shake a quantity of the powder for injection containing the equivalent of 40 mg of pantoprazole in 50 mL of solution A, dilute with sufficient solution A to produce 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 20 volumes. Dilute 1 volume of this solution to 10 volumes.

(3) 0.05% w/v of *pantoprazole for system suitability EPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 290 nm.

(g) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.01M *dipotassium hydrogen phosphate trihydrate*, adjusted to pH 7.0 with a 20% v/v solution of *orthophosphoric acid*.

Mobile phase B 1 volume of *water* and 99 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	90	10	isocratic
3-33	90→60	10→40	linear gradient
33-48	60→15	40→85	linear gradient
48-50	15→90	85→10	linear gradient
50-60	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to pantoprazole (retention time about 22 minutes) are: impurity C, about 0.6; impurity A, about 0.9; impurity D + F, about 1.1; impurity E, about 1.3 and impurity B, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D + F and pantoprazole is greater than 3.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity C using the chromatogram obtained with solution (3) and multiply the area of this peak by a correction factor of 0.6.

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In the chromatogram obtained with solution (1):

the area of any peak due to impurities D + F (combined peak area) is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a solution containing equal volumes of *acetonitrile* and 0.001M *sodium hydroxide* (solution A).

(1) Prepare 10 injections following the manufacturer's instructions and combine the resulting solutions. Dilute a quantity of the resulting solution with sufficient solution A to produce a solution containing the equivalent of 0.004% w/v of pantoprazole.
(2) 0.0045% w/v of *pantoprazole sodium BPCRS* in solution A.
(3) 0.0045% w/v of *pantoprazole sodium BPCRS* and 0.0005% w/v of *pantoprazole impurity A BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use an autosampler temperature of 5°.
(f) Use a detection wavelength of 290 nm.
(g) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile*, and 65 volumes of 0.01M *dipotassium hydrogen phosphate trihydrate*, previously adjusted to pH 7.0 with a 20% v/v solution of *orthophosphoric acid*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pantoprazole is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{15}F_2N_3O_4S$ in the powder for injection from the chromatograms obtained and using the declared content of $C_{16}H_{15}F_2N_3O_4S$ in *pantoprazole sodium BPCRS*.

STORAGE

The sealed container should be protected from light and stored at a temperature not exceeding 25°.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of pantoprazole.

IMPURITIES

The impurities limited by this monograph include those listed under Pantoprazole Sodium Sesquihydrate.

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Pantoprazole Gastro-resistant Tablets

General Notices

Gastro-resistant Pantoprazole Tablets

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Pantoprazole Gastro-resistant Tablets contain Pantoprazole Sodium Sesquihydrate. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pantoprazole, $C_{16}H_{15}F_2N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 50 mg of pantoprazole with 10 mL of *acetone*, filter (Whatman GF/C is suitable) and evaporate to dryness. Dry the residue at 60° for 30 minutes. The *infrared absorption spectrum* Appendix II A, is concordant with the reference spectrum of pantoprazole sodium *(RS 488)*.

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use as the medium 700 mL of *0.05M phosphate buffer solution pH 4.5*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) After 45 minutes, withdraw a sample of the medium, and filter the aliquot (0.45-µm PVDF is suitable). Dilute 1 volume of the filtrate to 5 volumes with *water*, and further dilute, if necessary, with sufficient *water* to produce a solution expected to contain about 0.00057% w/v of pantoprazole. Proceed immediately to the final stage.

(2) 0.0006% w/v of *pantoprazole sodium BPCRS* in *water*.

(3) 0.0018% w/v of *pantoprazole sodium BPCRS* and 0.0002% w/v of *pantoprazole impurity A BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 290 nm.

(g) Inject 50 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.01M *dipotassium hydrogen phosphate trihydrate*, previously adjusted to pH 7.0 with a 20% v/v solution of *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pantoprazole is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{15}F_2N_3O_4S$ in the medium using the declared content of $C_{16}H_{15}F_2N_3O_4S$ in *pantoprazole sodium BPCRS*.

LIMITS

The amount of pantoprazole released is not more than 10% of the stated amount.

Final stage (about pH 6.8)

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution A).

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 5 minutes of completion of the first stage, add to the vessel 200 mL of solution A, previously held and maintained at 37°.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) After 45 minutes, withdraw a sample of the medium, and filter the aliquot (0.45-µm PVDF is suitable). Dilute 1 volume of the filtrate to 5 volumes with *water*, and further dilute, if necessary, with sufficient *water* to produce a solution expected to contain about 0.00044% w/v of pantoprazole.

(2) 0.00047% w/v of *pantoprazole sodium BPCRS* in *water*.

(3) 0.0018% w/v of *pantoprazole sodium BPCRS* and 0.0002% w/v of *pantoprazole impurity A BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pantoprazole is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{15}F_2N_3O_4S$ in the medium using the declared content of $C_{16}H_{15}F_2N_3O_4S$ in *pantoprazole sodium BPCRS*.

LIMITS

The amount of pantoprazole released is not less than 65% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 40 volumes of mobile phase B and 60 volumes of mobile phase A.

(1) Shake a quantity of whole tablets containing the equivalent of 0.16 g of pantoprazole in 50 mL, mix with the aid of ultrasound and dilute to produce 100 mL. Dilute 5 volumes to 20 volumes.

(2) Dilute 1 volume of solution (1) to 20 volumes. Dilute 1 volume of this solution to 10 volumes.

(3) 0.05% w/v of *pantoprazole for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 290 nm.

(g) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.174% w/v solution of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.0 with *orthophosphoric acid*.

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Mobile phase B 48 volumes of mobile phase A and 52 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	60	40	isocratic
3-43	60→40	40→60	linear gradient
43-48	40→60	60→40	linear gradient
48-55	60	40	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to pantoprazole (retention time about 16 minutes) are: impurity C, about 0.4; impurity A, about 0.8; impurity D + F, about 1.3; impurity E, about 2.0 and impurity B, about 2.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to pantoprazole and impurity D + F is greater than 3.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity C using the chromatogram obtained with solution (3) and multiply the area of this peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A and impurity D + F (combined peak area) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a solution containing equal volumes of *acetonitrile* and 0.001M *sodium hydroxide* (solution B).

(1) Shake 10 tablets with 50 mL of solution B, mix with the aid of ultrasound and dilute to 100 mL with solution B. Centrifuge and dilute the supernatant liquid with solution B to give a solution containing the equivalent of 0.004% w/v of pantoprazole.
(2) 0.0045% w/v of *pantoprazole sodium BPCRS* in solution B.

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(3) 0.0045% w/v of *pantoprazole sodium BPCRS* and 0.0005% w/v of *pantoprazole impurity A BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pantoprazole is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{15}F_2N_3O_4S$ in the tablets from the chromatograms obtained and using the declared content of $C_{16}H_{15}F_2N_3O_4S$ in *pantoprazole sodium BPCRS*.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of pantoprazole.

IMPURITIES

The impurities limited by this monograph include those listed under Pantoprazole Sodium Sesquihydrate.

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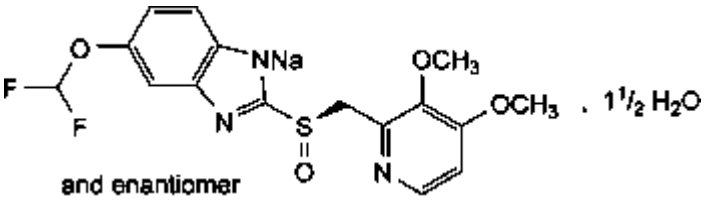
Pantoprazole Sodium Sesquihydrate

General Notices

(Ph. Eur. monograph 2296)



$C_{16}H_{14}F_2N_3NaO_4S,1½H_2O$ 432.4 *164579-32-2*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Preparations

Pantoprazole for Injection

Pantoprazole Gastro-resistant Tablets

Ph Eur

DEFINITION

Sodium 5-(difluoromethoxy)-2-[(*RS*)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]benzimidazol-1-ide sesquihydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

It is produced by methods of manufacture designed to guarantee the proper hydrate form and it complies, if tested, with a suitable test that demonstrates its sesquihydrate nature (for example near-infrared spectroscopy (*2.2.40*) or X-ray powder diffraction (*2.9.33*)).

CHARACTERS

Appearance

White or almost white powder.

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Solubility

Freely soluble in water and in ethanol (96 per cent), practically insoluble in hexane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pantoprazole sodium sesquihydrate CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

Dissolve 0.20 g in *water R* and dilute to 20.0 mL with the same solvent.

Optical rotation (*2.2.7*)

-0.4° to + 0.4°.

Dissolve 0.2 g in 10 mL of *water R*. Adjust to pH 11.5-12.0 with an 8 g/L solution of *sodium hydroxide R*. Dilute to 20.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, 40 mg/L solution of *sodium hydroxide R* (50:50 *V/V*).

Test solution Dissolve 23 mg of the substance to be examined in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of *pantoprazole for system suitability CRS* (containing impurities A, B, C, D and E) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

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— *mobile phase A*: 1.74 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 7.00 ± 0.05 with a 330 g/L solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	80 → 20	20 → 80
40 - 45	20 → 80	80 → 20

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 290 nm and, for impurity C, at 305 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *pantoprazole for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D + F and E.

Relative retention With reference to pantoprazole (retention time = about 11 min): impurity C = about 0.6; impurity A = about 0.9; impurities D and F = about 1.2; impurity E = about 1.3; impurity B = about 1.5.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities E and D + F;

— the chromatogram obtained is similar to the chromatogram supplied with *pantoprazole for system suitability CRS*.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.3;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of impurities D and F*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities B, C, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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Water (*2.5.12*)

5.9 per cent to 6.9 per cent, determined on 0.150 g.

ASSAY

Dissolve 0.200 g in 80 mL of *anhydrous acetic acid R*, add 5 mL of *acetic anhydride R* and mix for at least 10 min. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

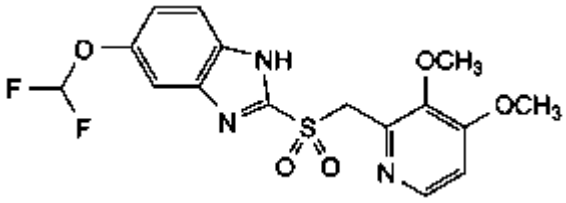
1 mL of *0.1 M perchloric acid* is equivalent to 20.27 mg of $C_{16}H_{14}F_2N_3NaO_4S$.

STORAGE

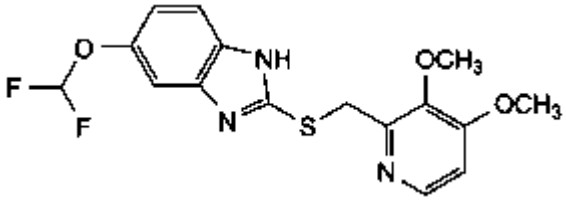
Protected from light.

IMPURITIES

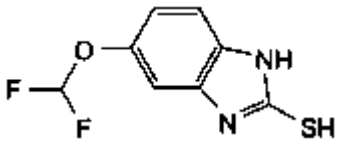
Specified impurities *A, B, C, D, E, F.*



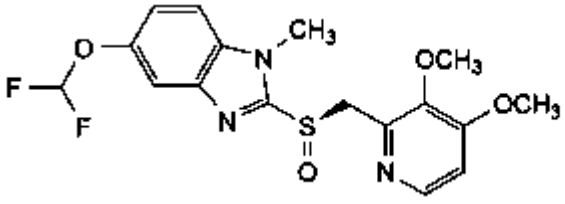
A. 5-(difluoromethoxy)-2-[[(3,4-dimethoxypyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole,



B. 5-(difluoromethoxy)-2-[[(3,4-dimethoxypyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole,



C. 5-(difluoromethoxy)-1*H*-benzimidazole-2-thiol,


and enantiomer

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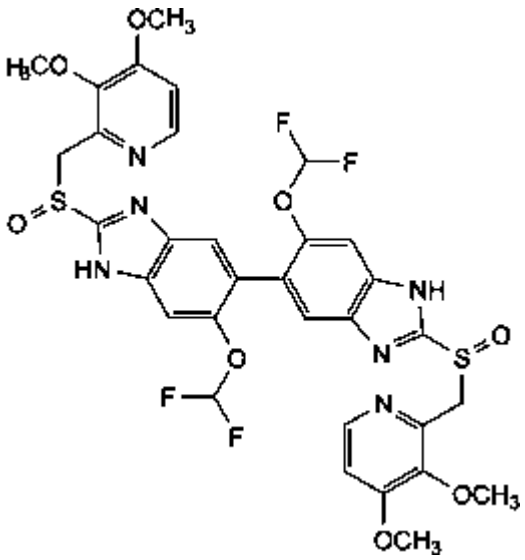
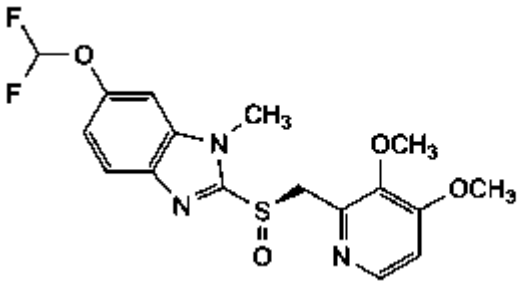
D. 5-(difluoromethoxy)-2-[(*RS*)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1*H*-benzimidazole,



E. mixture of the stereoisomers of 6,6′-bis(difluoromethoxy)-2,2′-bis[[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1*H*,1′*H*-5,5′-bibenzimidazolyl,



and enantiomer

F. 6-(difluoromethoxy)-2-[(*RS*)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1*H*-benzimidazole.

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Papaveretum

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Papaveretum is a mixture of 253 parts of Morphine Hydrochloride ($C_{17}H_{19}NO_3$,HCl,3H_2O, 375.9), 23 parts of Papaverine Hydrochloride ($C_{20}H_{21}NO_4$,HCl, 375.9) and 20 parts of Codeine Hydrochloride ($C_{18}H_{21}NO_3$,HCl,2H_2O, 371.9). It contains not less than 80.0% and not more than 88.4% of $C_{17}H_{19}NO_3$,HCl, not less than 8.3% and not more than 9.2% of $C_{20}H_{21}NO_4$,HCl and not less than 6.6% and not more than 7.4% of $C_{18}H_{21}NO_3$,HCl, calculated with reference to the dried material.

CHARACTERISTICS

A white or almost white, crystalline powder.

Soluble in *water*; sparingly soluble in *ethanol (96%)*.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) 1.5% w/v of the substance being examined.

(2) 1.28% w/v of *morphine sulfate BPCRS*.

(3) 0.115% w/v of *papaverine hydrochloride BPCRS*.

(4) 0.11% w/v of *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 100° to 105° for 15 minutes, allow it to cool and spray with *potassium iodobismuthate solution* and then with a 0.4% v/v solution of *sulfuric acid*.

MOBILE PHASE

2 volumes of 13.5M *ammonia*, 6 volumes of *ethanol (96%)*, 40 volumes of *acetone* and 40 volumes of *toluene*.

CONFIRMATION

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The chromatogram obtained with solution (1) shows three principal spots corresponding in position and colour to the principal spots in the chromatograms obtained with solutions (2), (3) and (4).

B. Yields the reactions characteristics of *chlorides*, Appendix VI.

TESTS

Acidity

pH of a 1.5% w/v solution, 3.7 to 4.7, Appendix V L.

Clarity and colour of solution

A 1.5% w/v solution in *water* is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* BY_5, Appendix IV B, Method II.

Loss on drying

When dried to constant weight at 130°, loses not less than 10.0% and not more than 14.0% of its weight. Use 0.5 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (60%)*.

(1) 0.15% w/v of the substance being examined.

(2) 0.128% w/v of *morphine sulfate BPCRS*.

(3) 0.128% w/v of *morphine sulfate BPCRS*, 0.0115% w/v of *papaverine hydrochloride BPCRS* and 0.011% w/v of *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 285 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium acetate* and 0.005M *dioctyl sodium sulfosuccinate* in *methanol (60%)* adjusted to pH 5.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

If necessary, adjust the proportion of methanol in the mobile phase in the range 55% v/v to 65% v/v so that the retention time of morphine in solution (2) is 4 to 5 minutes. Adjust the pH of the mobile phase with either *glacial acetic acid* or 2M *sodium hydroxide* in order to obtain optimum separation of the three principal components in solution (3). The retention times of codeine and papaverine relative to that of morphine are about 1.3 and 1.7 respectively.

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DETERMINATION OF CONTENT

For anhydrous morphine hydrochloride

Calculate the content of $C_{17}H_{19}NO_3$,HCl using the declared content of $C_{17}H_{19}NO_3$ in *morphine sulfate BPCRS*. Each mg of $C_{17}H_{19}NO_3$ is equivalent to 1.13 mg of $C_{17}H_{19}NO_3$,HCl.

For papaverine hydrochloride

Calculate the content of $C_{20}H_{21}NO_4$,HCl using the declared content of $C_{20}H_{21}NO_4$,HCl in *papaverine hydrochloride BPCRS*.

For anhydrous codeine hydrochloride

Calculate the content of $C_{18}H_{21}NO_3$,HCl using the declared content of $C_{18}H_{21}NO_3$ in *codeine phosphate BPCRS*. Each mg of $C_{18}H_{21}NO_3$ is equivalent to 1.09 mg of $C_{18}H_{21}NO_3$,HCl.

STORAGE

Papaveretum should be protected from light.

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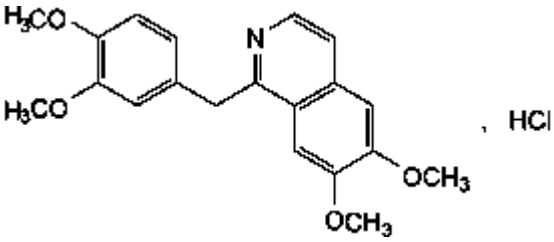
Papaverine Hydrochloride

General Notices

(Ph. Eur. monograph 0102)



$C_{20}H_{22}ClNO_4$ 375.9 *61-25-6*

Action and use

Phosphodiesterase inhibitor; smooth muscle relaxant.

Preparation

Papaverine Injection

Ph Eur

DEFINITION

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, or white or almost white crystals.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

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First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *papaverine hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 5 mg of *papaverine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *diethylamine R*, *ethyl acetate R*, *toluene R* (10:20:70 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying At 100-105 °C for 2 h.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 10 mL of solution S (see Tests) add 5 mL of *ammonia R* dropwise and allow to stand for 10 min. The precipitate, washed and dried, melts (2.2.14) at 146 °C to 149 °C.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.4 g in *carbon dioxide-free water R*, heating gently if necessary, and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

pH (2.2.3)

3.0 to 4.0 for solution S.

Related substances

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Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, mobile phase A (20:80 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 12 mg of noscapine CRS in 1.0 mL of the test solution and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: base-deactivated octylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: 3.4 g/L solution of potassium dihydrogen phosphate R adjusted to pH 3.0 with dilute phosphoric acid R;

— *mobile phase B*: acetonitrile R;

— *mobile phase C*: methanol R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 5	85	5	10
5 - 12	85 → 60	5	10 → 35
12 - 20	60	5	35
20 - 24	60 → 40	5 → 20	35 → 40
24 - 27	40	20	40
27 - 32	40 → 85	20 → 5	40 → 10

Flow rate 1 mL/min.

Detection Spectrophotometer at 238 nm.

Injection 10 µL.

Relative retention With reference to papaverine (retention time = about 24 min): impurity E = about 0.7; impurity C = about 0.75; impurity B = about 0.8; impurity A = about 0.9; impurity F = about 1.1; impurity D = about 1.2.

System suitability Reference solution (b):

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— *resolution*: minimum 1.5 between the peaks due to impurity A and papaverine.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 6.2; impurity C = 2.7; impurity D = 0.5;

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

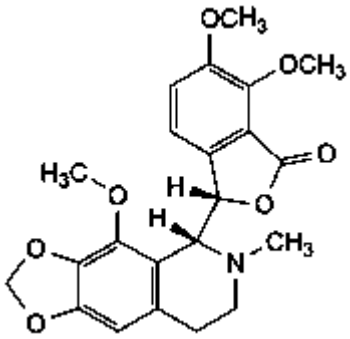
Maximum 0.1 per cent, determined on the residue from the test for loss on drying.

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 37.59 mg of $C_{20}H_{22}ClNO_4$.

IMPURITIES



A. (3*S*)-6,7-dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]isobenzofuran-1(3*H*)-one (noscapine),

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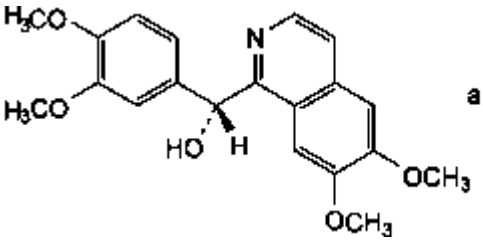
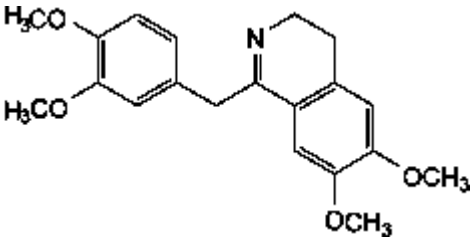
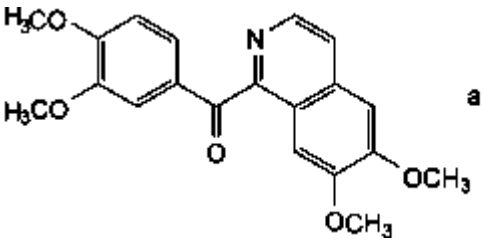


and enantiomer

B. (*RS*)-(3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanol (papaverinol),

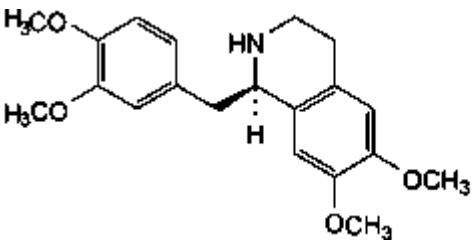


C. 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (dihydropapaverine),



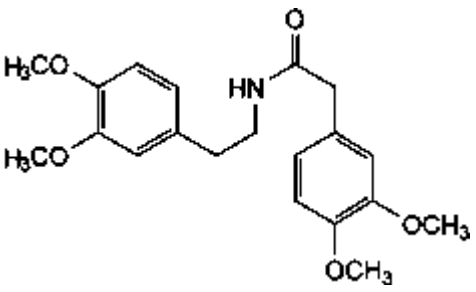
and enantiomer

D. (3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (papaveraldine),



and enantiomer

E. (1*RS*)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (tetrahydropapaverine),



F. 2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide.

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Papaverine Injection

General Notices

Action and use

Phosphodiesterase inhibitor; smooth muscle relaxant.

DEFINITION

Papaverine Injection is a sterile solution of Papaverine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of papaverine hydrochloride, $C_{20}H_{21}NO_4$, HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume of the injection containing 60 mg of Papaverine Hydrochloride add 2 mL of *ethanol (96%)*, evaporate to dryness on a steam bath with the aid of a stream of *nitrogen* and dry the residue at 105° for 2 hours. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of papaverine hydrochloride *(RS 415)*.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 2.0 to 4.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a volume of the injection, if necessary, with *methanol (50%)* to produce a solution containing 0.06% w/v of Papaverine Hydrochloride. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *methanol* (50%).Solution (3) contains 0.0005% w/v of *papaverine hydrochloride BPCRS* and 0.005% w/v of *noscapine* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *endcapped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C(18)2 is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture prepared by adding 700 mL of *methanol* containing 2.22 g of *dioctyl sodium sulfosuccinate* to 100 mL of *water* containing 1.36 g of *sodium acetate*, diluting to 1 litre with *water* and adjusting the pH to 5.5 with *glacial acetic acid* and (c) a detection wavelength of 250 nm.

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to papaverine hydrochloride and noscapine is at least 3.0.

In the chromatogram obtained with solution (1), the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.0045% w/v of *papaverine hydrochloride BPCRS* in *methanol (50%)*. For solution (2) dilute a volume of the injection, if necessary, with *methanol* (50%) to produce a solution containing 0.0045% w/v of Papaverine Hydrochloride.

The chromatographic method described under Related substances may be used.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to papaverine hydrochloride and noscapine is at least 3.0.

Calculate the content of $C_{20}H_{21}NO_4$,HCl in the injection using the declared content of $C_{20}H_{21}NO_4$,HCl in *papaverine hydrochloride BPCRS*.

STORAGE

Papaverine Injection should be protected from light.

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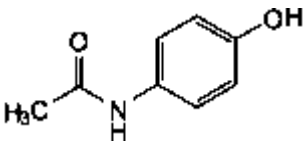
Paracetamol

General Notices

(Ph. Eur. monograph 0049)



$C_8H_9NO_2$ 151.2 *103-90-2*

Action and use

Analgesic; antipyretic.

Preparations

Co-codamol Tablets

Co-codamol Capsules

Co-codamol Effervescent Tablets

Paracetamol Effervescent Tablets

Co-dydramol Tablets

Co-proxamol Tablets

Paracetamol Capsules

Paediatric Paracetamol Oral Solution

Paediatric Paracetamol Oral Suspension

Paracetamol Oral Suspension

Paracetamol Suppositories

Paracetamol Tablets

Paracetamol and Caffeine Tablets

Paracetamol and Caffeine Soluble Tablets

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Paracetamol Dispersible Tablets

Paracetamol Soluble Tablets

Paracetamol, Codeine Phosphate and Caffeine Capsules

Paracetamol, Codeine Phosphate and Caffeine Tablets

Ph Eur

DEFINITION

N-(4-Hydroxyphenyl)acetamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Melting point (*2.2.14*).

Determination A Determine the melting point of the substance to be examined.

Result A 168 °C to 172 °C.

Determination B Mix equal parts of the substance to be examined and *paracetamol CRS* and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *paracetamol CRS*.

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TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture methanol R, water R (15:85 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 0.75 mL of methanol R and dilute to 5.0 mL with water R.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of paracetamol impurity J CRS in 25 mL of methanol R and dilute to 250.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 200.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of paracetamol impurity K CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 10.0 mL with the solvent mixture.

Reference solution (e) Mix 1 mL of reference solution (a) and 1 mL of reference solution (c) and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped solid core octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.7 g of potassium dihydrogen phosphate R and 1.8 g of dipotassium hydrogen phosphate R in water for chromatography R and dilute to 1000 mL with the same solvent;

— *mobile phase B*: methanol R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1.5	95	5
1.5 - 14.4	95 → 90	5 → 10
14.4 - 28.8	90	10
28.8 - 57.6	90 → 66	10 → 34

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
57.6 - 60	66	34

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 5 °C.

Injection 50 µL of the test solution and reference solutions (a), (b), (d) and (e).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity J; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity K.

Relative retention With reference to paracetamol (retention time = about 4 min): impurity K = about 0.4; impurity J = about 10.1.

System suitability Reference solution (e):

— *resolution*: minimum 5.0 between the peaks due to impurity K and paracetamol.

Calculation of contents:

— for impurity J, use the concentration of impurity J in reference solution (b);

— for impurity K, use the concentration of impurity K in reference solution (d);

— for impurities other than J and K, use the concentration of paracetamol in reference solution (a).

Limits:

— *impurity K*: maximum 50 ppm;

— *impurity J*: maximum 10 ppm;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent, except for impurities J and K.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.300 g in a mixture of 10 mL of *water R* and 30 mL of *dilute sulfuric acid R*. Boil under a reflux condenser for 1 h, cool and dilute to 100.0 mL with *water R*. To 20.0 mL of the solution add 40 mL of *water R*, 40 g of ice, 15 mL of *dilute hydrochloric acid R* and 0.1 mL of *ferroin R*. Titrate with *0.1 M cerium sulfate* until a greenish-yellow colour is obtained. Carry out a blank titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 7.56 mg of $C_8H_9NO_2$.

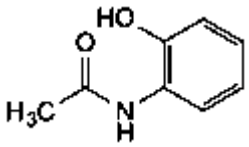
STORAGE

Protected from light.

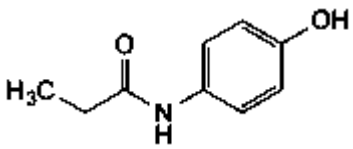
IMPURITIES

Specified impurities J, K.

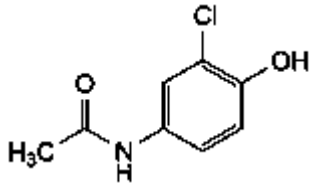
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I, L, M, N, O.



A. *N*-(2-hydroxyphenyl)acetamide,



B. *N*-(4-hydroxyphenyl)propanamide,



C. *N*-(3-chloro-4-hydroxyphenyl)acetamide,

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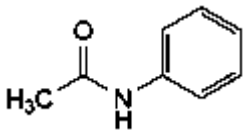
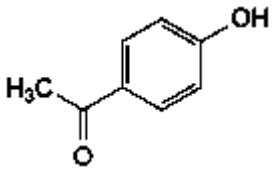
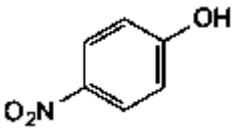


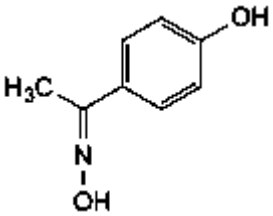
D. *N*-phenylacetamide,



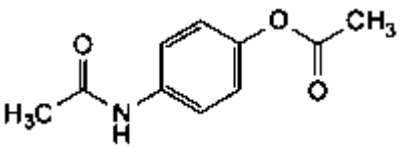
E. 1-(4-hydroxyphenyl)ethan-1-one,



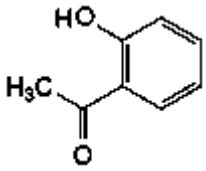
F. 4-nitrophenol,



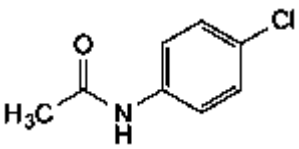
G. [1-(4-hydroxyphenyl)ethylidene]hydroxylamine,



H. 4-acetamidophenyl acetate,



I. 1-(2-hydroxyphenyl)ethan-1-one,



J. *N*-(4-chlorophenyl)acetamide (chloroacetanilide),

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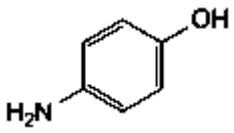
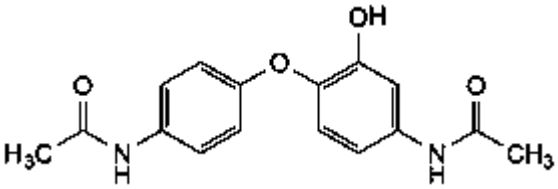
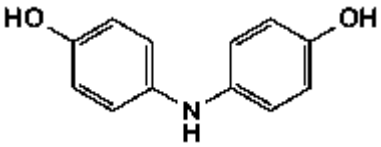


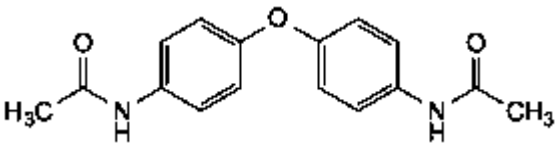
K. 4-aminophenol,



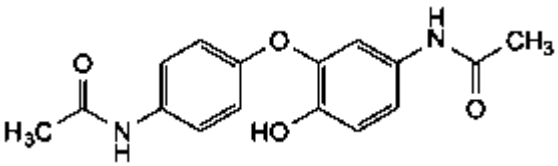
L. *N*-[4-(4-acetamido-2-hydroxyphenoxy)phenyl]acetamide,



M. 4,4′-azanediyldiphenol,



N. *N*,*N*′-[oxydi(4,1-phenylene)]diacetamide,



O. *N*-[4-(5-acetamido-2-hydroxyphenoxy)phenyl]acetamide.

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Paracetamol and Caffeine Tablets

General Notices

Action and use

Analgesic; antipyretic; central nervous system stimulant.

DEFINITION

Paracetamol and Caffeine Tablets contain Paracetamol and Caffeine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

Content of caffeine, $C_8H_{10}N_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of paracetamol *(RS 258)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 65 mg of Caffeine in 10 mL of *methanol*, and filter (a 0.2-µm nylon filter is suitable).

(2) 0.65% w/v of *caffeine BPCRS* in *methanol*.

(3) 0.65% w/v of *caffeine BPCRS* and 5% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *acetic acid*, 5 volumes of *ethanol*, 5 volumes of *water* and 50 volumes of *ethyl acetate*.

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SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The spot corresponding to caffeine in the chromatogram obtained with solution (1) corresponds in position to the principal spot in the chromatogram obtained with solution (2).

C. In the Assay for caffeine, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1, using the following conditions.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use as the medium 900 mL of a phosphate buffer (pH 5.8), at a temperature of 37°, prepared in the following manner. Mix 250 mL of *0.2M potassium dihydrogen phosphate* and 18 mL of *0.2M sodium hydroxide*, and dilute to 1000 mL with *water*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw a sample of the medium and filter. Use the filtered medium, diluted with dissolution medium, if necessary, to produce a solution expected to contain 0.0056% w/v of Paracetamol.

(2) 0.0056% w/v of *paracetamol BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 243 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium pentanesulfonate* in a mixture of 22 volumes of *methanol* and 78 volumes of *water*, adjusted to pH 2.8 using *2M hydrochloric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of paracetamol is about 3 minutes.

DETERMINATION OF CONTENT

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Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

LIMITS

The amount of paracetamol released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions prepared in solution A.

Solution A: 0.23% w/v of *sodium chloride* in a mixture of 30 volumes of mobile phase B and 70 volumes of mobile phase A.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Paracetamol with 50 mL and filter (Chromafil RC 45/25 is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.0001% w/v of *4-aminophenol* (paracetamol impurity K).
(4) 0.00001% w/v of *4'-chloroacetanilide* (paracetamol impurity J).
(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex C18 100A is suitable).
(b) Use gradient elution and the mobile phase as described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use a column temperature of 35°.
(e) Use detection wavelengths of 212 nm and 246 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 mM *sodium octanesulfonate*, adjusted to pH 2.2 with *orthophosphoric acid*.

Mobile phase B *methanol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	80→70	20→30	linear gradient
2.5-20	70	30	isocratic
20-30	70→20	30→80	linear gradient
30-32	20→80	80→20	linear gradient
32-37	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to paracetamol (retention time about 3 minutes) are: caffeine impurity B, about 0.6; caffeine impurity F, about 1.2; caffeine impurity A, about 1.3; caffeine, about 1.6;

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paracetamol impurity K, about 2.3; caffeine impurity E, about 2.5; paracetamol impurity J, about 6.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3) at 212 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity K is at least 10.

in the chromatogram obtained with solution (4) at 246 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity J is at least 10.

LIMITS

For paracetamol impurity J at 246 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to paracetamol impurity J is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (10 ppm).

For all other impurities at 212 nm

Identify any peaks due to caffeine impurity B and E, and multiply the peak areas by a correction factor of 2.9 and 3.3, respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to paracetamol impurity K is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (100 ppm);

the area of any other *secondary peak* is not greater than the area of the peak due to paracetamol in the chromatogram obtained with solution (5) (0.1%);

The total impurity content is not greater than 0.5%.

Disregard any peak, excluding paracetamol impurities J and K, with an area less than half the area of the peak due to paracetamol in the chromatogram obtained with solution (5) (0.05%).

ASSAY

For paracetamol

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 100 mL of the mobile phase, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 250 mL with the mobile phase.
(2) 0.005% w/v of *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

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DETERMINATION OF CONTENT

Calculate the content of $C_8H_9NO_2$ in the tablets using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

For caffeine

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing 30 mg of Caffeine with 100 mL of the mobile phase, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 50 mL with the mobile phase.
(2) 0.003% w/v of *caffeine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{10}N_4O_2$ in the tablets using the declared content of $C_8H_{10}N_4O_2$ in *caffeine BPCRS*.

LABELLING

The label states the quantities of Paracetamol and Caffeine.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities J and K listed under Paracetamol, and impurities A, B, E and F listed under Caffeine.

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Paracetamol Capsules

General Notices

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Capsules contain Paracetamol.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.5 g of Paracetamol with 20 mL of *acetone*, filter, evaporate the filtrate and dry at 105°.The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of paracetamol (*RS 258*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

Hard capsules

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 5.8*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 20-mL sample of the medium and measure the *absorbance* of the filtered sample, diluted with 0.1M *sodium hydroxide* to give a solution expected to contain about 0.00075% w/v of Paracetamol at the maximum at 257 nm, Appendix II B, using 0.1M *sodium hydroxide* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

Soft capsules

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 20-mL sample of the medium and measure the *absorbance* of the filtered sample, diluted with *0.1M hydrochloric acid* to give a solution expected to contain about 0.00075% w/v of Paracetamol at the maximum at 257 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D. *Prepare the solutions immediately before use and protect from light*.

(1) Disperse a quantity of the contents of the capsules containing 0.2 g of Paracetamol in 8 mL of the mobile phase with the aid of ultrasound, add sufficient mobile phase to produce 10 mL, mix well and filter.

(2) Dilute 1 volume of solution (1) to 20 volumes with the mobile phase and dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

(3) 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.

(4) Dilute a 0.02% w/v solution of *4'-chloroacetanilide* in *methanol* with the mobile phase to produce a solution containing 0.00002% w/v of *4'-chloroacetanilide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 12 times the retention time of the principal peak.

MOBILE PHASE

250 volumes of *methanol* containing 1.15 g of a 40% w/v solution of *tetrabutylammonium hydroxide*, 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (10 ppm);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%).

ASSAY

Weigh the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D. *Prepare the solutions immediately before use and protect from light*.

(1) Disperse a quantity of the contents of the capsules containing 0.5 g of Paracetamol in 80 mL of the mobile phase with the aid of ultrasound, add sufficient mobile phase to produce 100 mL, mix well, filter and dilute 1 volume of the resulting solution to 100 volumes with the mobile phase.

(2) 0.005% w/v of *paracetamol BPCRS* in the mobile phase.

(3) 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

250 volumes of *methanol* containing 1.15 g of a 40% w/v solution of *tetrabutylammonium hydroxide*, 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_9NO_2$ in the capsules, using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

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STORAGE

Paracetamol Capsules should be stored in an airtight container, protected from moisture.

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Paracetamol Dispersible Tablets

General Notices

Dispersible Paracetamol Tablets

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Dispersible Tablets contain Paracetamol in a suitable dispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Disperse in *water* to form a uniform suspension.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits a maximum only at 257 nm.

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *toluene*, 25 volumes of *acetone* and 65 volumes of *chloroform* as the mobile phase but allowing the solvent front to ascend 14 cm above the line of application. Apply separately to the plate 40 µL of each of solutions (1), (2) and (3). Pour the mobile phase into the unlined tank, immediately place the prepared plate in the tank and close the tank. For solution (1) add 50 mL of *ethanol* (*96%*) to a quantity of the powdered tablets containing 0.10 g of Paracetamol, shake for 10 minutes, add sufficient *ethanol* (*96%*) to produce 100 mL and filter. Solution (2) contains 0.10% w/v of *paracetamol BPCRS* in *ethanol* (*96%*). For solution (3) dissolve 0.25 g of *4′-chloroacetanilide* and 0.10 g of *paracetamol* in sufficient *ethanol* (*96%*) to produce 100 mL. After removal of the plate, dry it in a current of warm air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots, the spot corresponding to 4′-chloroacetanilide having the higher Rf value.

TESTS

Disintegration

Comply with the requirements for Dispersible Tablets.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light. For solution (1) disperse a quantity of powdered tablets containing to 0.2 g of Paracetamol in 8 mL of the mobile phase with the aid of ultrasound, add sufficient mobile phase to produce 10 mL, mix well and filter. For solution (2) dilute 1 volume of solution (1) to 20 volumes with mobile phase and dilute 1 volume of this solution to 20 volumes with mobile phase. Solution (3) contains 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.Solution (4) contains 0.00002% w/v of *4′-chloroacetanilide* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute, with a temperature of 35°C, a mixture of 250 volumes of *methanol* containing 1.15 g of a 40% v/v solution of *tetrabutylammonium hydroxide* with 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate* and (c) a detection wavelength of 245 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

Inject solution (1) and allow the chromatography to proceed for 12 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in solution (3) (0.1%), the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in solution (4) (10 ppm) and no other impurity is greater than the area of the principal peak obtained with solution (2) (0.25%).

ASSAY

Weigh and powder 20 tablets. Add 50 mL of 0.1M *sodium hydroxide* slowly to a quantity of the powder containing 0.2 g of Paracetamol, dilute with 100 mL of *water*, shake for 15 minutes and add sufficient *water* to produce 250 mL. Mix, filter and dilute 10 mL of the filtrate to 100 mL with *water*. Add 10 mL of the resulting solution to 10 mL of 0.1M *sodium hydroxide*, dilute to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 257 nm, Appendix II B. Calculate the content of $C_8H_9NO_2$ taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

STORAGE

Paracetamol Dispersible Tablets should be protected from light.

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Paracetamol Effervescent Tablets

General Notices

Effervescent Paracetamol Tablets

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Effervescent Tablets contain Paracetamol in a suitable soluble, effervescent basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve, with vigorous effervescence, on the addition of warm *water* to produce a slightly opalescent solution.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits a maximum only at 257 nm.

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *toluene*, 25 volumes of *acetone* and 65 volumes of *chloroform* as the mobile phase but allowing the solvent front to ascend 14 cm above the line of application. Apply separately to the plate 40 µL of each of solutions (1), (2) and (3). Pour the mobile phase into the unlined tank, immediately place the prepared plate in the tank and close the tank. For solution (1) add 50 mL of *ethanol* (*96%*) to a quantity of the powdered tablets containing 0.10 g of Paracetamol, shake for 10 minutes, add sufficient *ethanol* (*96%*) to produce 100 mL and filter. Solution (2) contains 0.10% w/v of *paracetamol BPCRS* in *ethanol* (*96%*). For solution (3) dissolve 0.25 g of *4′-chloroacetanilide* and 0.10 g of *paracetamol* in sufficient *ethanol* (*96%*) to produce 100 mL. After removal of the plate, dry it in a current of warm air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots, the spot corresponding to 4′-chloroacetanilide having the higher Rf value.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light. For solution (1) disperse a quantity of powdered tablets containing 0.2 g of Paracetamol in 8 mL of the mobile phase

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with the aid of ultrasound, add sufficient mobile phase to produce 10 mL, mix well and filter. For solution (2) dilute 1 volume of solution (1) to 20 volumes with the mobile phase and dilute 1 volume of this solution to 20 volumes with the mobile phase. Solution (3) contains 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.Solution (4) contains 0.00002% w/v of *4′-chloroacetanilide* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute, with a temperature of 35°C, a mixture of 250 volumes of *methanol* containing 1.15 g of a 40% v/v solution of *tetrabutylammonium hydroxide* with 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate* and (c) a detection wavelength of 245 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

Inject solution (1) and allow the chromatography to proceed for 12 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in solution (3) (0.1%), the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in solution (4) (10 ppm) and no other impurity is greater than the area of the principal peak obtained with solution (2) (0.25%).

ASSAY

Weigh and powder 20 tablets. Add 50 mL of 0.1M *sodium hydroxide* slowly to a quantity of the powdered tablets containing 0.2 g of Paracetamol. Wait until effervescence has ceased, dilute with 100 mL of *water*, shake for 15 minutes and add sufficient *water* to produce 250 mL. Mix, filter and dilute 10 mL of the filtrate to 100 mL with *water*. Add 10 mL of the resulting solution to 10 mL of 0.1M *sodium hydroxide*, dilute to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 257 nm, Appendix II B. Calculate the content of $C_8H_9NO_2$ taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

STORAGE

Paracetamol Effervescent Tablets should be protected from light.

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Paracetamol Oral Suspension

General Notices

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Oral Suspension is a suspension of Paracetamol in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the preparation being examined with *methanol* to produce a solution containing 0.24% w/v of Paracetamol and filter if necessary.

(2) 0.24% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, examine under *ultraviolet light (254 nm)* and also reveal the spots using *Method 1*.

MOBILE PHASE

0.5 volume of *glacial acetic acid*, 10 volumes of *toluene*, 25 volumes of *acetone* and 65 volumes of *chloroform*.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to paracetamol in the chromatogram obtained with solution (2).

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4-Aminophenol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 5 mL of the preparation being examined with 15 mL of the mobile phase, dilute with the mobile phase to contain 0.48% w/v of Paracetamol and filter if necessary.

(2) 0.0024% w/v of *4-aminophenol* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 272 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium butanesulfonate* in a mixture of 0.4 volumes of *formic acid*, 15 volumes of *methanol* and 85 volumes of *water*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminophenol is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

Peaks with a long retention time may occur due to preservatives in the preparation.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a weighed quantity of the preparation being examined containing 24 mg of Paracetamol with 100 mL of the mobile phase, dilute to 200 mL with the mobile phase and filter if necessary.

(2) 0.012% w/v of *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure may be carried out as described under the test for 4-Aminophenol using a detection wavelength of 243 nm.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the preparation, Appendix V G, and calculate the percentage content of $C_8H_9NO_2$, weight in volume, using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

STORAGE

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Paracetamol Oral Suspension should be protected from light.

When paediatric paracetamol oral suspension or paediatric paracetamol mixture is prescribed or demanded, Paracetamol Oral Suspension containing 2.4% w/v of Paracetamol shall be dispensed or supplied unless otherwise stated by the prescriber.

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Paracetamol Suppositories

General Notices

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Suppositories contain Paracetamol in a suitable suppository basis.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add sufficient *methanol* to 1 suppository to produce a final solution containing 0.1% w/v of Paracetamol and warm on a water-bath until the suppository has melted. Allow the solution to cool, with occasional stirring, and filter.

(2) 0.1% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *methanol* and 4 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Cut into small pieces. To a quantity of the suppositories containing 50 mg of Paracetamol add 1 mL of *hydrochloric acid* and heat to boiling for 3 minutes; add 10 mL of *water* and cool. No precipitate is produced. Add 0.05 mL of *potassium dichromate solution R1*. A violet colour develops which does not change to red.

TESTS

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D. *Prepare the solutions immediately before use and protect from light*.

(1) Cut into small pieces. Dissolve a minimum of 5 suppositories in the minimum volume of *ethanol* (*96%*), warming if necessary, and dilute with sufficient *water* to obtain a solution containing 0.5% w/v of Paracetamol.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(3) 0.0005% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.

(4) Dilute a 0.005% w/v solution of *4′-chloroacetanilide* in *methanol* with the mobile phase to produce a solution containing 0.000005% w/v of *4′-chloroacetanilide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 12 times the retention time of the principal peak.

MOBILE PHASE

250 volumes of *methanol* containing 1.15 g of a 40% w/v solution of *tetrabutylammonium hydroxide*, 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (10 ppm);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

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Disregard any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.03%).

ASSAY

For suppositories containing 150 mg or more

To 1 suppository add 30 mL of *water* and 100 mL of 1M *sulfuric acid*. Boil under a reflux condenser for 1 hour, cool and add 100 mL of *water*, 50 g of ice, 50 mL of *dilute hydrochloric acid* and 0.2 mL of *ferroin solution*. Titrate with 0.2M *ammonium cerium(IV) sulfate VS* until a yellow colour is obtained. Each mL of 0.2M *ammonium cerium(IV) sulfate VS* is equivalent to 15.12 mg of $C_8H_9NO_2$. Repeat the test using a further 4 suppositories and calculate the average content per suppository from the 5 individual results thus obtained.

For suppositories containing less than 150 mg and more than 60 mg

To 1 suppository add 10 mL of *water* and 30 mL of *dilute sulfuric acid*. Boil under a reflux condenser for 1 hour, cool and add 40 mL of *water*, 40 g of ice, 15 mL of *dilute hydrochloric acid* and 0.1 mL of *ferroin solution*. Titrate with 0.1M *ammonium cerium(IV) sulfate VS* until a yellow colour is obtained. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 7.56 mg of $C_8H_9NO_2$. Repeat the test using a further 4 suppositories and calculate the average content per suppository from the 5 individual results thus obtained.

For suppositories containing 60 mg or less

To 1 suppository add 10 mL of *water* and 30 mL of *dilute sulfuric acid*. Boil under a reflux condenser for 1 hour, cool and add 40 mL of *water*, 40 g of ice, 15 mL of *dilute hydrochloric acid* and 0.1 mL of *ferroin solution*. Titrate with 0.025M *ammonium cerium(IV) sulfate VS* until a yellow colour is obtained. Each mL of 0.025M *ammonium cerium(IV) sulfate VS* is equivalent to 1.89 mg of $C_8H_9NO_2$. Repeat the test using a further 4 suppositories and calculate the average content per suppository from the 5 individual results thus obtained.

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Paracetamol Tablets

General Notices

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Tablets contain Paracetamol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of Paracetamol with 20 mL of *acetone*, filter, evaporate the filtrate to dryness and dry at 105°. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of paracetamol (*RS 258*).

B. Boil 0.1 g with 1 mL of *hydrochloric acid* for 3 minutes, add 10 mL of *water* and cool; no precipitate is produced. Add 0.05 mL of 0.0167 M *potassium dichromate*; a violet colour is produced slowly which does not turn red.

C. *Melting point*, about 169°, Appendix V A.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *phosphate buffer pH 5.8* and rotate the paddle at 50 revolutions per minute. Withdraw a sample of 20 mL of the medium and filter. Dilute the filtrate with 0.1M *sodium hydroxide* to give a solution expected to contain about 0.00075% w/v of Paracetamol. Measure the *absorbance* of this solution, Appendix II B, at the maximum at 257 nm using 0.1M *sodium hydroxide* in the reference cell. Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare the solutions immediately before use and protect from light*. For solution (1) disperse a quantity of powdered tablets containing 0.2 g of Paracetamol in 8 mL of the mobile phase

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with the aid of ultrasound, add sufficient mobile phase to produce 10 mL, mix well and filter. For solution (2) dilute 1 volume of solution (1) to 20 volumes with mobile phase and dilute 1 volume of this solution to 20 volumes with mobile phase. Solution (3) contains 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.For solution (4) dilute a 0.02% w/v solution of *4′-chloroacetanilide* in *methanol* with the mobile phase to produce a solution containing 0.00002% w/v of *4′-chloroacetanilide*.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute, at a temperature of 35°C, a mixture of 250 volumes of *methanol* containing 1.15 g of a 40% w/v solution of *tetrabutylammonium hydroxide* with 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate* and (c) a detection wavelength of 245 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

Inject solution (1) and allow the chromatography to proceed for 12 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in solution (3) (0.1%), the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in solution (4) (10 ppm) and no other impurity is greater than the area of the principal peak obtained with solution (2) (0.25%).

ASSAY

Weigh and powder 20 tablets. Add a quantity of the powder containing 0.15 g of Paracetamol to 50 mL of 0.1M *sodium hydroxide*, dilute with 100 mL of *water*, shake for 15 minutes and add sufficient *water* to produce 200 mL. Mix, filter and dilute 10 mL of the filtrate to 100 mL with *water*. Add 10 mL of the resulting solution to 10 mL of 0.1M *sodium hydroxide*, dilute to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 257 nm, Appendix II B. Calculate the content of $C_8H_9NO_2$ taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

STORAGE

Paracetamol Tablets should be protected from light.

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Paracetamol, Codeine Phosphate and Caffeine Capsules

General Notices

Action and use

Analgesic; antipyretic; opioid receptor agonist; central nervous system stimulant.

DEFINITION

Paracetamol, Codeine Phosphate and Caffeine Capsules contain Paracetamol, Codeine Phosphate and Caffeine.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

Content of codeine phosphate, $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$

95.0 to 105.0% of the stated amount.

Content of caffeine, $C_8H_{10}N_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the capsule contents containing 0.5 g of Paracetamol with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of paracetamol *(RS 258)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the capsule contents containing 24 mg of Codeine Phosphate with 30 mL of *water* and centrifuge. Decant, add 10 mL of 1M *sodium hydroxide* and 30 mL of *dichloromethane* to the supernatant liquid, shake and filter the dichloromethane layer through glass-fibre paper (Whatman GF/C is suitable).

(2) 0.08% w/v of *codeine phosphate BPCRS* in *methanol (50%)*.

(3) 0.08% w/v each of *codeine phosphate BPCRS* and *dihydrocodeine tartrate BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *ethanolic iron(III) chloride solution* and heat at 105° for 10 minutes and examine in daylight.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots of different colours.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

C. In the Assay for codeine phosphate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

D. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 65 mg of Caffeine in 10 mL of *methanol*, and filter (a 1.2-µm GF/C filter is suitable).

(2) 0.65% w/v of *caffeine BPCRS* in *methanol*.

(3) 0.65% w/v of *caffeine BPCRS* and 5% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *acetic acid*, 5 volumes of *ethanol*, 5 volumes of *water* and 50 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The spot corresponding to caffeine in the chromatogram obtained with solution (1) corresponds in position to the principal spot in the chromatogram obtained with solution (2).

E. In the Assay for caffeine, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1, using the following conditions.

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use as the medium 900 mL of a phosphate buffer (pH 5.8), at a temperature of 37°, prepared in the following manner. Mix 250 mL of *0.2M potassium dihydrogen phosphate* and 18 mL of *0.2M sodium hydroxide*, and dilute to 1000 mL with *water*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered dissolution medium diluted with the mobile phase, if necessary, to produce a solution expected to contain 0.0056% w/v of Paracetamol.

(2) 0.0056% w/v solution of *paracetamol BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase as described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 243 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium pentanesulfonate* in a mixture of 22 volumes of *methanol* and 78 volumes of *water*, adjusted to pH 2.8 using *2M hydrochloric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of paracetamol is about 3 minutes.

DETERMINATION OF CONTENT

Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

LIMITS

The amount of paracetamol released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions prepared in solution A.

Solution A: 0.23% w/v of *sodium chloride* in a mixture of 30 volumes of mobile phase B and 70 volumes of mobile phase A.

(1) Mix with the aid of ultrasound a quantity of the mixed capsule contents containing 0.5 g of Paracetamol with 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.0005% w/v of *codeine phosphate BPCRS* and 0.0001% w/v of *4'-chloroacetanilide* (paracetamol impurity J).

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(4) 0.0001% w/v of *4-aminophenol* (paracetamol impurity K).

(5) 0.00001% w/v of *4'-chloroacetanilide* (paracetamol impurity J).

(6) 0.01% w/v of *methylcodeine* (codeine impurity A).

(7) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex C18 100A is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 35°.

(e) Use detection wavelengths of 212 nm and 246 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 mM *sodium octanesulfonate*, adjusted to pH 2.2 with *orthophosphoric acid*.

Mobile phase B *methanol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	80→70	20→30	linear gradient
2.5-20	70	30	isocratic
20-30	70→20	30→80	linear gradient
30-32	20→80	80→20	linear gradient
32-37	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to paracetamol (retention time about 3 minutes) are: caffeine impurity B, about 0.6; caffeine impurity F, about 1.2; caffeine impurity A, about 1.3; caffeine, about 1.6; paracetamol impurity K, about 2.3; caffeine impurity E, about 2.5; codeine impurity B, about 2.9; codeine, about 4.8; paracetamol impurity J, about 6.1; codeine impurity A, about 8.0, and codeine impurity C, about 8.5.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3) at 246 nm, the *resolution* between the peaks due to codeine and paracetamol impurity J is at least 2.2.

in the chromatogram obtained with solution (4) at 212 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity K is at least 10.

in the chromatogram obtained with solution (5) at 246 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity J is at least 10.

LIMITS

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For paracetamol impurity J at 246 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to paracetamol impurity J is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (10 ppm).

For all other impurities at 212 nm

Identify any peaks due to caffeine impurity B, D, and E, and multiply the peak areas by a correction factor of 2.9, 1.3, and 3.3, respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to codeine impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (6) (1%);

the area of any peak corresponding to paracetamol impurity K is not greater than the area of the corresponding peak in the chromatogram obtained with solution (4) (100 ppm);

the area of any other *secondary peak* with a relative retention of 2.7 or less (with reference to paracetamol) is not greater than the area of the peak due to paracetamol in the chromatogram obtained with solution (7) (0.1%);

the area of any other *secondary peak* with a relative retention greater than 2.7 (with reference to paracetamol) is not greater than twice the area of the peak due to codeine in the chromatogram obtained with solution (7) (0.2%);

The total impurity content, excluding codeine impurity A, is not greater than 0.75%.

Disregard any peak, excluding paracetamol impurities J and K, with an area less than half the area of the peak due to paracetamol in the chromatogram obtained with solution (7) (0.05%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Codeine Phosphate comply with the requirements stated under Capsules, with respect to the content of Codeine Phosphate, using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 100 mL of the mobile phase to the contents of one capsule and mix with the aid of ultrasound until completely dispersed. Shake and dilute to 200 mL with the mobile phase. Filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.
(2) 0.004% w/v of *codeine phosphate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in each capsule using the declared content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in *codeine phosphate BPCRS*.

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ASSAY

For paracetamol

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 0.5 g of Paracetamol with 100 mL of the mobile phase, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 250 mL with the mobile phase.
(2) 0.005% w/v of *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_9NO_2$ in the capsules using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS.*

For codeine phosphate

For capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of codeine phosphate

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing the equivalent of 2 mg or more and 2% w/w or more of codeine phosphate

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 8 mg of Codeine Phosphate with 100 mL of the mobile phase, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.
(2) 0.004% w/v of *codeine phosphate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in the capsules using the declared content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in *codeine phosphate BPCRS*.

For caffeine

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Shake a quantity of the contents of the capsules containing 30 mg of Caffeine with 100 mL of the mobile phase, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 50 mL with the mobile phase.

(2) 0.003% w/v of *caffeine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{10}N_4O_2$ in the capsules using the declared content of $C_8H_{10}N_4O_2$ in *caffeine BPCRS.*

IMPURITIES

The impurities limited by the requirements of this monograph include impurities J and K listed under Paracetamol, impurities A, B, C, H, I and J listed under Codeine Phosphate, and impurities A, B, E and F listed under Caffeine.

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Paracetamol, Codeine Phosphate and Caffeine Tablets

General Notices

Action and use

Analgesic; antipyretic; opioid receptor agonist; central nervous system stimulant.

DEFINITION

Paracetamol, Codeine Phosphate and Caffeine Tablets contain Paracetamol, Codeine Phosphate and Caffeine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

Content of codeine phosphate, $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$

95.0 to 105.0% of the stated amount.

Content of caffeine, $C_8H_{10}N_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of paracetamol *(RS 258)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 24 mg of Codeine Phosphate with 30 mL of *water* and centrifuge. Decant, add 10 mL of 1M *sodium hydroxide* and 30 mL of *dichloromethane* to the supernatant liquid, shake and filter the dichloromethane layer through glass-fibre paper (Whatman GF/C is suitable).

(2) 0.08% w/v of *codeine phosphate BPCRS* in *methanol (50%)*.

(3) 0.08% w/v each of *codeine phosphate BPCRS* and *dihydrocodeine tartrate BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *ethanolic iron(III) chloride solution* and heat at 105° for 10 minutes and examine in daylight.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots of different colours.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

C. In the Assay for codeine phosphate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

D. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 65 mg of Caffeine in 10 mL of *methanol* and filter (a 0.2-µm nylon filter is suitable).

(2) 0.65% w/v of *caffeine BPCRS* in *methanol*.

(3) 0.65% w/v of *caffeine BPCRS* and 5% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *acetic acid*, 5 volumes of *ethanol*, 5 volumes of *water* and 50 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The spot corresponding to caffeine in the chromatogram obtained with solution (1) corresponds in position to the principal spot in the chromatogram obtained with solution (2).

E. In the Assay for caffeine, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1, using the following conditions.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use as the medium 900 mL of a phosphate buffer (pH 5.8), at a temperature of 37°, prepared in the following manner. Mix 250 mL of *0.2M potassium dihydrogen orthophosphate* and 18 mL of *0.2M sodium hydroxide*, and dilute to 1000 mL with *water*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw a sample of the medium and filter. Use the filtered dissolution medium, diluted with the mobile phase, if necessary, to produce a solution expected to contain 0.0056% w/v of Paracetamol.

(2) 0.0056% w/v of *paracetamol BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase as described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 243 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium pentanesulfonate* in a mixture of 22 volumes of *methanol* and 78 volumes of *water*, adjusted to pH 2.8 using *2M hydrochloric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of paracetamol is about 3 minutes.

DETERMINATION OF CONTENT

Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

LIMITS

The amount of paracetamol released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions prepared in solution A.

Solution A: 0.23% w/v of *sodium chloride* in a mixture of 30 volumes of mobile phase B and 70 volumes of mobile phase A.

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(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Paracetamol with 50 mL and filter (Chromafil RC 45/25 is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.0005% w/v of *codeine phosphate BPCRS* and 0.0001% w/v of *4'-chloroacetanilide* (paracetamol impurity J).

(4) 0.0001% w/v of *4-aminophenol* (paracetamol impurity K).

(5) 0.00001% w/v of *4'-chloroacetanilide* (paracetamol impurity J).

(6) 0.01% w/v of *methylcodeine* (codeine impurity A).

(7) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex C18 100A is suitable).

(b) Use gradient elution and the mobile phase as described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 35°.

(e) Use detection wavelengths of 212 nm and 246 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 mM *sodium octanesulfonate*, adjusted to pH 2.2 with *orthophosphoric acid*.

Mobile phase B *methanol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	80→70	20→30	linear gradient
2.5-20	70	30	isocratic
20-30	70→20	30→80	linear gradient
30-32	20→80	80→20	linear gradient
32-37	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to paracetamol (retention time about 3 minutes) are: caffeine impurity B, about 0.6; caffeine impurity F, about 1.2; caffeine impurity A, about 1.3; caffeine, about 1.6; paracetamol impurity K, about 2.3; caffeine impurity E, about 2.5; codeine impurity B, about 2.9; codeine, about 4.8; paracetamol impurity J, about 6.1; codeine impurity A, about 8.0, and codeine impurity C, about 8.5.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3) at 246 nm, the *resolution* between the peaks due to codeine and paracetamol impurity J is at least 2.2.

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in the chromatogram obtained with solution (4) at 212 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity K is at least 10.

in the chromatogram obtained with solution (5) at 246 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity J is at least 10.

LIMITS

For paracetamol impurity J at 246 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to paracetamol impurity J is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (10 ppm).

For all other impurities at 212 nm

Identify any peaks due to caffeine impurity B and E, and multiply the peak areas by a correction factor of 2.9 and 3.3, respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to codeine impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (6) (1%);

the area of any peak corresponding to paracetamol impurity K is not greater than the area of the corresponding peak in the chromatogram obtained with solution (4) (100 ppm);

the area of any other *secondary peak* with a relative retention of 2.7 or less (with reference to paracetamol) is not greater than the area of the peak due to paracetamol in the chromatogram obtained with solution (7) (0.1%);

the area of any other *secondary peak* with a relative retention greater than 2.7 (with reference to paracetamol) is not greater than twice the area of the peak due to codeine in the chromatogram obtained with solution (7) (0.2%);

The total impurity content, excluding codeine impurity A, is not greater than 0.75%.

Disregard any peak, excluding paracetamol impurities J and K, with an area less than half the area of the peak due to paracetamol in the chromatogram obtained with solution (7) (0.05%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Codeine Phosphate comply with the requirements stated under Tablets, with respect to the content of Codeine Phosphate, using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 100 mL of the mobile phase to one tablet and mix with the aid of ultrasound until completely dispersed. Shake and dilute to 200 mL with the mobile phase. Filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.
(2) 0.004% w/v of *codeine phosphate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a detection wavelength of 220 nm.

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DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in each tablet using the declared content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in *codeine phosphate BPCRS*.

ASSAY

For paracetamol

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 100 mL of the mobile phase, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 250 mL with the mobile phase.
(2) 0.005% w/v of *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_9NO_2$ in the tablets using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

For codeine phosphate

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of codeine phosphate

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of codeine phosphate

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 8 mg of Codeine Phosphate with 100 mL of the mobile phase, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and use the filtrate.
(2) 0.004% w/v of *codeine phosphate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in the tablets using the declared content of $C_{18}H_{21}NO_3,H_3PO_4,½H_2O$ in *codeine phosphate BPCRS*.

For caffeine

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Shake a quantity of the powdered tablets containing 30 mg of Caffeine with 100 mL of the mobile phase, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 50 mL with the mobile phase.

(2) 0.003% w/v of *caffeine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{10}N_4O_2$ in the tablets using the declared content of $C_8H_{10}N_4O_2$ in *caffeine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities J and K listed under Paracetamol, impurities, A, B, C, H, I and J listed under Codeine Phosphate, and impurities A, B, E and F listed under Caffeine.

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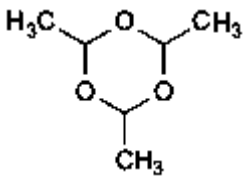
Paraldehyde

General Notices

(Ph. Eur. monograph 0351)



$C_6H_{12}O_3$ 132.2 *123-63-7*

Action and use

Anticonvulsant.

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DEFINITION

2,4,6-Trimethyl-1,3,5-trioxane (cyclic trimer of acetaldehyde).

It may contain a suitable quantity of an antioxidant.

CHARACTERS

Appearance

Colourless or slightly yellow, transparent liquid. It solidifies on cooling to form a crystalline mass.

Solubility

Soluble in water, but less soluble in boiling water, miscible with ethanol (96 per cent) and with essential oils.

IDENTIFICATION

A. Solution S (see Tests) is clear (*2.2.1*) but becomes turbid on warming.

B. To 5 mL add 0.1 mL of *dilute sulfuric acid R* and heat. Acetaldehyde, recognisable by its odour, is evolved.

C. To 5 mL of solution S in a test-tube add 5 mL of *ammoniacal silver nitrate solution R* and heat in a water-bath. Silver is deposited as a mirror on the wall of the tube.

TESTS

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Solution S

Dissolve 20.0 mL in *carbon dioxide-free water R* and dilute to 200.0 mL with the same solvent.

Acidity

To 50.0 mL of solution S add 0.05 mL of *phenolphthalein solution R*. Not more than 1.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Refractive index (*2.2.6*)

1.403 to 1.406.

Relative density (*2.2.5*)

0.991 to 0.996.

Distillation range (*2.2.11*)

A maximum of 10 per cent distils below 123 °C and a minimum of 95 per cent distils below 126 °C.

Freezing point (*2.2.18*)

10 °C to 13 °C.

Acetaldehyde

To 5.0 mL add a mixture of 0.2 mL of *methyl orange solution R*, 5 mL of *ethanol (60 per cent V/V) R* and 5 mL of *alcoholic hydroxylamine solution R* and shake. Not more than 0.8 mL of *0.5 M sodium hydroxide* is required to change the colour of the indicator to pure yellow.

Peroxides

Place 50.0 mL of solution S in a ground-glass-stoppered flask, add 5 mL of *dilute sulfuric acid R* and 10 mL of *potassium iodide solution R*, close the flask and allow to stand protected from light for 15 min. Titrate with *0.1 M sodium thiosulfate* using 1 mL of *starch solution R* as indicator. Allow to stand for 5 min and, if necessary complete the titration. Not more than 2.0 mL of *0.1 M sodium thiosulfate* is required.

Non-volatile residue

Maximum 0.6 g/L.

Heat 5.0 mL in a tared evaporating dish on a water-bath and dry at 105 °C for 1 h. The residue weighs a maximum of 3 mg.

STORAGE

In a small, well-filled, airtight container, protected from light. If the substance has solidified the whole contents of the container must be liquefied before use.

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Paraldehyde Injection

General Notices

DEFINITION

Paraldehyde Injection is Paraldehyde that has been sterilised. It does not contain any added antimicrobial preservatives.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

IDENTIFICATION

A. A 10.0% v/v solution in *carbon dioxide-free water* (solution A) is *clear*, Appendix IV A, but becomes turbid on warming.

B. Heat 5 mL with 0.1 mL of 1M *sulfuric acid*. Acetaldehyde is evolved.

C. To 5 mL of solution A in a test tube add 5 mL of *ammoniacal silver nitrate solution* and heat on a water bath. Silver is deposited as a mirror on the side of the tube.

TESTS

Acidity

Titrate 50 mL of solution A with *0.1M sodium hydroxide VS* using 0.05 mL of *phenolphthalein solution* as indicator. Not more than 1.5 mL of *0.1M sodium hydroxide VS* is required to change the colour of the solution.

Distillation range

Not more than 10% distils below 123° and not less than 95% distils below 126°, Appendix V C.

Freezing point

10° to 13°, Appendix V B.

Refractive index

1.403 to 1.406, Appendix V E.

Relative density

0.991 to 0.996, Appendix V G.

Acetaldehyde

Shake 5 mL with a mixture of 5 mL of *ethanol* (*60%*), 5 mL of *alcoholic hydroxylamine solution* and 0.2 mL of *methyl orange solution*. Not more than 0.8 mL of *0.5M sodium hydroxide VS* is required to change the colour of the solution to pure yellow.

Peroxides

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Peroxides

To 50 mL of solution A in a ground-glass-stoppered flask add 5 mL of 1M *sulfuric acid* and 10 mL of *potassium iodide solution*, close the flask and allow to stand in the dark for 15 minutes. Titrate with 0.1M *sodium thiosulfate VS* using 1 mL of *starch solution* as indicator; allow to stand for 5 minutes and, if necessary, complete the titration. Not more than 2.0 mL of 0.1M *sodium thiosulfate VS* is required.

STORAGE

Paraldehyde Injection should be supplied in single-dose glass ampoules sealed by fusion of the glass. It should be kept in complete darkness.

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Parenteral Nutrition Solutions

General Notices

Parenteral Nutrition

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used for parenteral nutrition.

DEFINITION

Parenteral Nutrition Solutions are infusions containing essential nutrition requirements in the form of protein (amino acids), carbohydrate (glucose) and fat (lipids), together with electrolytes, trace elements and vitamins. The infusions will contain some, but not necessarily all, of these ingredients.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the infusion also complies with the requirements stated under Unlicensed Medicines.

PREPARATION

A suitable assessment is carried out to demonstrate that the appropriate amount of glucose is present.

For lipid-containing formulations a suitable method should be carried out to demonstrate the stability of the lipid emulsion, for example a method to determine the globule size distribution.

NOTE: *In order to minimise the risk of exposure to aluminium, only Calcium Gluconate Injection and sodium glycerophosphate that have been stored in plastic containers should be used in the preparation of Parenteral Nutrition Solutions.*

Content of calcium, Ca, magnesium, Mg, potassium, K, sodium, Na, chloride, Cl, as appropriate

90.0 to 110.0% of the stated amount.

IDENTIFICATION

The infusion complies with the following tests, as appropriate.

A. When heated with *cupri-tartaric solution R1*, a red precipitate is produced (identification of glucose).
B. Yields reaction (a) characteristic of *calcium salts*, Appendix VI.
C. Yields reaction (b) characteristic of *magnesium salts*, Appendix VI.
D. Yields reaction (b) characteristic of *potassium salts*, Appendix VI.
E. Yields reaction (b) characteristic of *sodium salts*, Appendix VI.

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F. Yields reaction (a) characteristic of *chlorides*, Appendix VI.

TESTS

Aluminium

Not more than 25 µg/L, when determined by the following method.

Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, using the following solutions. Use a matrix modifier (for example, *nitric acid* and *magnesium nitrate* in *water*) in the same quantity for each solution.

(1) Dilute the infusion with *water*, if necessary, to a concentration suitable for the instrument to be used.

(2) *By Method I (direct calibration)* Prepare the standard solutions using *aluminium standard solution (25 ppm Al)*, diluting with acidified *water*.

By Method II (standard additions) Prepare at least three reference solutions in the range spanning the expected aluminium concentration of the test solution by diluting *aluminium standard solution (25 ppm Al)* with solution (1).

(3) *Water* (blank).

Measure the *absorbance* at 309.3 nm using an aluminium hollow-cathode lamp as the radiation source and a graphite furnace.

Bacterial endotoxins

The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C.

Sterility

Complies with the test for *sterility*, Appendix XVI A.

ASSAY

Carry out the following Assays, as appropriate.

For calcium

Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, Method I, using the following solutions.

(1) Dilute the infusion with *water*, if necessary, to a concentration suitable for the instrument to be used; add 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solution.

(2) Prepare the standard solutions using *calcium standard solution (400 ppm Ca)* and adding 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solutions.

Measure the absorbance at 422.7 nm using a calcium hollow-cathode lamp as the radiation source and an air-propane or air-acetylene flame.

For magnesium

Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, Method I, using the following solutions.

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(1) Dilute the infusion with *water*, if necessary, to a concentration suitable for the instrument to be used; add 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solution.

(2) Prepare the standard solutions using *magnesium standard solution (100 ppm Mg)* and adding 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solutions.

Measure the absorbance at 285.2 nm using a magnesium hollow-cathode lamp as the radiation source and an air-propane or air-acetylene flame.

For potassium

Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, Method I, using the following solutions.

(1) Dilute the infusion with *water*, if necessary, to a concentration suitable for the instrument to be used; add 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solution.

(2) Prepare the standard solutions using *potassium standard solution (100 ppm K)* and adding 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solutions.

Measure the absorbance at 766.5 nm using a potassium hollow-cathode lamp as the radiation source and an air-propane or air-acetylene flame.

For sodium

Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, Method I, using the following solutions.

(1) Dilute the infusion with *water*, if necessary, to a concentration suitable for the instrument to be used; add 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solution.

(2) Prepare the standard solutions using *sodium standard solution (200 ppm Na)* and adding 10 mL of a 2% w/v solution of *lanthanum chloride heptahydrate* to the final solutions.

Measure the absorbance at either 589.0 nm or 589.6 nm (sodium emits as a doublet) using a sodium hollow-cathode lamp as the radiation source and an air-propane or air-acetylene flame.

For chloride

Dilute an accurately measured volume of the infusion containing the equivalent of about 0.68 mEq of chloride with a volume of *water* sufficient to immerse the electrode. Carry out a *potentiometric titration*, Appendix VIII B, using 0.1M *silver nitrate*. Take the point between the two points of inflexion as the end point. Each mL of 0.1M *silver nitrate* is equivalent to 3.545 mg of Cl.

STORAGE

Parenteral Nutrition Solutions should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The label states: (1) the formula of the solution for parenteral nutrition, giving the total quantities of available nitrogen (in grams), calories and electrolytes (in mmol) and vitamins in the final container; (2) the nominal volume of the solution; (3) where applicable, the name and amount of any added antioxidant; (4) the conditions under which it should be stored.

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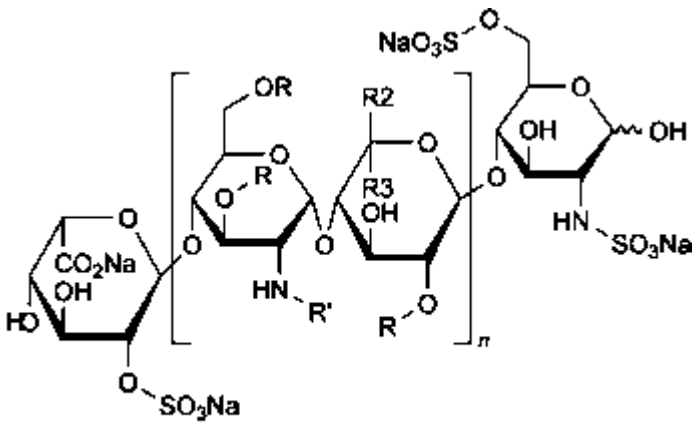
Parnaparin Sodium

General Notices

(Ph. Eur. monograph 1252)



Action and use

Low molecular weight heparin.

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DEFINITION

Sodium salt of a low-molecular-mass heparin that is obtained by radical-catalysed depolymerisation, with hydrogen peroxide and with a cupric salt, of heparin from porcine intestinal mucosa. The majority of the components have a 2-*O*-sulfo-α-L-idopyranuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain.

Parnaparin sodium complies with the monograph Low-molecular-mass heparins (0828), with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 4000 and 6000 with a characteristic value of about 5000.

The degree of sulfatation is 2.0 to 2.6 per disaccharide unit.

The potency is not less than 75 IU and not more than 110 IU of anti-factor Xa activity per milligram calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.5 and 3.0.

IDENTIFICATION

Carry out identification test A as described in the monograph *Low-molecular-mass heparins (0828)* using *parnaparin sodium CRS*.

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Carry out identification test C as described in the monograph *Low-molecular-mass heparins (0828)*. In order to verify the suitability of the system in the lower molecular mass ranges (for example M_r 2000), a suitable reference preparation is used. The following requirements apply.

The mass-average relative molecular mass ranges between 4000 and 6000. The mass percentage of chains lower than 3000 is not more than 30 per cent. The mass percentage of chains between 3000 and 8000 ranges between 50 per cent and 60 per cent.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 1.5 g in 10 mL of *water R*.

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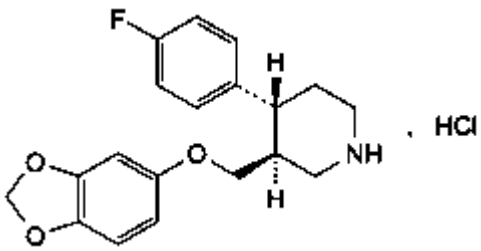
Paroxetine Hydrochloride

General Notices

Anhydrous Paroxetine Hydrochloride

(Ph. Eur. monograph 2283)



$C_{19}H_{21}ClFNO_3$ 365.8 *78246-49-8*

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

Preparation

Paroxetine Tablets

Ph Eur

DEFINITION

(3*S*,4*R*)-3-[[(1,3-Benzodioxol-5-yl)oxy]methyl]-4-(4-fluorophenyl)piperidine hydrochloride.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

Impurity G

Maximum 1 ppm, determined by a suitable validated method.

CHARACTERS

Appearance

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White or almost white, hygroscopic, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *anhydrous paroxetine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, mix 1 part of the substance to be examined and 1 part of the reference substance separately with 30 parts of anhydrous *acetone R* and heat to boiling to dissolve. Recrystallise and record new spectra using the residues.

B. Water (see Tests).

C. Dissolve 20 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1).

D. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *paroxetine impurity D CRS* in 2 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1 mL of reference solution (a) to 10 mL with the test solution.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *α_1-acid-glycoprotein silica gel for chiral separation R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Dissolve 8.7 g of *dipotassium hydrogen phosphate R* in 1000 mL of *water for chromatography R* and adjust to pH 6.5 with *phosphoric acid R*; mix 930 mL of this solution and 70 mL of *acetonitrile R*.

Flow rate 0.9 mL/min.

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Detection Spectrophotometer at 295 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 2.5 times the retention time of paroxetine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to paroxetine (retention time = about 13 min): impurity D = about 0.7.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to paroxetine.

Limit:

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture tetrahydrofuran R, water R (10:90 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 5.0 mL of the test solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of anhydrous paroxetine hydrochloride impurity H CRS in 25 mL of tetrahydrofuran R and dilute to 50.0 mL with water R.

Reference solution (c) Dissolve 5.0 mg of anhydrous paroxetine hydrochloride impurity C CRS in 25 mL of tetrahydrofuran R and dilute to 50.0 mL with water R.

Reference solution (d) To 5.0 mL of reference solution (a) add 1.0 mL of reference solution (b) and dilute to 100.0 mL with the solvent mixture.

Reference solution (e) To 5.0 mL of reference solution (a) add 5.0 mL of reference solution (b) and 5.0 mL of reference solution (c). Dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (f) Dissolve 2.5 mg of paroxetine impurity E CRS in the solvent mixture, add 2.5 mL of the test solution and dilute to 100 mL with the solvent mixture.

Reference solution (g) Dissolve 5 mg of paroxetine impurity A CRS in the solvent mixture and dilute to 50 mL with the solvent mixture. Use this solution to identify the peak due to impurity A.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *tetrahydrofuran R*, *water for chromatography R* (0.5:10:90 *V/V/V*);

— *mobile phase B*: *trifluoroacetic acid R*, *tetrahydrofuran R*, *acetonitrile R* (0.5:10:90 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	80	20
30 - 50	80 → 20	20 → 80
50 - 55	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 295 nm.

Injection 20 µL of the test solution and reference solutions (d), (e), (f) and (g).

Relative retention With reference to paroxetine (retention time = about 28 min): impurity A = about 0.8; impurity E = about 0.9; impurity C = about 1.5.

Relative retention With reference to impurity C: impurity F = about 0.97; impurity J = about 1.02.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurity E and paroxetine in the chromatogram obtained with reference solution (f);

— *signal-to-noise ratio*: minimum 3 for the peak due to paroxetine in the chromatogram obtained with reference solution (e).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.6; impurity F = 1.7; impurity J = 1.3;

— *impurity A*: not more than 0.6 times the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.3 per cent);

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— *impurities C, F, J*: for each impurity, not more than 0.2 times the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.10 per cent);

— *total*: not more than the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *disregard limit*: the area of the peak due to paroxetine in the chromatogram obtained with reference solution (e) (0.05 per cent).

Impurities H and I

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 263 nm.

Injection Test solution and reference solutions (d) and (e).

Relative retention With reference to paroxetine (retention time = about 28 min): impurity I = about 0.2; impurity H = about 0.4.

System suitability Reference solution (e):

— *signal-to-noise ratio*: minimum 3 for the peak due to impurity H.

Limits:

— *impurities H, I*: for each impurity, not more than the area of the peak due to impurity H in the chromatogram obtained with reference solution (d) (0.1 per cent).

Acetone (2.4.24, System B)

Maximum 3.5 per cent.

2-Propanol (2.4.24, System B)

Maximum 4.3 per cent.

Water (2.5.12)

Maximum 1.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

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Reference solution (a) Dissolve 51.2 mg of *paroxetine hydrochloride hemihydrate CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *paroxetine hydrochloride hemihydrate CRS* and 5 mg of *paroxetine impurity A CRS* in *water R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *trimethylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 3.85 g of *ammonium acetate R* in *water for chromatography R*, adjust to pH 5.5 with *anhydrous acetic acid R* and dilute to 600 mL with *water for chromatography R*; add 400 mL of *acetonitrile R*; slowly add, with stirring, 10 mL of *triethylamine R* and adjust to pH 5.5 with *anhydrous acetic acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 295 nm.

Injection 10 µL.

Run time Twice the retention time of paroxetine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to paroxetine (retention time = about 8 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and paroxetine.

Calculate the percentage content of $C_{19}H_{21}ClFNO_3$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *paroxetine hydrochloride hemihydrate CRS*.

STORAGE

In an airtight container, at a temperature not exceeding 25 °C.

IMPURITIES

Specified impurities *A, C, D, F, G, H, I, J.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, E.*

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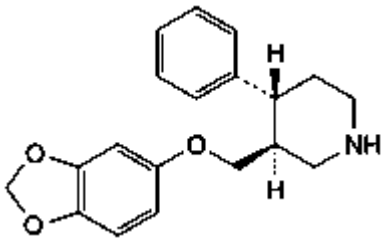
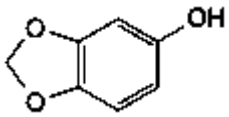
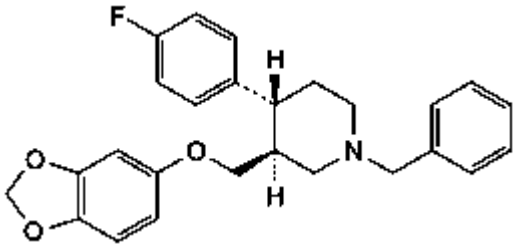


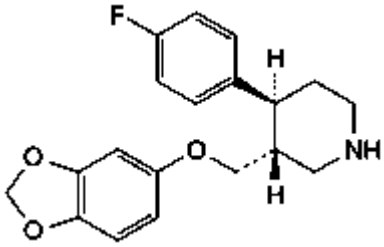
A. (3*S*,4*R*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-phenylpiperidine (defluoroparoxetine),



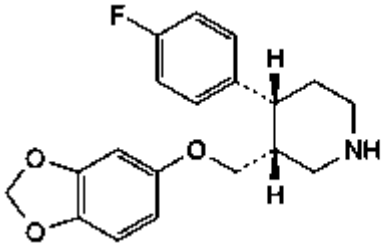
B. 1,3-benzodioxol-5-ol (sesamol),



C. (3*S*,4*R*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-1-benzyl-4-(4-fluorophenyl)piperidine (*N*-benzylparoxetine),



D. (3*R*,4*S*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-fluorophenyl)piperidine ((+)-*trans*-paroxetine),



E. (3*RS*,4*RS*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-fluorophenyl)piperidine (*cis*-paroxetine),

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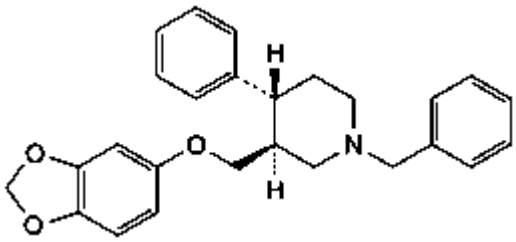
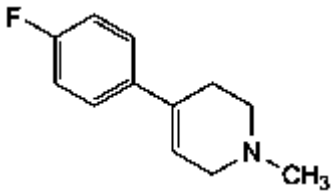
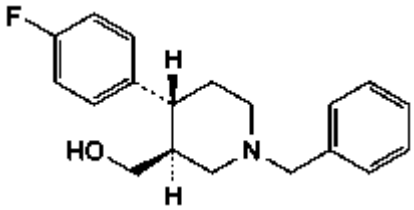


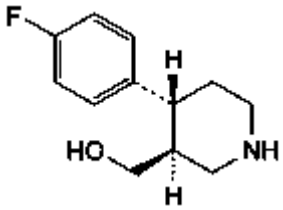
F. (3*S*,4*R*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-1-benzyl-4-phenylpiperidine (*N*-benzyldefluoroparoxetine),



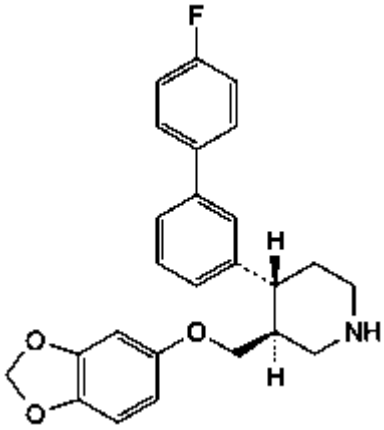
G. 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine,



H. [(3*S*,4*R*)-1-benzyl-4-(4-fluorophenyl)piperidin-3-yl]methanol,



I. [(3*S*,4*R*)-4-(4-fluorophenyl)piperidin-3-yl]methanol,



J. (3*S*,4*R*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4′-fluoro[1,1′-biphenyl]-3-yl)piperidine.

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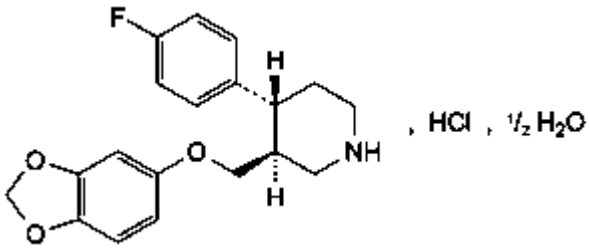
Paroxetine Hydrochloride Hemihydrate

General Notices

(Ph. Eur. monograph 2018)



$C_{19}H_{21}ClFNO_3,½H_2O$ 374.8 *110429-35-1*

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

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DEFINITION

(3*S*,4*R*)-3-[[(1,3-Benzodioxol-5-yl)oxy]methyl]-4-(4-fluorophenyl)piperidine hydrochloride hemihydrate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

Impurity G

Maximum 1 ppm, determined by a suitable, validated method.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent) and in methylene chloride.

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It shows pseudopolymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *paroxetine hydrochloride hemihydrate CRS*.

If the spectra obtained show differences, dissolve 1 part of the substance to be examined and 1 part of the reference substance separately in 10 parts of a mixture of 1 volume of *water R* and 9 volumes of *2-propanol R* and heat to 70 °C to dissolve. Recrystallise and record new spectra using the residues.

B. Enantiomeric purity (see Tests).

C. Water (see Tests).

D. Dissolve 21 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in 20 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *paroxetine impurity D CRS* and 5 mg of *paroxetine hydrochloride hemihydrate CRS* in 2 mL of *methanol R* and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *α_1-acid-glycoprotein silica gel for chiral separation R* (5 µm).

Mobile phase Mix 2 volumes of *methanol R* and 8 volumes of a 5.8 g/L solution of *sodium chloride R*.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 295 nm.

Injection 10 µL.

Run time 2.5 times the retention time of paroxetine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to paroxetine (retention time = about 30 min): impurity D = about 0.4.

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System suitability Reference solution (b):

— *resolution*: minimum 2.2 between the peaks due to impurity D and paroxetine.

Limit:

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture tetrahydrofuran R, water R (10:90 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 5.0 mL of the test solution to 50.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 200.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of paroxetine for system suitability CRS (containing impurity C) in 1 mL of the solvent mixture.

Reference solution (c) Dissolve 2 mg of paroxetine impurity A CRS in the solvent mixture and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: trifluoroacetic acid R, tetrahydrofuran R, water for chromatography R (0.5:10:90 *V/V/V*);

— *mobile phase B*: trifluoroacetic acid R, tetrahydrofuran R, acetonitrile R (0.5:10:90 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	80	20
30 - 50	80 → 20	20 → 80
50 - 60	20	80

Flow rate 1 mL/min.

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Detection Spectrophotometer at 295 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram supplied with *paroxetine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to paroxetine (retention time = about 28 min): impurity A = about 0.8; impurity C = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to paroxetine and impurity C.

Limits:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

2.2 per cent to 2.7 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *paroxetine hydrochloride hemihydrate CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *paroxetine hydrochloride hemihydrate CRS* and 5 mg of *paroxetine impurity A CRS* in *water R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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— *stationary phase*: *trimethylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 3.85 g of *ammonium acetate R* in *water for chromatography R*, adjust to pH 5.5 with *anhydrous acetic acid R* and dilute to 600 mL with *water for chromatography R*; add 400 mL of *acetonitrile R*; slowly add, with stirring, 10 mL of *triethylamine R* and readjust to pH 5.5 with *anhydrous acetic acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 295 nm.

Injection 10 µL.

Run time Twice the retention time of paroxetine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to paroxetine (retention time = about 8 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and paroxetine.

Calculate the percentage content of $C_{19}H_{21}ClFNO_3$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *paroxetine hydrochloride hemihydrate CRS*.

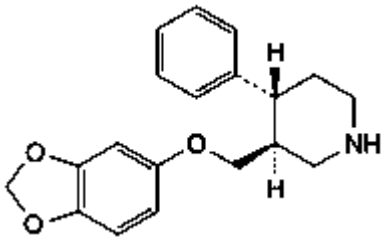
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, D, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, E, F.*



A. (3*S*,4*R*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-phenylpiperidine (defluoroparoxetine),

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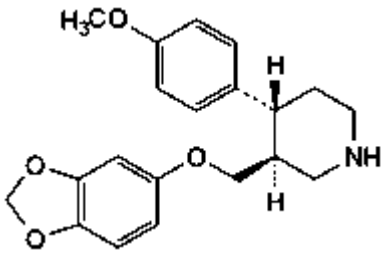
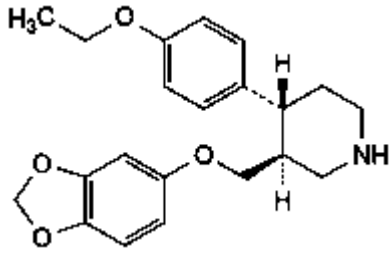
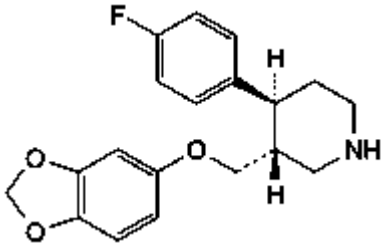


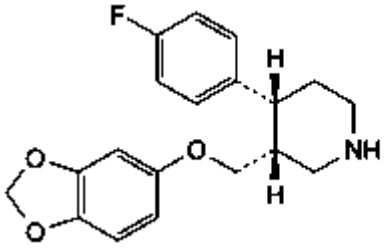
B. (3*S*,4*R*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-methoxyphenyl)piperidine,



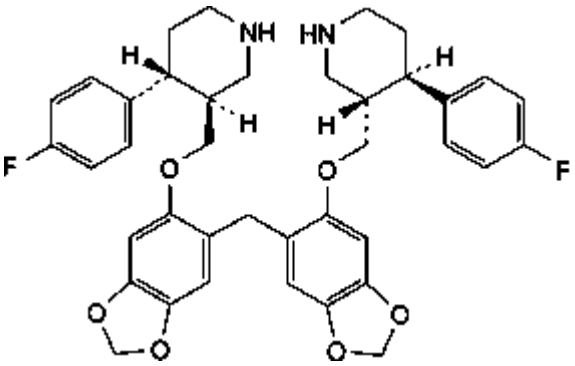
C. (3*S*,4*R*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-ethoxyphenyl)piperidine,



D. (3*R*,4*S*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-fluorophenyl)piperidine ((+)-*trans*-paroxetine),



E. (3*RS*,4*RS*)-3-[[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-fluorophenyl)piperidine (*cis*-paroxetine),



F. 3,3′-[methylenebis(1,3-benzodioxole-6,5-diyloxymethylene)]bis[(3*S*,4*R*)-4-(4-fluorophenyl)piperidine],

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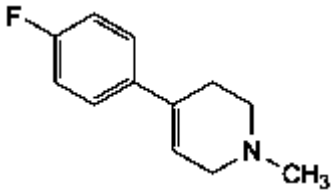

G. 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine.

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Paroxetine Tablets

General Notices

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

DEFINITION

Paroxetine Tablets contain Paroxetine Hydrochloride Hemihydrate or Paroxetine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

The manufacturing process of Paroxetine Hydrochloride, used in the formulation of Paroxetine Tablets, is validated to show that the content of 4-(4′-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine is not more than 1 ppm.

Content of anhydrous paroxetine hydrochloride, $C_{19}H_{20}FNO_3,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Dissolution test exhibits a maximum at 294 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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(1) After 45 minutes withdraw a sample of the medium and filter through a plastic filter with a GF/A filter (Millipore Swinnex is suitable). Measure the a*bsorbance* of the filtrate, suitably diluted with the dissolution medium if necessary, at the maximum at 294 nm, Appendix II B, using the dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *paroxetine hydrochloride hemihydrate BPCRS* in 0.1M *hydrochloric acid* at the maximum at 294 nm using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of paroxetine hydrochloride, $C_{19}H_{20}FNO_3$,HCl, in the medium from the absorbances obtained and from the declared content of $C_{19}H_{20}FNO_3$,HCl in *paroxetine hydrochloride hemihydrate BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 50 mg of anhydrous paroxetine hydrochloride with 10 mL of *methanol* for 30 minutes. Filter through a 0.45-µm membrane filter (Gelman acrodisc GHP is suitable), dilute 1 volume of the solution with 1 volume of mobile phase B.

(2) Dilute 1 volume of solution (1) to 50 volumes with mobile phase A and further dilute 1 volume of the resulting solution to 10 volumes with mobile phase A.

(3) 0.25% w/v of *paroxetine impurity standard BPCRS* in mobile phase A.

(4) 0.00075% w/v of *paroxetine impurity A EPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Equal volumes of *acetonitrile* and phosphate buffer pH 6.0 prepared by dissolving 4.9 g of *orthophosphoric acid* in about 800 mL of *water*, adjusting the pH to 6.0 with 1M *sodium hydroxide* and diluting to 1000 mL with *water*.

Mobile phase B Phosphate buffer pH 6.0 prepared by dissolving 4.9 g of *orthophosphoric acid* in about 800 mL, adjusting the pH to 6.0 with 1M *sodium hydroxide* and diluting to 1000 mL with *water*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	25→75	75→25	linear gradient
20-30	75	25	isocratic
30-35	75→25	25→75	linear gradient
35-45	25	75	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *paroxetine impurity standard BPCRS*.

LIMITS

Identify any peak due to impurity I in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity I is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

Disregard any peak with with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse with the aid of ultrasound a quantity of powdered tablets containing the equivalent of 25 mg of anhydrous paroxetine hydrochloride in 70 mL of *water* and 5 mL of 0.05M *hydrochloric acid*. Mix with the aid of ultrasound until all the granular material has dispersed. Add 150 mL of *propan-2-ol*, shake thoroughly and mix with the aid of ultrasound with occasional swirling for 15 minutes. Cool, add sufficient *propan-2-ol* to produce 250 mL, filter through a glass microfibre filter (Whatman GF/F is suitable) and use the filtrate.
(2) 0.01% w/v of *paroxetine hydrochloride hemihydrate BPCRS* in a solution containing 1 volume of 0.01M *hydrochloric acid*, 14 volumes of *water* and 35 volumes of *propan-2-ol*.

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(3) 0.25% w/v of *paroxetine impurity standard BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Equal volumes of *acetonitrile* and phosphate buffer pH 6.0 prepared by dissolving 4.9 g of *orthophosphoric acid* in about 800 mL of *water*, adjusting the pH to 6.0 with 1M *sodium hydroxide* and diluting to 1000 mL with *water*.

SYSTEM SUITABILITY

The test is not valid unless, the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *paroxetine impurity standard BPCRS*.

DETERMINATION OF CONTENT

Calculate the content of paroxetine hydrochloride, $C_{19}H_{20}FNO_3$,HCl, in the tablets using the declared content of $C_{19}H_{20}FNO_3$,HCl in *paroxetine hydrochloride hemihydrate BPCRS*.

LABELLING

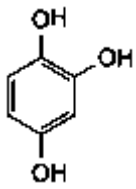
When the active ingredient is Paroxetine Hydrochloride Hemihydrate, the quantity is stated in terms of the equivalent amount of anhydrous paroxetine hydrochloride.

STORAGE

Paroxetine Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Paroxetine Hydrochloride and Paroxetine Hydrochloride Hemihydrate, impurities B and I listed under Paroxetine Hydrochloride and the following:



1. 1,2,4-trihydroxybenzene.

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Partially Dehydrated Liquid Sorbitol

General Notices

(Sorbitol, Liquid, Partially Dehydrated, Ph. Eur. monograph 2048)

Action and use

Excipient.

Ph Eur

DEFINITION

Partially dehydrated liquid sorbitol is obtained by acid-catalysed partial internal dehydration of liquid sorbitol. It contains not less than 68.0 per cent *m/m* and not more than 85.0 per cent *m/m* of anhydrous substances, composed of a mixture of mainly D-sorbitol and 1,4-sorbitan, with mannitol, hydrogenated oligo- and disaccharides, and sorbitans.

Content

(nominal value):

— 1,4-sorbitan ($C_6H_{12}O_5$): minimum 15.0 per cent (anhydrous substance);

— D-sorbitol ($C_6H_{14}O_6$): minimum 25.0 per cent (anhydrous substance).

The contents of 1,4-sorbitan and D-sorbitol are within 95.0 per cent to 105.0 per cent of the nominal values.

CHARACTERS

Appearance

Clear, colourless, syrupy liquid.

Solubility

Miscible with water, practically insoluble in mineral oils and vegetable oils.

IDENTIFICATION

Examine the chromatograms obtained in the assay.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time and size to the peaks in the chromatogram obtained with reference solution (a).

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TESTS

Solution S

Dilute the substance to be examined with *carbon dioxide-free water R* prepared from *distilled water R* to obtain a solution containing 50.0 per cent *m/m* of anhydrous substance.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Conductivity (*2.2.38*)

Maximum 20 $\mu S \cdot cm^{-1}$.

Measure the conductivity of solution S, while gently stirring with a magnetic stirrer.

Reducing sugars

Maximum 0.3 per cent, calculated as glucose (anhydrous substance).

To an amount of the substance to be examined equivalent to 3.3 g of anhydrous substance, add 3 mL of *water R*, 20.0 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min. Maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 mL of *hydrochloric acid R* and 94 mL of *water R*. When the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 2 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Water (*2.5.12*)

15.0 per cent to 32.0 per cent, determined on 0.100 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.400 g of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

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Reference solution (a) Dissolve 50.0 mg of *sorbitol CRS* and 20.0 mg of *1,4-sorbitan CRS* in *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 0.100 g of *mannitol R* and 0.100 g of *sorbitol R* in *water R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 80 ± 5 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 30-35 °C).

Injection 40 µL.

Relative retention With reference to D-sorbitol (retention time = about 25 min): 1,4-sorbitan = about 0.5; mannitol = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to mannitol and D-sorbitol.

Calculate the percentage contents of 1,4-sorbitan ($C_6H_{12}O_5$) and D-sorbitol ($C_6H_{14}O_6$) taking into account the assigned contents of *1,4-sorbitan CRS* and *sorbitol CRS*.

LABELLING

The label states the content of D-sorbitol and the content of 1,4-sorbitan (= nominal values).

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Partially Hydrated Magnesium Chloride

General Notices

(Magnesium Chloride 4.5-Hydrate, Ph. Eur. monograph 1341)

$MgCl_2,xH_2O$ with $x \approx 4.5$ 95.21 (anhydrous substance)

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DEFINITION

Content

52.5 per cent to 55.5 per cent (calculated on an as-is basis, without allowing for the results of the test for water).

CHARACTERS

Appearance

White or almost white, hygroscopic, granular powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Water (see Tests).

B. It gives reaction (a) of chlorides (*2.3.1*).

C. It gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

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To 5 mL of solution S add 0.05 mL of *phenol red solution R*. Not more than 0.3 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromides

Maximum 500 ppm.

Dilute 2.0 mL of solution S to 10.0 mL with *water R*. To 1.0 mL of the solution add 4.0 mL of *water R*, 2.0 mL of *phenol red solution R3* and 1.0 mL of *chloramine solution R2* and mix immediately. After exactly 2 min, add 0.30 mL of *0.1 M sodium thiosulfate*, mix and dilute to 10.0 mL with *water R*. The absorbance (*2.2.25*) of the solution measured at 590 nm, using *water R* as the compensation liquid, is not greater than that of a standard prepared at the same time and in the same manner using 5.0 mL of a 3 mg/L solution of *potassium bromide R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Aluminium (*2.4.17*)

Maximum 1 ppm, if intended for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions, or haemofiltration solutions.

Prescribed solution Dissolve 4 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Calcium (*2.4.3*)

Maximum 0.1 per cent.

Dilute 1 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Potassium

Maximum 500 ppm, if intended for use in the manufacture of parenteral preparations.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

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Reference solutions Prepare the reference solutions using the following solution, diluted as necessary with *water R*: dissolve 1.144 g of *potassium chloride R*, previously dried at 100-105 °C for 3 h, in *water R* and dilute to 1000.0 mL with the same solvent (600 µg of K per millilitre).

Wavelength 766.5 nm.

Water (*2.5.12*)

44.0 per cent to 48.0 per cent, determined on 50.0 mg.

ASSAY

Dissolve 0.250 g in 50 mL of *water R*. Carry out the complexometric titration of magnesium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 9.521 mg of $MgCl_2$.

STORAGE

In an airtight container.

LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions or haemofiltration solutions;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Pea Starch

General Notices

(Ph. Eur. monograph 2403)

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DEFINITION

Pea starch is obtained from the seeds of *Pisum sativum* L.

CHARACTERS

Appearance

White or almost white, very fine powder.

Solubility

Practically insoluble in cold water and in ethanol (96 per cent).

IDENTIFICATION

A. Microscopic examination (*2.8.23*) using a 50 per cent *V/V* solution of *glycerol R*. It presents a majority of large elliptical granules, 25-45 µm in size, sometimes irregular, or reniform. It also presents a minority of small rounded granules, 5-8 µm in size (Figure 2403.-1). Granules can present cracks or irregularities. Sometimes, granules show barely visible concentric striations. Exceptionally, granules show a slit along the main axis. Between orthogonally oriented polarising plates or prisms, the granules show a distinct black cross.

B. Suspend 1 g in 50 mL of *water R*, boil for 1 min and cool. A thin, cloudy mucilage is formed.

C. To 1 mL of the mucilage obtained in identification test B, add 0.05 mL of *iodine solution R1*. A dark blue colour is produced, which disappears on heating.

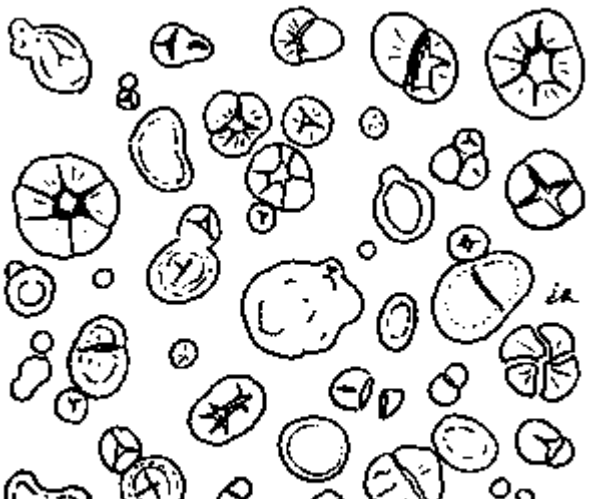

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Figure 2403.-1. - *Illustration for identification test A of pea starch*

TESTS

pH (*2.2.3*)

5.0 to 8.0.

Shake 5.0 g with 25.0 mL of *carbon dioxide-free water R* for 60 s. Allow to stand for 15 min and shake again.

Foreign matter

Examined under a microscope using a 50 per cent *V/V* solution of *glycerol R*, not more than traces of matter other than starch granules are present. No starch granules of any other origin are present.

Oxidising substances (*2.5.30*)

Maximum 20 ppm, calculated as H_2O_2.

Sulfur dioxide (*2.5.29*)

Maximum 50 ppm.

Iron (*2.4.9*)

Maximum 50 ppm.

Shake 1.0 g with 50 mL of *dilute hydrochloric acid R*. Filter. The filtrate complies with the test for iron.

Loss on drying (*2.2.32*)

Maximum 16.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 90 min.

Sulfated ash (*2.4.14*)

Maximum 0.6 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

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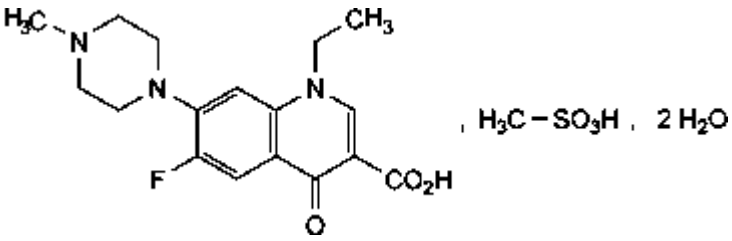
Pefloxacin Mesilate

General Notices

(Perfloxacin Mesilate Dihydrate, Ph. Eur. monograph 1460)



$C_{18}H_{24}FN_3O_6S,2H_2O$ 465.5 *149676-40-4*

Action and use

Antibacterial.

Ph Eur

DEFINITION

1-Ethyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methanesulfonate dihydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in pefloxacin mesilate dihydrate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

Fine, white or almost white powder.

Solubility

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Freely soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 0.1 g in 10 mL of water R. Add 5 mL of 1 M sodium hydroxide. Adjust to pH 7.4 ± 0.1 with phosphoric acid R and shake with 2 quantities, each of 30 mL, of methylene chloride R. Combine the organic layers and dry over anhydrous sodium sulfate R. Evaporate to dryness. Examine the residue as a disc of potassium bromide R.

Comparison Repeat the operations using 0.1 g of pefloxacin mesilate dihydrate CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 40 mg in water R and dilute to 1 mL with the same solvent.

Reference solution Dissolve 60 mg of methanesulfonic acid R in water R and dilute to 10 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase water R, ammonia R, butanol R, acetone R (5:10:20:65 *V/V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with a 0.4 g/L solution of bromocresol purple R in ethanol (50 per cent V/V) R, adjusted to pH 10 using 1 M sodium hydroxide.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 1.0 g in carbon dioxide-free water R and dilute to 10.0 mL with the same solvent.

Appearance of solution

Examined within 1 h after its preparation, solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than intensity 3 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

pH (2.2.3)

3.5 to 4.5.

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Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *pefloxacin impurity B CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. In 2.0 mL of this solution, dissolve the contents of a vial of *pefloxacin impurity C CRS*.

Reference solution (b) Dissolve 10.0 mg of *norfloxacin impurity A CRS* (impurity F) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 6 mm;

— *stationary phase*: *octadecylsilyl vinyl polymer for chromatography R* (5 µm).

Mobile phase Mix 30 volumes of *acetonitrile R*, 70 volumes of a solution containing 2.70 g/L of *cetyltrimethylammonium bromide R* and 6.18 g/L of *boric acid R* (exactly adjusted to pH 8.30 with *1 M sodium hydroxide*), and 0.2 volumes of thiodiethylene glycol R.

Flow rate 1 mL/min.

Detection Spectrophotometer at 258 nm and at 273 nm.

Injection 20 µL.

Run time 4 times the retention time of pefloxacin (about 60 min).

Relative retentions and correction factors:

	Approximate relative retention	Correction factor
Impurity E	0.2	–
Impurity D	0.3	–
Impurity A	0.5	–
Impurity G	0.8	1.4
Pefloxacin	1	–
Impurity C	1.7	2.4
Impurity B	1.8	–
Impurity H	2.4	1.8

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	Approximate relative retention	Correction factor
Impurity F	3.5	–

System suitability Reference solution (a) at 273 nm:

— *resolution*: minimum 1.5 between the peaks due to impurities C and B.

From the chromatogram obtained at 258 nm with the test solution, calculate the percentage content of impurities C, F, G and H using the area of the principal peak in the chromatogram obtained at 258 nm with reference solution (b) (external standardisation) taking into account the correction factors indicated in the table.

From the chromatogram obtained at 273 nm with the test solution, calculate the percentage content of impurities A, B, D and E and of any other impurity from the areas of the peaks in the chromatogram obtained with the test solution by the normalisation procedure.

Limits:

— *impurities A, B, D, E and any other impurity at 273 nm and impurities C, F, G, H at 258 nm*: for each impurity, maximum 0.5 per cent and not more than 3 impurities have a content between 0.2 per cent and 0.5 per cent;

— *total*: maximum 1.0 per cent;

— *disregard limit at 273 nm*: 0.0005 times the area of the principal peak in the chromatogram obtained with the test solution (0.05 per cent).

Water (*2.5.12*)

7.0 per cent to 8.5 per cent, determined on 50.0 mg using a mixture of 10 volumes of *methanol R* and 50 volumes of *methylene chloride R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 15.0 mL of *anhydrous acetic acid R* and add 75.0 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 21.48 mg of $C_{18}H_{24}FN_3O_6S$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H.*

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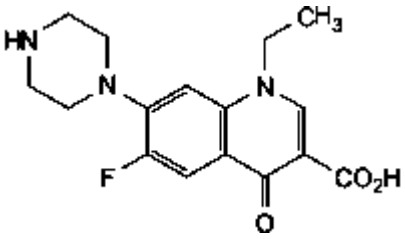
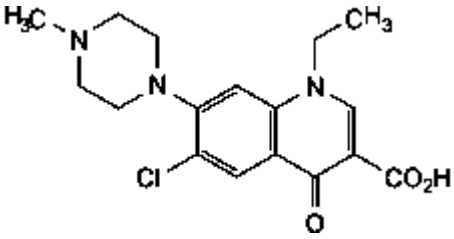
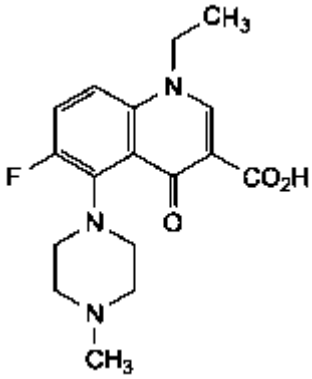


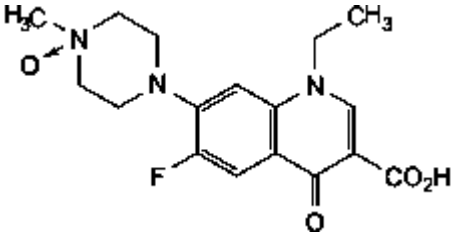
A. 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (demethylated pefloxacin or norfloxacin),



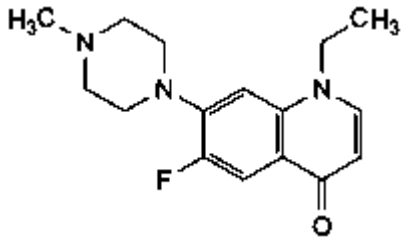
B. 6-chloro-1-ethyl-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (chlorinated homologue of pefloxacin),



C. 1-ethyl-6-fluoro-5-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (isopefloxacin),



D. 4-(3-carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinolin-7-yl)-1-methylpiperazine 1-oxide (*N*-oxide of pefloxacin),



E. 1-ethyl-6-fluoro-7-(4-methylpiperazin-1-yl)quinoline-4(1*H*)-one (decarboxylated pefloxacin),

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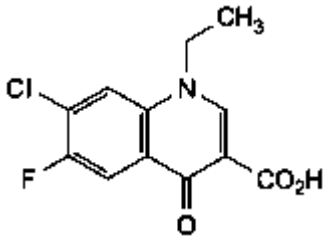
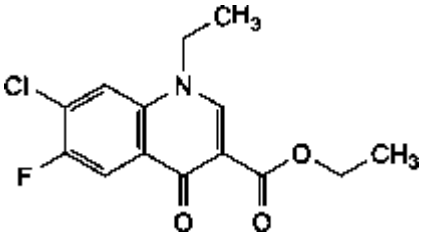
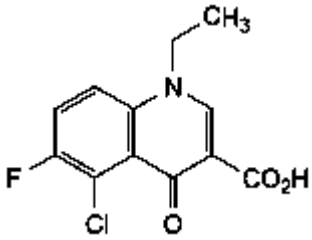


F. 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (*N*-ethyl acid) (norfloxacin impurity A),



G. ethyl 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (*N*-ethyl ester),



H. 5-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (iso-*N*-ethyl acid).

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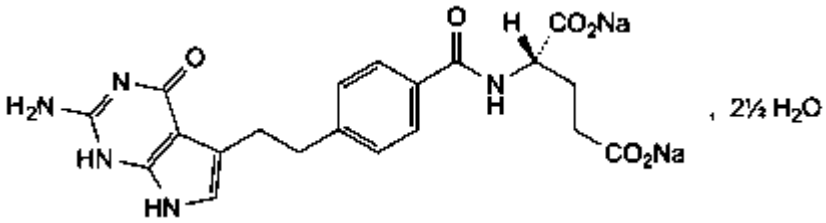
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Pemetrexed Disodium 2.5-Hydrate

General Notices

(Ph. Eur. monograph 3046)



$C_{20}H_{19}N_5Na_2O_6,2½H_2O$ 516.4 *357166-30-4*

Action and use

Thymidylate synthetase inhibitor; antineoplastic

Ph Eur

DEFINITION

Disodium (2*S*)-2-[4-[2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]pentanedioate 2.5-hydrate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

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Comparison *pemetrexed disodium 2.5-hydrate CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

C. Enantiomeric purity (see Tests).

D. Water (see Tests).

TESTS

Solution S

Dissolve 0.48 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution GY_4 or Y_4 (*2.2.2, Method II*).

pH (*2.2.3*)

7.5 to 8.4 for solution S.

Enantiomeric purity

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or store them at 2-8 °C and use them within 24 h*.

Solution A Dissolve 8 g of *β-cyclodextrin R* in 900 mL of *water for chromatography R*. Add 15 mL of *triethylamine R* then 6 mL of *phosphoric acid R* and adjust to pH 6.0 with *phosphoric acid R*. Dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 12.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 6 mg of *pemetrexed for system suitability CRS* (containing impurity E) in *water R* and dilute to 25 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 3.0 mL of this solution to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile for chromatography R*, solution A (5:95 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

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Injection 50 µL.

Run time 1.5 times the retention time of pemetrexed.

Relative retention With reference to pemetrexed (retention time = about 30 min): impurity E = about 0.94.

System suitability:

— *symmetry factor*: maximum 2.0 for the principal peak in the chromatogram obtained with reference solution (b);

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to pemetrexed in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— for impurity E, use the concentration of pemetrexed disodium 2.5-hydrate in reference solution (b).

Limit:

— *impurity E*: maximum 0.3 per cent.

Column rinse: the following programme is given for information only.

Use a gradient column rinse before column storage or after 30 sample injections to avoid build-up on the column. If a drifting baseline is observed, allow additional time for equilibration with the mobile phase. If a blank chromatogram exhibits broad humps, perform a gradient column rinse.

Rinsing solution A *water for chromatography R*.

Rinsing solution B *acetonitrile for chromatography R*.

Time (min)	Mobile phase (per cent *V/V*)	Rinsing solution A (per cent *V/V*)	Rinsing solution B (per cent *V/V*)
0 - 4	100 → 0	0 → 50	0 → 50
4 - 9	0	50	50
9 - 14	0	50 → 10	50 → 90
14 - 54	0	10	90
54 - 69	0	10 → 95	90 → 5
69 - 100	0	95	5

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C and use them within 24 h*.

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Solution A 1.45 g/L solution of *ammonium formate R* in *water for chromatography R*, adjusted to pH 3.5 with *formic acid R*.

Test solution Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) In order to prepare impurities B and C *in situ*, dissolve 30 mg of the substance to be examined in 10 mL of a 4.0 g/L solution of *sodium hydroxide R*, heat at 70 °C for 40 min and allow to cool. Dilute 1 mL of the solution to 10 mL with *water R*.

Reference solution (c) Dissolve the contents of a vial of *pemetrexed impurity mixture CRS* (impurities A and D) in 1 mL of *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, solution A (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R*, solution A (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 45	100 → 0	0 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *pemetrexed impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and D; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to pemetrexed (retention time = about 26 min): impurity A = about 0.82; impurity B = about 0.87; impurity C = about 0.88; impurity D = about 0.90.

System suitability:

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C in the chromatogram obtained with reference solution (b);

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— *signal-to-noise ratio*: minimum 30 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.5;

— for each impurity, use the concentration of pemetrexed disodium 2.5-hydrate in reference solution (a).

Limits:

— *impurities A, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

8.0 per cent to 11.0 per cent, determined on 0.050 g.

ASSAY

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or store them at 2-8 °C and use them within 24 h*.

Acetate buffer Mix 1.7 mL of *glacial acetic acid R* and 900 mL of *water for chromatography R*, adjust to pH 5.3 with a 760 g/L solution of *sodium hydroxide R* in *water for chromatography R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 25.9 mg of the substance to be examined in *water R* and dilute to 200.0 mL with the same solvent.

Reference solution Dissolve 30.0 mg of *pemetrexed disodium heptahydrate CRS* in *water R* and dilute to 200.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, acetate buffer (11:89 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 285 nm.

Injection 20 µL.

Run time Twice the retention time of pemetrexed (retention time = about 3 min).

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Calculate the percentage content of $C_{20}H_{19}N_5Na_2O_6$ taking into account the assigned content of *pemetrexed disodium heptahydrate CRS*.

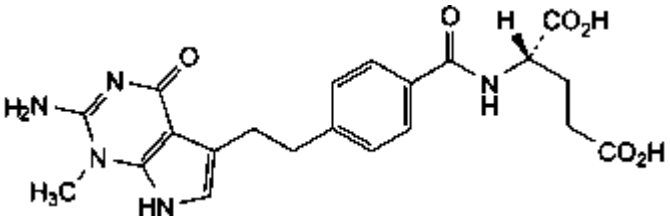
STORAGE

In an airtight container at a temperature of 2 °C to 8 °C.

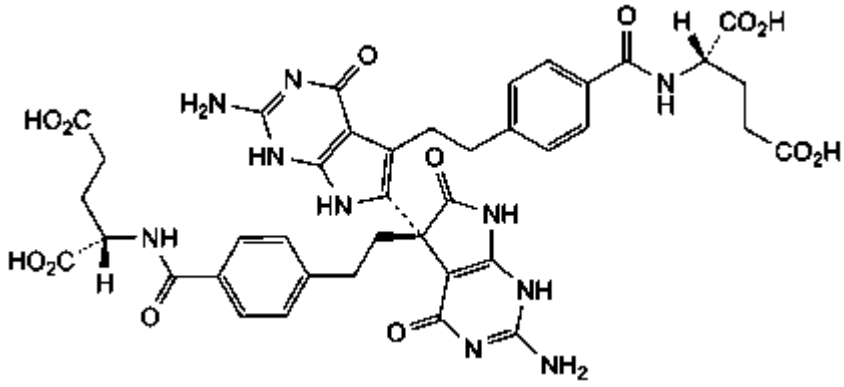
IMPURITIES

Specified impurities *A, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C.*



A. (2*S*)-2-[4-[2-(2-amino-1-methyl-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]pentanedioic acid,



B. (2*S*,2′*S*)-2,2′-[(4^5*R*)-4^2,5^2-diamino-4^4,4^6,5^4-trioxo-4^1,4^4,4^6,4^7,5^4,5^7-hexahydro-5^1*H*-4(5,5),5(6,5)-bis(pyrrolo[2,3-*d*]pyrimidina)-1,8(1)-dibenzenaoctaphane-1^4,8^4-dicarboxamido]dipentanedioic acid,

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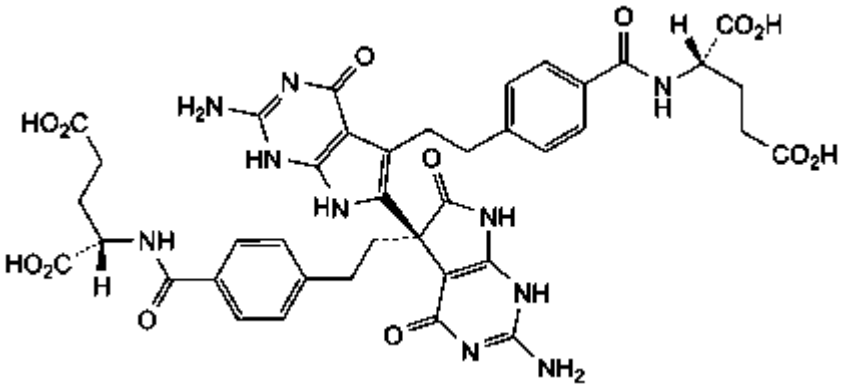
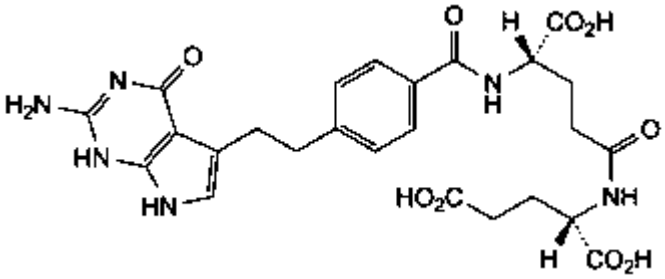
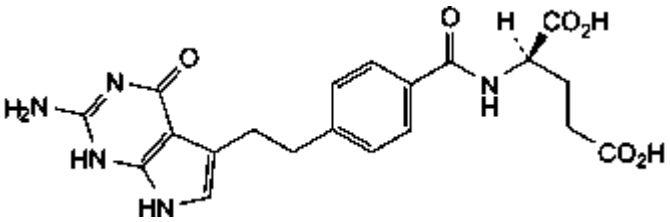


C. (2*S*,2′*S*)-2,2′-[(4^{5}*S*)-4^{2},5^{2}-diamino-4^{4},4^{6},5^{4}-trioxo-4^{1},4^{4},4^{6},4^{7},5^{4},5^{7}-hexahydro-5^{1}*H*-4(5,5),5(6,5)-bis(pyrrolo[2,3-*d*]pyrimidina)-1,8(1)-dibenzenaoctaphane-1^{4},8^{4}-dicarboxamido]dipentanedioic acid,



D. (2*S*)-2-[(4*S*)-4-[4-[2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]-4-carboxybutanamido]pentanedioic acid,



E. (2*R*)-2-[4-[2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]pentanedioic acid.

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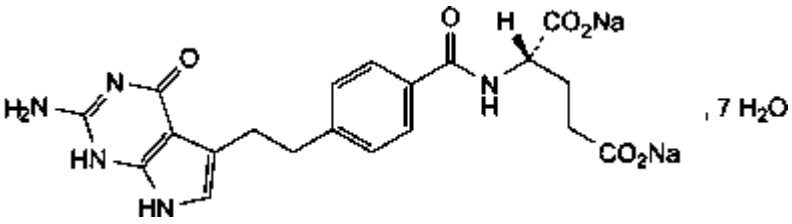
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Pemetrexed Disodium Heptahydrate

General Notices

(Ph. Eur. monograph 2637)



$C_{20}H_{19}N_5Na_2O_6,7H_2O$ 597.5 *357166-29-1*

Action and use

Thymidylate synthetase inhibitor; cytostatic.

Ph Eur

DEFINITION

Disodium (2*S*)-2-[4-[2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]pentanedioate heptahydrate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

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Comparison *pemetrexed disodium heptahydrate CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

C. Enantiomeric purity (see Tests).

D. Water (see Tests).

TESTS

Solution S

Dissolve 0.56 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution GY_4 or Y_4 (*2.2.2, Method II*).

pH (*2.2.3*)

7.5 to 8.4 for solution S.

Enantiomeric purity

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or store them at 2-8 °C for not more than 24 h*.

Solution A Dissolve 8 g of *β-cyclodextrin R* in 900 mL of *water for chromatography R*. Add 15 mL of *triethylamine R* then 6 mL of *phosphoric acid R* and adjust to pH 6.0 with *phosphoric acid R*. Dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 12.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 6 mg of *pemetrexed for system suitability CRS* (containing impurity E) in *water R* and dilute to 25 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 3.0 mL of this solution to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile for chromatography R*, solution A (5:95 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

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Injection 50 µL.

Run time 1.5 times the retention time of pemetrexed.

Relative retention With reference to pemetrexed (retention time = about 30 min): impurity E = about 0.94.

System suitability:

— *symmetry factor*: maximum 2.0 for the principal peak in the chromatogram obtained with reference solution (b);

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to pemetrexed in the chromatogram obtained with reference solution (a).

Calculation of percentage content:

— for impurity E, use the concentration of pemetrexed disodium heptahydrate in reference solution (b).

Limit:

— *impurity E*: maximum 0.3 per cent.

Column rinse: the following program is given for information only.

Use a gradient column rinse before column storage or after 30 sample injections to avoid build-up on the column. If a drifting baseline is observed, allow additional time for equilibration with the mobile phase. If a blank chromatogram exhibits broad humps, perform a gradient column rinse.

Rinsing solution A *water for chromatography R*.

Rinsing solution B *acetonitrile for chromatography R*.

Time (min)	Mobile phase (per cent *V/V*)	Rinsing solution A (per cent *V/V*)	Rinsing solution B (per cent *V/V*)
0 - 4	100 → 0	0 → 50	0 → 50
4 - 9	0	50	50
9 - 14	0	50 → 10	50 → 90
14 - 54	0	10	90
54 - 69	0	10 → 95	90 → 5
69 - 100	0	95	5

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C for not more than 24 h*.

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Solution A 1.45 g/L solution of *ammonium formate R* in *water for chromatography R*, adjusted to pH 3.5 with *formic acid R*.

Test solution Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with, *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) In order to prepare impurities B and C *in situ*, dissolve 30 mg of the substance to be examined in 10 mL of a 4.0 g/L solution of *sodium hydroxide R*, heat at 70 °C for 40 min and allow to cool. Dilute 1 mL of the solution to 10 mL with *water R*.

Reference solution (c) Dissolve the contents of a vial of *pemetrexed impurity mixture CRS* (impurities A and D) in 1 mL of *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, solution A (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R*, solution A (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 45	100 → 0	0 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *pemetrexed impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and D; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to pemetrexed (retention time = about 26 min): impurity A = about 0.82; impurity B = about 0.87; impurity C = about 0.88; impurity D = about 0.90.

System suitability:

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C in the chromatogram obtained with reference solution (b);

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— *signal-to-noise ratio*: minimum 30 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.5;

— for each impurity, use the concentration of pemetrexed disodium heptahydrate in reference solution (a).

Limits:

— *impurities A, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

19.5 per cent to 22.1 per cent, determined on 0.050 g.

ASSAY

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C for not more than 24 h*.

Acetate buffer Mix 1.7 mL of *glacial acetic acid R* and 900 mL of *water for chromatography R*, adjust to pH 5.3 with a 760 g/L solution of *sodium hydroxide R* in *water for chromatography R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 30.0 mg of the substance to be examined in *water R* and dilute to 200.0 mL with the same solvent.

Reference solution Dissolve 30.0 mg of *pemetrexed disodium heptahydrate CRS* in *water R* and dilute to 200.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, acetate buffer (11:89 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 285 nm.

Injection 20 µL.

Run time Twice the retention time of pemetrexed (retention time = about 3 min).

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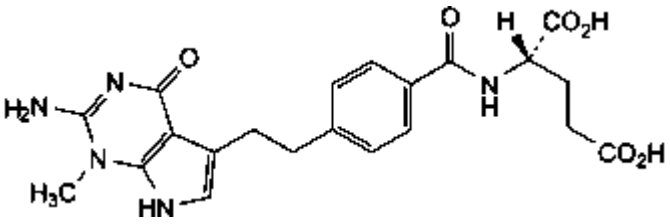
Calculate the percentage content of $C_{20}H_{19}N_5Na_2O_6$ taking into account the assigned content of *pemetrexed disodium heptahydrate CRS*.

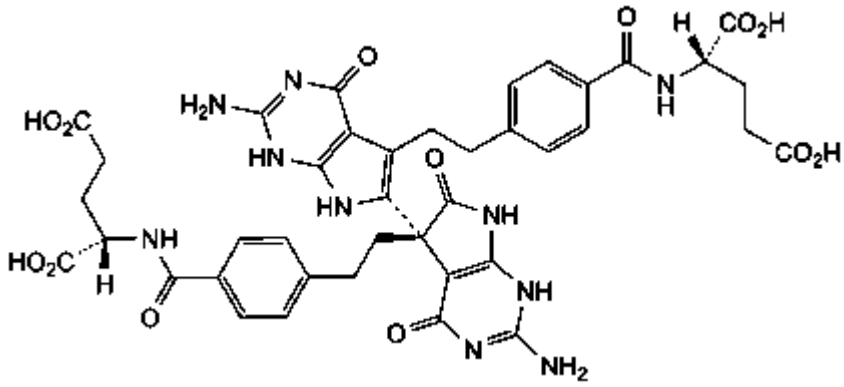
IMPURITIES

Specified impurities A, D, E.

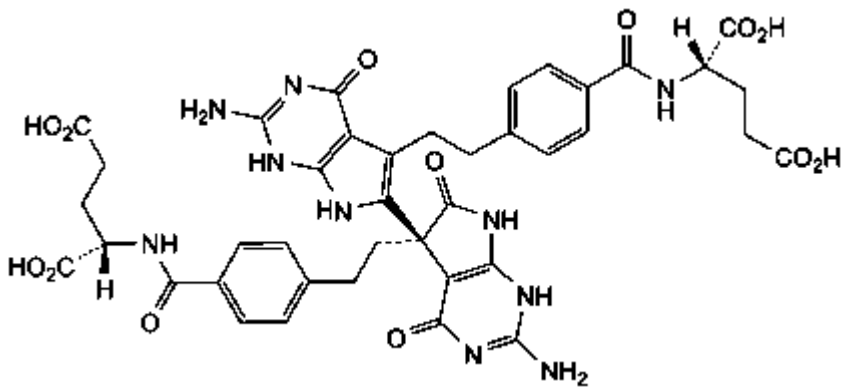
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. (2*S*)-2-[4-[2-(2-amino-1-methyl-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]pentanedioic acid,



B. (2*S*,2′*S*)-2,2′-[(4^5*R*)-4^2,5^2-diamino-4^4,4^6,5^4-trioxo-4^1,4^4,4^6,4^7,5^4,5^7-hexahydro-5^1*H*-4(5,5),5(6,5)-bis(pyrrolo[2,3-*d*]pyrimidina)-1,8(1)-dibenzenaoctaphane-1^4,8^4-dicarboxamido]dipentanedioic acid,



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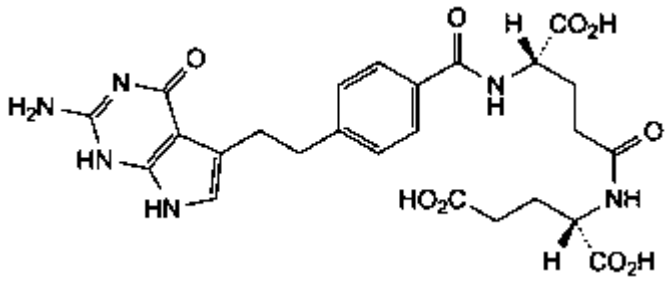
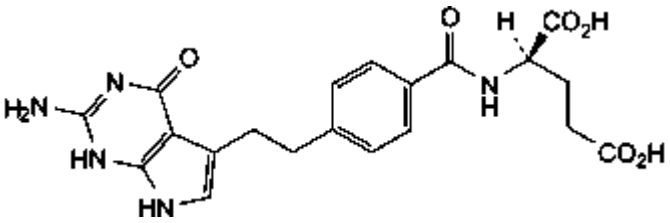
C. (2*S*,2′*S*)-2,2′-[(4^{5}*S*)-4^{2},5^{2}-diamino-4^{4},4^{6}, 5^{4}-trioxo-4^{1},4^{4},4^{6},4^{7},5^{4},5^{7}-hexahydro-5^{1}*H*-4(5,5),5(6,5)-bis(pyrrolo[2,3-*d*]pyrimidina)-1,8(1)-dibenzenaoctaphane-1^{4},8^{4}-dicarboxamido]dipentanedioic acid,



D. (2*S*)-2-[(4*S*)-4-[4-[2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]-4-carboxybutanamido]pentanedioic acid,



E. (2*R*)-2-[4-[2-(2-amino-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzamido]pentanedioic acid.

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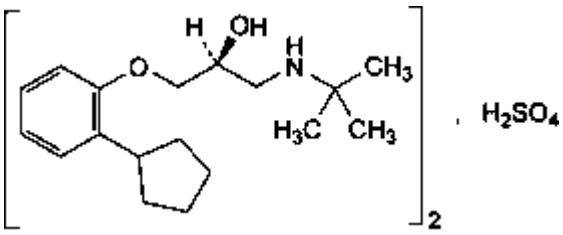
Penbutolol Sulfate

General Notices

Penbutolol Sulphate

(Ph. Eur. monograph 1461)



$C_{36}H_{60}N_2O_8S$ 681 *38363-32-5*

Action and use

Beta-adrenoceptor antagonist.

Ph Eur

DEFINITION

Di[(2*S*)-1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]propan-2-ol] sulfate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, soluble in methanol, practically insoluble in cyclohexane.

IDENTIFICATION

First identification: A, C, D.

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Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *penbutolol sulfate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 40 mg of the substance to be examined in 1 mL of *methanol R*.

Reference solution Dissolve 40 mg of *penbutolol sulfate CRS* in 1 mL of *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R*, *ethyl acetate R* (10:20:35:35 *V/V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 50 mg in a mixture of 5 mL of *water R* and 1 mL of *0.1 M hydrochloric acid*. The solution gives reaction (a) of sulfates (2.3.1).

D. Specific optical rotation (see Tests).

TESTS

Solution S

Dissolve 1.00 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Acidity or alkalinity

To 4 mL of solution S add 4 mL of *carbon dioxide-free water R*. Add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*; the solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*; the solution is red.

Specific optical rotation (2.2.7)

-23 to -25 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

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Solvent mixture Mobile phase B, mobile phase A (40:60 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 4.0 mg of the substance to be examined and 1.0 mg of *penbutolol impurity A CRS* in 5.0 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 200.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5.0 mg of *penbutolol impurity A CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, *methanol R* (39:61 *V/V*);

— *mobile phase B*: dissolve 11 g of *sodium heptanesulfonate R* in 1000 mL of *water R*, add 5.0 mL of *triethylamine R* and adjust to pH 2.7 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	60	40
15 - 35	60 → 80	40 → 20

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 10 µL.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the 2 principal peaks.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

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— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 40 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

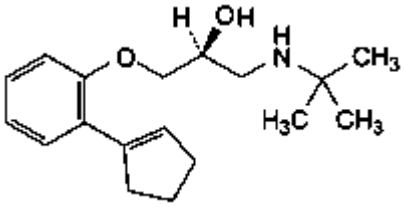
1 mL of *0.1 M perchloric acid* is equivalent to 68.10 mg of $C_{36}H_{60}N_2O_8S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities A.



A. (2*S*)-1-[2-(cyclopent-1-enyl)phenoxy]-3-[(1,1-dimethylethyl)amino]propan-2-ol.

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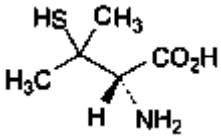
Penicillamine

General Notices

(Ph. Eur. monograph 0566)



$C_5H_{11}NO_2S$ 149.2 *52-67-5*

Action and use

Disease-modifying antirheumatic drug; chelating agent; treatment of Wilson's disease; heavy metal poisoning; cystinuria.

Preparation

Penicillamine Tablets

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-methyl-3-sulfanylbutanoic acid.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B, D.

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Second identification: A, C, D.

A. Dissolve 0.5 g in a mixture of 0.5 mL of *hydrochloric acid R* and 4 mL of warm *acetone R*, cool in iced water and initiate crystallisation by scratching the wall of the tube with a glass rod. A white precipitate is formed. Filter with the aid of vacuum, wash with *acetone R* and dry with suction. A 10 g/L solution of the precipitate is dextrorotatory.

B. Examine the chromatograms obtained in the test for impurity A.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in 4 mL of *water R*.

Reference solution Dissolve 10 mg of *penicillamine CRS* in 4 mL of *water R*.

Plate *TLC silica gel G plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (18:18:72 *V/V/V*).

Application 2 µL.

Development Over a path of 10 cm.

Drying At 100-105 °C for 5-10 min.

Detection Expose to iodine vapour for 5-10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 40 mg in 4 mL of *water R* and add 2 mL of *phosphotungstic acid solution R*. Allow to stand for 5 min. A blue colour develops.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 5.5.

Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*.

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Specific optical rotation (2.2.7)

-65.0 to -61.0 (dried substance).

Dissolve 0.500 g in a 40 g/L solution of *sodium hydroxide R* and dilute to 10.0 mL with the same solution.

Ultraviolet-absorbing substances

Maximum 0.5 per cent of penilloic acid.

Dissolve 0.100 g in *water R* and dilute to 50.0 mL with the same solvent. The absorbance (2.2.25) of the solution at 268 nm is not greater than 0.07.

Impurity A

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 40 mg of *penicillamine CRS* in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (b) Dissolve 20.0 mg of *penicillamine disulfide CRS* (impurity A) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 40 mg of the substance to be examined in reference solution (b) and dilute to 10 mL with the same solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Solution containing 0.1 g/L of *sodium edetate R* and 2 g/L of *methanesulfonic acid R*.

Flow rate 1.7 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time Twice the retention time of penicillamine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to penicillamine (retention time = about 6 min): impurity A = about 1.8.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to penicillamine and impurity A.

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Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (1 per cent).

Impurity B

Maximum 0.1 ppm.

Carry out all the operations in a penicillin-free atmosphere and with equipment reserved for this test. Sterilise the equipment at 180 °C for 3 h and the buffer solutions at 121 °C for 20 min before use.

Test solution (a) Dissolve 1.000 g in 8 mL of *buffer solution pH 2.5 R* and add 8 mL of *ether R*. Shake vigorously for 1 min. Repeat the extraction and combine the ether layers. Add 8 mL of *buffer solution pH 2.5 R*. Shake for 1 min, allow to settle and quantitatively separate the upper layer, taking care to eliminate the aqueous phase completely (*penicillin is unstable at pH 2.5; carry out operations at this pH within 6-7 min*). Add 8 mL of *phosphate buffer solution pH 6.0 R2* to the ether phase, shake for 5 min, allow to settle, then separate the aqueous layer and check that the pH is 6.0.

Test solution (b) To 2 mL of test solution (a) add 20 µL of *penicillinase solution R* and incubate at 37 °C for 1 h.

Reference solution (a) Dissolve 5 mg of *benzylpenicillin sodium R* in 500 mL of *phosphate buffer solution pH 6.0 R2*. Dilute 0.25 mL of the solution to 200.0 mL with *buffer solution pH 2.5 R*. Carry out the extraction using 8 mL of this solution as described for test solution (a).

Reference solution (b) To 2 mL of reference solution (a) add 20 µL of *penicillinase solution R* and incubate at 37 °C for 1 h.

Blank solution Prepare the solution as described for test solution (a) but omitting the substance to be examined.

Liquefy a suitable nutrient medium such as that described below and inoculate it at a suitable temperature with a culture of *Kocuria rhizophila* (ATCC 9341), to give 5×10^4 micro-organisms per millilitre or a different quantity if necessary to obtain the required sensitivity and formation of clearly defined inhibition zones of suitable diameter. Immediately pour the inoculated medium into 5 Petri dishes 10 cm in diameter to give uniform layers 2-5 mm deep. The medium may alternatively consist of 2 layers, only the upper layer being inoculated. Store the dishes so that no appreciable growth or death of the micro-organisms occurs before use and so that the surface of the agar is dry at the time of use. In each dish, place 5 stainless steel hollow cylinders 6 mm in diameter on the surface of the agar evenly spaced on a circle with a radius of about 25 mm and concentric with the dish. For each dish, place in separate cylinders 0.15 mL of test solutions (a) and (b), reference solutions (a) and (b) and the blank solution. Maintain at 30 °C for at least 24 h. Measure the diameters of the inhibition zones to the nearest 0.1 mm. The test is valid if reference solution (a) gives a clear inhibition zone and if reference solution (b) and the blank solution give no inhibition zone. If test solution (a) gives an inhibition zone, this is caused by penicillin if test solution (b) gives no inhibition zone. If this is so, the average diameter of the inhibition zones given by test solution (a) for the 5 Petri dishes is less than the average diameter of the inhibition zones given by reference solution (a) measured in the same conditions.

Nutrient medium (pH 6.0)

Peptone	5 g
Yeast extract	1.5 g
Meat extract	1.5 g

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Sodium chloride	3.5 g
Agar	15 g
Distilled water R	1000 mL

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

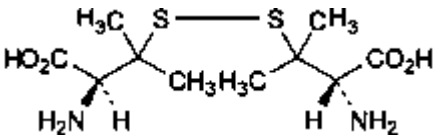
ASSAY

Dissolve 0.1000 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

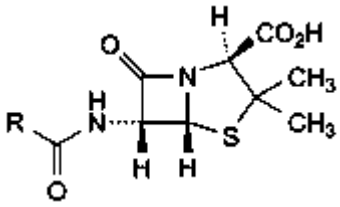
1 mL of *0.1 M perchloric acid* is equivalent to 14.92 mg of $C_5H_{11}NO_2S$.

IMPURITIES

Specified impurities *A, B.*



A. 3,3′-(disulfanediyl)bis[(2*S*)-2-amino-3-methylbutanoic] acid (penicillamine disulfide),



B. penicillin.

Ph Eur

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Penicillamine Tablets

General Notices

Action and use

Disease-modifying antirheumatic drug; chelating agent; treatment of Wilson's disease; heavy metal poisoning; cystinuria.

DEFINITION

Penicillamine Tablets contain Penicillamine. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of penicillamine, $C_5H_{11}NO_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Penicillamine with 4 mL of *water* and filter. Add to the filtrate 2 mL of *phosphotungstic acid solution* and allow to stand for a few minutes. A deep blue colour is produced.

B. Dissolve a quantity of the powdered tablets containing 10 mg of Penicillamine in 5 mL of *water* and add 0.3 mL of 5M *sodium hydroxide* and 20 mg of *ninhydrin*. An intense blue or violet-blue colour is produced immediately.

TESTS

Mercuric salts

Not more than 10 ppm, calculated with reference to the content of penicillamine, when determined by the following method. Disperse a quantity of the powdered tablets containing 1 g of Penicillamine in 10 mL of *water* in a stoppered flask, add 0.2 mL of 9M *perchloric acid* and swirl to dissolve. Add 1 mL of *ammonium pyrrolidinedithiocarbamate solution*, mix, add 2 mL of *4-methylpentan-2-one*, shake well for 1 minute and add sufficient *water* to produce 25 mL. Determine by *atomic absorption spectrophotometry*, Appendix II D, introducing the methylpentanone layer into the flame, measuring at 254 nm and using *4-methylpentan-2-one* in place of *water*. Use *mercury standard solution (10 ppm Hg)* for the standard solutions, adjusted to contain the same concentrations of 9M perchloric acid, ammonium pyrrolidinedithiocarbamate solution and 4-methylpentan-2-one as the solution being examined.

Penicillamine disulfide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 40 mg of Penicillamine with 10 mL of the mobile phase, filter and use the filtrate.

(2) 0.004% w/v of *penicillamine disulfide EPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher 5 C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01% w/v of *disodium edetate* and 0.2% w/v of *methane sulfonic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to penicillamine disulfide is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.1 g of Penicillamine as completely as possible in 50 mL of *water* and filter. Add to the filtrate 5 mL of 1M *sodium hydroxide* and 0.2 mL of a 0.1% w/v solution of *dithizone* in *ethanol* (*96%*) and titrate with *0.02M mercury(II) nitrate VS*. Each mL of *0.02M mercury(II) nitrate VS* is equivalent to 5.968 mg of $C_5H_{11}NO_2S$.

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Pentamidine Injection

General Notices

Action and use

Antiprotozoal.

DEFINITION

Pentamidine Injection is a sterile solution of Pentamidine Isetionate in Water for Injections. It is prepared by dissolving Pentamidine Isetionate for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Pentamidine Injection deteriorates on storage and should be used immediately after preparation.

PENTAMIDINE ISETIONATE FOR INJECTION

DEFINITION

Pentamidine Isetionate for Injection is a sterile material consisting of Pentamidine Isetionate without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of pentamidine isetionate, $C_{19}H_{24}N_4O_2,2C_2H_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of pentamidine isetionate (*RS 259*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.002% w/v solution in 0.01M *hydrochloric acid* exhibits a maximum only at 262 nm. The *absorbance* at 262 nm is about 0.95.

C. To 10 mL of a 0.05% w/v solution add 1 mL of a 0.1% w/v solution of *glyoxal sodium bisulfite* and 1 mL of a solution prepared by dissolving 4 g of *boric acid* in a mixture of 27 mL of 1M *sodium hydroxide* and sufficient *water* to produce 100 mL. Heat on a water bath for 10 minutes. A magenta colour is produced.

TESTS

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Acidity

pH of a 5% w/v solution, 4.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.1% w/v of the contents of the sealed container in the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Add to 0.1 g of the contents of the sealed container 40 mL of *water* and some glass beads, adjust the pH to 10.5 with 2M *sodium hydroxide*, heat under a reflux condenser for 20 minutes, cool and dilute to 50 mL with *water*. Dilute 1 volume of this solution to 50 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3.5 times the retention time of the principal peak.

MOBILE PHASE

7 volumes of a 3% w/v solution of *ammonium acetate* and 13 volumes of *methanol*, the pH of the mixture being adjusted to 7.5 with *triethylamine*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two principal peaks and the *resolution factor* between these peaks is greater than 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.2 times the area of the peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all such peaks is not greater than 0.4 times of the area of the peak in the chromatogram obtained with solution (2) (0.4%).

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

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Dissolve 0.25 g of the mixed contents of the 10 containers in 50 mL of *dimethylformamide* and carry out Method II for *non-aqueous titration*, Appendix VIII A, using 0.1M *tetrabutylammonium hydroxide VS* as titrant and determining the end point potentiometrically. Each mL of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 29.63 mg of $C_{19}H_{24}N_4O_2,2C_2H_6O_4S$. Calculate the content of pentamidine isetionate, $C_{19}H_{24}N_4O_2,2C_2H_6O_4S$, in a container of average content weight.

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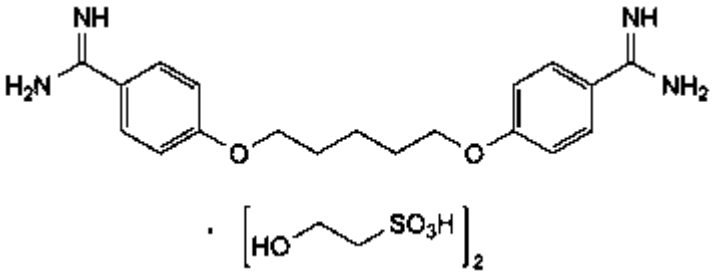
Pentamidine Isetionate

General Notices

(Pentamidine Diisetionate, Ph. Eur. monograph 1137)



$C_{23}H_{36}N_4O_{10}S_2$ 592.7 *140-64-7*

Action and use

Antiprotozoal.

Preparation

Pentamidine Injection

Ph Eur

DEFINITION

4,4′-[Pentane-1,5-diylbis(oxy)]dibenzimidamide bis(2-hydroxyethanesulfonate).

Content

98.5 per cent to 101.5 per cent (dried substance).

PRODUCTION

It is considered that alkyl 2-hydroxyethanesulfonate esters are potential impurities in pentamidine diisetionate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation including, where necessary, demonstration that alkyl 2-hydroxyethanesulfonate esters are not detectable in the final product.

CHARACTERS

Appearance

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White or almost white powder or colourless crystals, hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison *pentamidine diisetionate CRS*.

B. Dissolve about 40 mg in 5 mL of *water R* and add dropwise with shaking 1 mL of a 10 g/L solution of *sodium chloride R*. Allow to stand for 5 min. The mixture remains clear.

C. Treat 0.15 g by the oxygen-flask method (*2.5.10*). Use 10 mL of *dilute hydrogen peroxide solution R* to absorb the combustion products. The solution gives reaction (a) of sulfates (*2.3.1*).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent.

pH (*2.2.3*)

4.5 to 6.5.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) To 0.1 g in a conical flask, add 40 mL of *water R* and glass beads. Adjust to pH 10.5 with *dilute sodium hydroxide solution R* and boil under reflux for 20 min. Cool and dilute to 50 mL with *water R*. Dilute 1 mL of the solution to 50 mL with the mobile phase.

Column:

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— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 65 volumes of *methanol R* and 35 volumes of a 30 g/L solution of *ammonium acetate R* previously adjusted to pH 7.5 with *triethylamine R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 10 µL.

Run time 3.5 times the retention time of pentamidine.

System suitability Reference solution (b):

— the chromatogram obtained shows 2 principal peaks;

— *resolution*: minimum 2.0 between the 2 principal peaks.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Loss on drying (*2.2.32*)

Maximum 4.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *dimethylformamide R*. Add 0.25 mL of *thymol blue solution R*. Titrate with 0.1 M tetrabutylammonium hydroxide, under a current of *nitrogen R*, until the colour of the indicator changes to blue. Carry out a blank titration.

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 29.63 mg of $C_{23}H_{36}N_4O_{10}S_2$.

STORAGE

In an airtight container.

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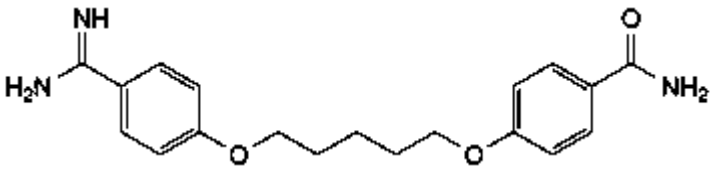
IMPURITIES



A. 4-[[5-(4-amidinophenoxy)pentyl]oxy]benzenecarboxamide.

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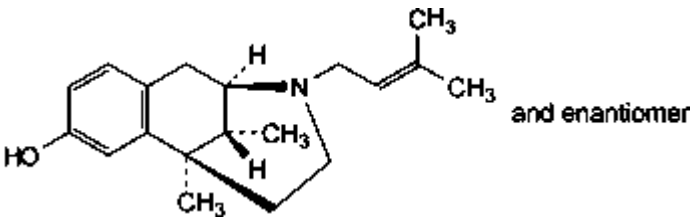
Pentazocine

General Notices

(Ph. Eur. monograph 1462)



$C_{19}H_{27}NO$ 285.4 *359-83-1*

Action and use

Opioid receptor agonist; analgesic.

Preparation

Pentazocine Injection

Ph Eur

DEFINITION

Pentazocine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (2*RS*,6*RS*,11*RS*)-6,11-dimethyl-3-(3-methylbut-2-enyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, practically insoluble in water, freely soluble in methylene chloride and soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the *Ph. Eur. reference spectrum for pentazocine (form A)*.

TESTS

Absorbance (*2.2.25*)

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Dissolve 0.100 g in a mixture of 20 mL of *water R* and 1 mL of *1 M hydrochloric acid*, and dilute to 100.0 mL with *water R*. To 10.0 mL add 1 mL of *1 M hydrochloric acid* and dilute to 100.0 mL with *water R*. The absorbance at the absorption maximum at 278 nm is 0.67 to 0.71, calculated with reference to the dried substance.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel F_{254} plate R*.

Test solution Dissolve 0.20 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 100 mL with *methylene chloride R*.

Reference solution (b) Dilute 5 mL of reference solution (a) to 10 mL with *methylene chloride R*.

Reference solution (c) Dilute 5 mL of reference solution (a) to 20 mL with *methylene chloride R*.

Apply to the plate 10 µL of each solution. Develop over a path corresponding to two thirds of the plate height using a mixture of 3 volumes of *isopropylamine R*, 3 volumes of *methanol R* and 94 volumes of *methylene chloride R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Heat the plate at 100-105 °C for 15 min, allow to cool, expose to iodine vapour and re-examine under ultraviolet light at 254 nm. By each method of visualisation: any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot obtained with reference solution (a) (1 per cent); not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent) and not more than 4 such spots are more intense than the spot in the chromatogram obtained with reference solution (c) (0.25 per cent).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.7 kPa for 4 h.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 28.54 mg of $C_{19}H_{27}NO$.

STORAGE

Store protected from light.

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Pentazocine Capsules

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Pentazocine Capsules contain Pentazocine Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of pentazocine hydrochloride, $C_{19}H_{27}NO,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing 50 mg of Pentazocine Hydrochloride with 3 mL of 0.1M *sodium hydroxide* and 3 mL of *dichloromethane* and allow to separate. Filter the dichloromethane layer through a phase separation paper (Whatman 1PS is suitable) and evaporate the filtrate using a rotary evaporator at a temperature of 40°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pentazocine (form B) (*RS 261*).

B. Yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1,

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 278 nm, Appendix II B, using *water* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of pentazocine hydrochloride, $C_{19}H_{27}NO,HCl$, in the medium taking 61.2 as the value of A(1%, 1 cm) at the maximum at 278 nm.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 0.2 g of Pentazocine Hydrochloride with 10 mL of 0.1M *methanolic ammonia*, centrifuge and use the clear supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes with the same solvent.
(3) Dilute 1 volume of solution (1) to 200 volumes with the same solvent.
(4) Dilute 1 volume of solution (1) to 400 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F_{254} (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Heat the plate at 105° for 15 minutes, allow to cool, expose to iodine vapour and re-examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *isopropylamine*, 3 volumes of *methanol* and 94 volumes of *chloroform*.

LIMITS

By each method of visualisation, in the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2)(1%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3)(0.5%);

and not more than four such spots are more intense than the spot in the chromatogram obtained with solution (4)(0.25%).

Disregard any spot remaining on the line of application.

ASSAY

Shake a quantity of the mixed contents of 20 capsules containing 50 mg of Pentazocine Hydrochloride with 200 mL of *water* for 15 minutes, add 5 mL of 1M *hydrochloric acid* and sufficient *water* to produce 500 mL, mix and filter. Measure the *absorbance* of the filtrate at the maximum at 278 nm, Appendix II B. Calculate the content of $C_{19}H_{27}NO,HCl$ taking 61.2 as the value of A(1%, 1 cm) at the maximum at 278 nm.

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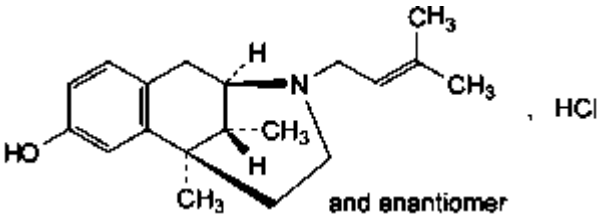
Pentazocine Hydrochloride

General Notices

(Ph. Eur. monograph 1463)



$C_{19}H_{28}ClNO$ 321.9 *64024-15-3*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Pentazocine Capsules

Pentazocine Tablets

Ph Eur

DEFINITION

Pentazocine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (2*RS*,6*RS*,11*RS*)-6,11-dimethyl-3-(3-methylbut-2-enyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, sparingly soluble in water, soluble in ethanol (96 per cent) and sparingly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the *Ph. Eur. reference spectrum of pentazocine hydrochloride*.

B. It gives reaction (a) of chlorides (*2.3.1*).

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TESTS

pH (2.2.3)

Dissolve 0.1 g in 10 mL of *carbon dioxide-free water R*. The pH of the solution is 4.0 to 6.0.

Absorbance (2.2.25)

Dissolve 0.100 g in a mixture of 20 mL of *water R* and 1 mL of *1 M hydrochloric acid*, and dilute to 100.0 mL with *water R*. To 10.0 mL add 1 mL of *1 M hydrochloric acid* and dilute to 100.0 mL with *water R*. The absorbance at the absorption maximum at 278 nm is 0.59 to 0.63, calculated with reference to the dried substance.

Related substances

Examine by thin-layer chromatography (2.2.27), using a *TLC silica gel F_{254} plate R*.

Test solution Dissolve 0.20 g in 3 mL of *methanol R* and dilute to 10 mL with *methylene chloride R*.

Reference solution (a) Dilute 1 mL of the test solution to 100 mL with *methylene chloride R*.

Reference solution (b) Dilute 5 mL of reference solution (a) to 10 mL with *methylene chloride R*.

Reference solution (c) Dilute 5 mL of reference solution (a) to 20 mL with *methylene chloride R*.

Apply to the plate 10 µL of each solution. Develop over a path corresponding to two-thirds of the plate height using a mixture of 3 volumes of *isopropylamine R*, 3 volumes of *methanol R* and 94 volumes of *methylene chloride R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Heat the plate at 100-105 °C for 15 min, allow to cool, expose to iodine vapour and re-examine under ultraviolet light at 254 nm. By each method of visualisation: any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot obtained with reference solution (a) (1 per cent); not more than 1 such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent); and not more than 4 such spots are more intense than the spot in the chromatogram obtained with reference solution (c) (0.25 per cent).

Loss on drying (2.2.32)

Not more than 0.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.7 kPa for 4 h.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R*. Add 5 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflection.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.19 mg of $C_{19}H_{28}ClNO$.

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STORAGE

Store protected from light.

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Pentazocine Injection

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Pentazocine Injection is a sterile solution in Water for Injections of either Pentazocine Lactate or pentazocine lactate prepared by the interaction of Pentazocine and Lactic Acid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of pentazocine, $C_{19}H_{27}NO$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. To a volume containing the equivalent of 90 mg of pentazocine add 5 mL of 0.1M *sodium hydroxide* and shake the resulting solution with 5 mL of *chloroform*. Wash the chloroform extract with 2 mL of *water*, dry over *anhydrous sodium sulfate* and filter. Evaporate the chloroform using a rotary evaporator and dry the oily residue at a temperature not exceeding 25° at a pressure of 2 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pentazocine (form B) (*RS 261*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 10 volumes of 18M *ammonia*, 10 volumes of *ethyl acetate*, 30 volumes of *water* and 50 volumes of *absolute ethanol* as the mobile phase but allowing the solvent front to ascend 10 cm above the line of application. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) dilute a quantity of the injection with sufficient *methanol* to produce a solution containing the equivalent of 0.75% w/v of pentazocine. Solution (2) contains 0.4% w/v of *calcium lactate* in *methanol*. After removal of the plate, allow it to dry in air, spray with a 1% w/v solution of *potassium permanganate* and examine in daylight. The principal spot in the chromatogram obtained with solution (1) is similar in colour, position and size to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 5.0, Appendix V L.

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Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 3 volumes of *methanol*, 3 volumes of *isopropylamine* and 94 volumes of *chloroform* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) dilute a quantity of the injection with sufficient *ethanol* (*96%*) to produce a solution containing the equivalent of 2.0% w/v of pentazocine. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *ethanol* (*96%*). For solution (3) dilute 1 volume of solution (1) to 200 volumes with *ethanol* (*96%*). For solution (4) dilute 1 volume of solution (1) to 400 volumes with *ethanol* (*96%*). After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Heat the plate at 105° for 15 minutes, allow to cool, expose to iodine vapour and re-examine under *ultraviolet light (254 nm)*. By each method of visualisation any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%), not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%) and not more than four such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.25%). Disregard any spot remaining on the line of application.

ASSAY

To a quantity containing the equivalent of 0.15 g of pentazocine add sufficient *water* to produce 100 mL. To 5 mL add 1 mL of 1M *hydrochloric acid*, dilute to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 278.5 nm, Appendix II B. Calculate the content of $C_{19}H_{27}NO$ taking 69.0 as the value of A(1%, 1 cm) at the maximum at 278.5 nm.

STORAGE

Pentazocine Injection should be protected from light.

LABELLING

The strength is stated in terms of the equivalent amount of pentazocine in a suitable dose-volume.

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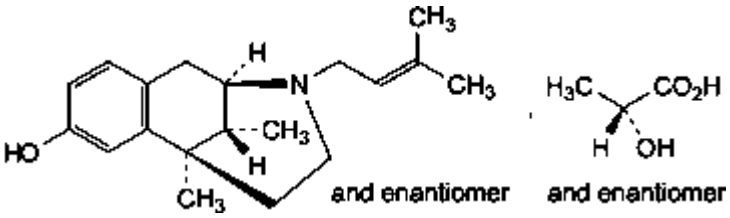
Pentazocine Lactate

General Notices

(Ph. Eur. monograph 2000)



$C_{22}H_{33}NO_4$ 375.5 *17146-95-1*

Action and use

Opioid receptor agonist; analgesic.

Preparation

Pentazocine Injection

Ph Eur

DEFINITION

(2*RS*,6*RS*,11*RS*)-6,11-Dimethyl-3-(3-methylbut-2-enyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol (2*RS*)-2-hydroxypropanoate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, slightly soluble in methylene chloride.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of pentazocine lactate*.

TESTS

pH (2.2.3)

5.5 to 6.5.

Dissolve 0.1 g in 10 mL of *carbon dioxide-free water R*.

Absorbance (2.2.25)

0.50 to 0.54, determined at the absorption maximum at 278 nm.

Dissolve 0.10 g in 10.0 mL of *1 M hydrochloric acid* and dilute to 100.0 mL with *water R*. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Related substances

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 100 mg of the substance to be examined in *acetic anhydride R* and dilute to 5 mL with the same solvent. Heat at 80 °C for 10 min. Dilute 1 mL of the solution to 10 mL with *methanol R*. Mix 1 mL of this solution with 1 mL of the test solution.

Reference solution (b) Dilute 1 mL of the test solution to 100 mL with *methylene chloride R*. Dilute 2 mL of this solution to 10 mL with *methylene chloride R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *isopropylamine R*, *methanol R*, *methylene chloride R* (3:3:94 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm. Heat at 100-105 °C for 15 min. Allow to cool. Expose to iodine vapour and re-examine in ultraviolet light at 254 nm.

System suitability Reference solution (a):

— the chromatogram shows 2 clearly separated spots.

Limits By each method of detection:

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— *any impurity*: any spots, apart from the principal spot, are not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 30 mL of *anhydrous acetic acid R* and add 30 mL of *dioxan R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 37.55 mg of $C_{22}H_{33}NO_4$.

STORAGE

Protected from light.

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Pentazocine Tablets

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Pentazocine Tablets contain Pentazocine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pentazocine hydrochloride, $C_{19}H_{27}NO,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.1 g of Pentazocine Hydrochloride with 10 mL of *water,* filter (Whatman GF/C is suitable), add 1 mL of 1M *sodium hydroxide* and shake the resulting solution with 20 mL of *chloroform*. Wash the chloroform extract with 5 mL of *water*, dry over *anhydrous sodium sulfate* and filter. Evaporate the chloroform using a rotary evaporator and dry the oily residue at 60° at a pressure of 2 kPa for 1 hour. The *infrared absorption spectrum* of the powdered residue, Appendix II A, is concordant with the *reference spectrum* of pentazocine (form B) (*RS 261*). If the spectra are not concordant, dissolve the residue in *chloroform*, evaporate to dryness and prepare a new spectrum of the residue.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 94 volumes of *chloroform*, 3 volumes of *methanol* and 3 volumes of *isopropylamine* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.2 g of Pentazocine Hydrochloride with 10 mL of 0.1M *methanolic ammonia* for 10 minutes, centrifuge and use the supernatant liquid. For solution (2) dilute 1 volume of solution (1) to 100 volumes with the same solvent. For solution (3) dilute 1 volume of solution (1) to 200 volumes with the same solvent. For solution (4) dilute 1 volume of solution (1) to 400 volumes with the same solvent. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Heat the plate at 105° for 15 minutes, allow to cool, expose to iodine vapour and re-examine under *ultraviolet light (254 nm)*. By each method of visualisation any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2), not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) and not more than four such spots are more intense than the spot in the chromatogram obtained with solution (4). Disregard any spot remaining on the line of application.

ASSAY

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Weigh and powder 20 tablets. Shake a quantity of the powder containing 25 mg of Pentazocine Hydrochloride with 100 mL of *water* for 15 minutes, add 2.5 mL of 1M *hydrochloric acid* and sufficient *water* to produce 250 mL and filter. Measure the *absorbance* of the filtrate at the maximum at 278 nm, Appendix II B. Calculate the content of $C_{19}H_{27}NO,HCl$ taking 61.2 as the value of A(1%, 1 cm) at the maximum at 278 nm.

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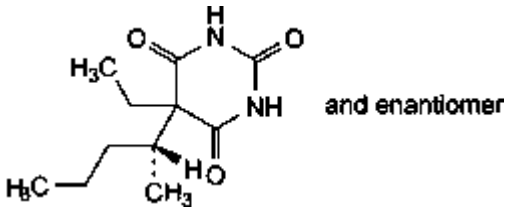
Pentobarbital

General Notices

(Ph. Eur. monograph 0200)



$C_{11}H_{18}N_2O_3$ 226.3 *76-74-4*

Action and use

Barbiturate.

Ph Eur

DEFINITION

5-Ethyl-5-[(2*RS*)-pentan-2-yl]-1,3-diazinane-2,4,6-trione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane. It forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *pentobarbital CRS*.

If the spectra obtained in the solid state show differences, weigh 10 mg of the substance to be examined and 10 mg of the reference substance separately in glass vials; heat in an oven at 140 °C for 1 h, then allow to stand at room temperature for 3 h. Record new spectra.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_9 (*2.2.2, Method II*).

Dissolve 1.0 g in a mixture of 4 mL of *dilute sodium hydroxide solution R* and 6 mL of *water R*.

Acidity

Boil 1.0 g with 50 mL of *water R* for 2 min, allow to cool and filter. To 10 mL of the filtrate add 0.15 mL of *methyl red solution R*. The solution is orange-yellow. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to produce a pure yellow colour.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (b) to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.5 mg of *pentobarbital impurity E CRS* in the mobile phase and dilute to 25 mL with the mobile phase. Dilute 1 mL of the solution to 100 mL with the mobile phase. Dissolve 5 mg of the substance to be examined in 5 mL of this solution.

Reference solution (c) Dissolve 25.0 mg of *pentobarbital CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.5 with *dilute phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

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Run time 2.5 times the retention time of pentobarbital.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to pentobarbital (retention time = about 10 min): impurity E = about 0.92.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity E and pentobarbital.

Calculation of percentage contents:

— for each impurity, use the concentration of pentobarbital in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.1 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{11}H_{18}N_2O_3$ taking into account the assigned content of *pentobarbital CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F.

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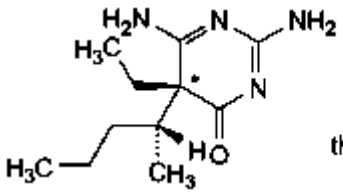
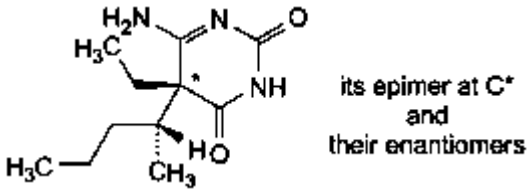
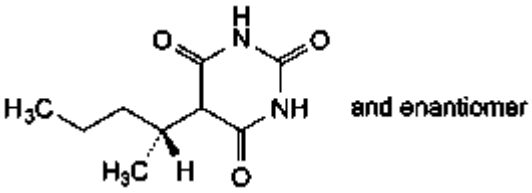


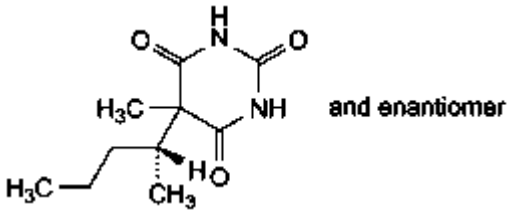
A. mixture of (5*R*)-2,6-diamino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidin-4(5*H*)-one and (5*S*)-2,6-diamino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidin-4(5*H*)-one,



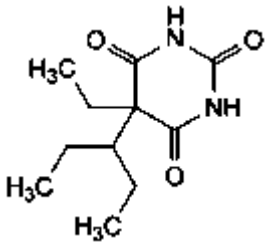
B. mixture of (5*R*)-6-amino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidine-2,4(3*H*,5*H*)-dione and (5*S*)-6-amino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidine-2,4(3*H*,5*H*)-dione,



C. 5-[(2*RS*)-pentan-2-yl]-1,3-diazinane-2,4,6-trione,



D. 5-methyl-5-[(2*RS*)-pentan-2-yl]-1,3-diazinane-2,4,6-trione,



E. 5-ethyl-5-(pentan-3-yl)-1,3-diazinane-2,4,6-trione,

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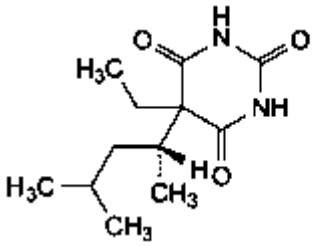

F. 5-ethyl-5-[(2*RS*)-4-methylpentan-2-yl]-1,3-diazinane-2,4,6-trione.

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Pentobarbital Sodium

General Notices

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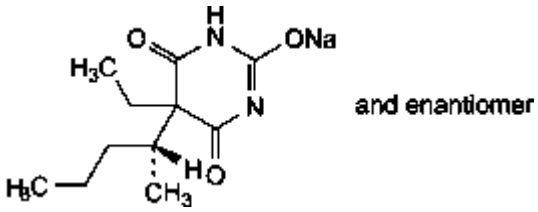

and enantiomer

$C_{11}H_{17}N_2NaO_3$ 248.3 *57-33-0*

Action and use

Barbiturate.

Preparation

Pentobarbital Tablets

Ph Eur

DEFINITION

Sodium 5-ethyl-4,6-dioxo-5-[(2*RS*)-pentan-2-yl]-1,4,5,6-tetrahydropyrimidin-2-olate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *pentobarbital sodium CRS*.

If the spectra obtained in the solid state show differences, dissolve 10 mg of the substance to be examined and 10 mg of the reference substance separately in 0.2 mL of *methanol R*. Evaporate the solvent by heating in an oven at 80 °C for 2 h. Record new spectra using the residues.

B. Ignite 1 g. The residue gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_9 (2.2.2, *Method II*).

Dissolve 1.0 g in 10 mL of *ethanol (50 per cent V/V) R*. Examine immediately after preparation.

pH (2.2.3)

9.6 to 11.0, measured immediately after preparation.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 27.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (b) to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.5 mg of *pentobarbital impurity E CRS* in the mobile phase and dilute to 25 mL with the mobile phase. Dilute 1 mL of the solution to 100 mL with the mobile phase. Dissolve 5 mg of the substance to be examined in 5 mL of this solution.

Reference solution (c) Dissolve 25.0 mg of *pentobarbital CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.5 with *dilute phosphoric acid R*.

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Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Run time 2.5 times the retention time of pentobarbital.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to pentobarbital (retention time = about 10 min): impurity E = about 0.92.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity E and pentobarbital.

Calculation of percentage contents:

— for each impurity, use the concentration of pentobarbital sodium in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.1 per cent;

— *reporting threshold*: 0.05 per cent.

Free pentobarbital

Maximum 3.5 per cent.

Dissolve 2.00 g in 75 mL of *dimethylformamide R*, heating gently if necessary. Titrate with *0.1 M sodium methoxide* until the colour changes from olive-green to blue, using 0.25 mL of a 10 g/L solution of *thymol blue R* in *dimethylformamide R* as indicator. Carry out a blank titration.

1 mL of *0.1 M sodium methoxide* is equivalent to 22.63 mg of pentobarbital.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{11}H_{17}N_2NaO_3$ taking into account the assigned content of *pentobarbital CRS* and a conversion factor of 1.097.

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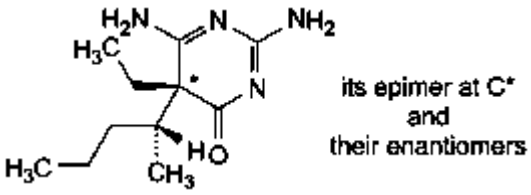
STORAGE

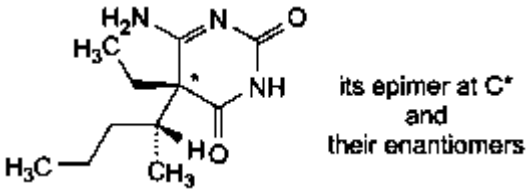
In an airtight container.

IMPURITIES

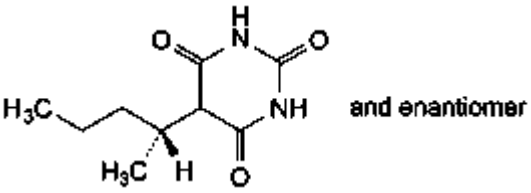
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F.



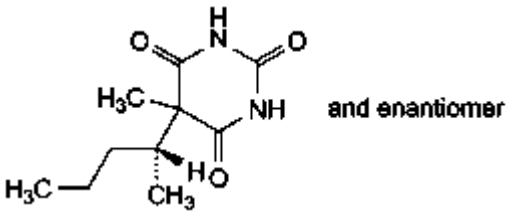
A. mixture of (5*R*)-2,6-diamino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidin-4(5*H*)-one and (5*S*)-2,6-diamino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidin-4(5*H*)-one,



B. mixture of (5*R*)-6-amino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidine-2,4(3*H*,5*H*)-dione and (5*S*)-6-amino-5-ethyl-5-[(2*RS*)-pentan-2-yl]pyrimidine-2,4(3*H*,5*H*)-dione,



C. 5-[(2*RS*)-pentan-2-yl]-1,3-diazinane-2,4,6-trione,



D. 5-methyl-5-[(2*RS*)-pentan-2-yl]-1,3-diazinane-2,4,6-trione,

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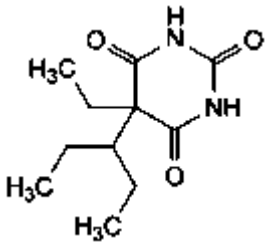
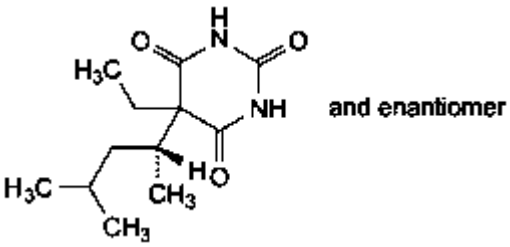


E. 5-ethyl-5-(pentan-3-yl)-1,3-diazinane-2,4,6-trione,



F. 5-ethyl-5-[(2*RS*)-4-methylpentan-2-yl]-1,3-diazinane-2,4,6-trione.

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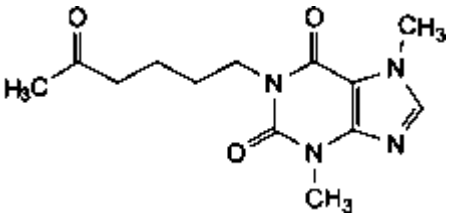
Pentoxifylline

General Notices

(Ph. Eur. monograph 0851)



$C_{13}H_{18}N_4O_3$ 278.3 *6493-05-6*

Action and use

Vasodilator.

Ph Eur

DEFINITION

3,7-Dimethyl-1-(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

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A. Melting point (2.2.14): 103 °C to 107 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *pentoxifylline CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *pentoxifylline CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *ethyl acetate R* (15:85 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives the reaction of xanthines (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

A 40 per cent *V/V* solution of solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Acidity

To 8 mL of solution S add 12 mL of *carbon dioxide-free water R* and 0.05 mL of *bromothymol blue solution R1*. The solution is green or yellow. Not more than 0.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Liquid chromatography (2.2.29).

Solution A 5.44 g/L solution of *potassium dihydrogen phosphate R*.

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Solvent mixture methanol R, solution A (50:50 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 10.0 mL of reference solution (a) to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of caffeine R (impurity F) and 2 mg of theophylline R (impurity C) in the solvent mixture, add 1 mL of the test solution and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 5.0 mg of caffeine R (impurity F), 5.0 mg of theobromine R (impurity A) and 5.0 mg of theophylline R (impurity C) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: base-deactivated octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: methanol R, solution A (30:70 *V/V*);

— *mobile phase B*: solution A, methanol R (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	85	15
6 - 13	85 → 10	15 → 90
13 - 30	10	90
30 - 35	10 → 85	90 → 15
35 - 45	85	15

Flow rate 1 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL.

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Relative retention With reference to pentoxifylline (retention time = about 12 min): impurity A = about 0.3; impurity C = about 0.4; impurity F = about 0.5; impurity J = about 1.6.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to impurities C and F.

Limits:

— *impurities A, C, F*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *impurity J*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent).

Chlorides (2.4.4)

Maximum 100 ppm.

Place 20 mL of solution S in a separating funnel and shake with 2 quantities, each of 20 mL, of *2-methylpropanol R*. Dilute 10 mL of the aqueous layer to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 200 ppm, determined on 15 mL of solution S.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 5 mL of *anhydrous acetic acid R*. Add 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 27.83 mg of $C_{13}H_{18}N_4O_3$.

STORAGE

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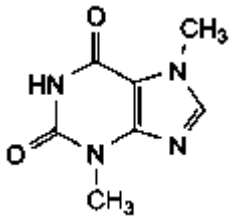
Protected from light.

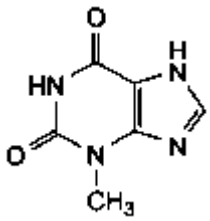
IMPURITIES

Specified impurities *A, C, F, J.*

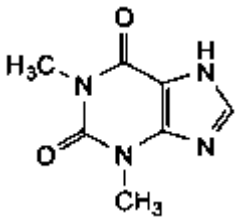
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E, G, H, I, K.*



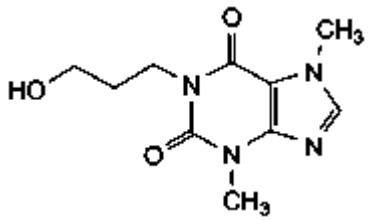
A. theobromine,



B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



C. theophylline,



D. 1-(3-hydroxypropyl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione,

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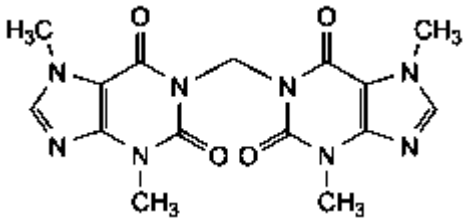
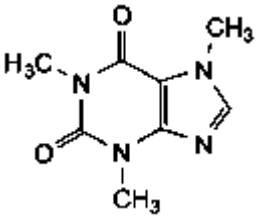
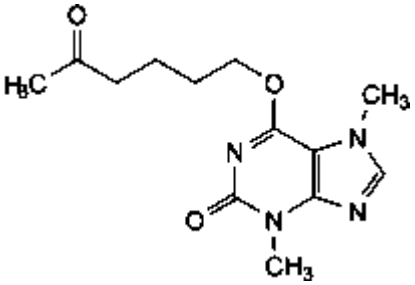


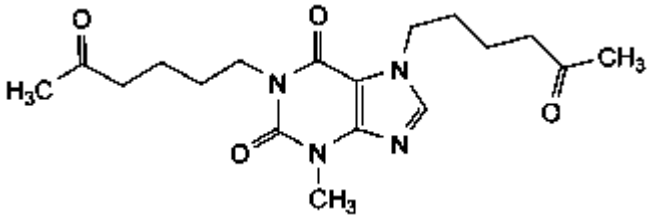
E. 1,1′-methylenebis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione),



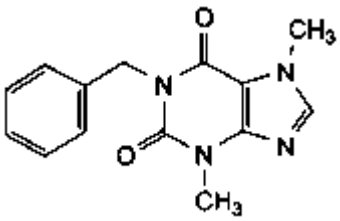
F. caffeine,



G. 3,7-dimethyl-6-(5-oxohexyloxy)-3,7-dihydro-2*H*-purin-2-one,



H. 3-methyl-1,7-bis(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione,



I. 1-benzyl-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione,

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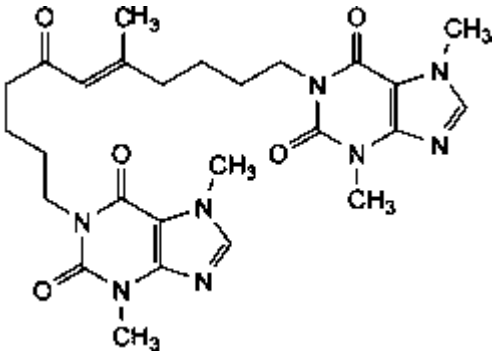
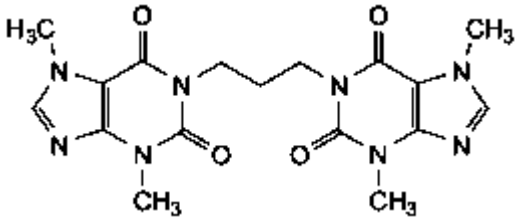


J. 1-[(5*E*)-11-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-5-methyl-7-oxoundec-5-enyl]-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione,



K. 1,1′-(propane-1,3-diyl)bis(3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione).

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Pentobarbital Tablets

General Notices

Action and use

Barbiturate.

DEFINITION

Pentobarbital Tablets contain Pentobarbital Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pentobarbital sodium, $C_{11}H_{17}N_2NaO_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Heat 0.2 g of the residue obtained in the Assay on a water bath with the minimum quantity of *ethanol* (*25%*) until dissolved, filter while hot and allow the filtrate to cool. Filter, wash the crystals with a small quantity of *ethanol* (*25%*) and dry at 105°. The *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of pentobarbital (*RS 264*).

B. The powdered tablets yield the reactions characteristic of *sodium salts*, Appendix VI.

TESTS

Isomer

Dissolve a quantity of the powdered tablets containing 0.3 g of Pentobarbital Sodium in 5 mL of a 5% w/v solution of *anhydrous sodium carbonate*, heating gently if necessary. Add 10 mL of a 3% w/v solution of *4-nitrobenzyl chloride* in *ethanol* (*96%*) and heat under a reflux condenser for 30 minutes. Cool to 25°, filter and wash the precipitate with five 5 mL quantities of *water*. Heat the precipitate with 25 mL of *ethanol* (*96%*) in a small flask under a reflux condenser until dissolved (about 10 minutes). Filter the hot solution, cool to 25° and, if necessary, scratch the side of the flask with a glass rod to induce crystallisation. Filter, wash the precipitate with two 5 mL quantities of *water* and dry at 100° to 105° for 30 minutes. The *melting point* of the dried precipitate is 136° to 148°, Appendix V A, Method I.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.3 g of Pentobarbital Sodium as completely as possible in 10 mL of a 2% w/v solution of *sodium hydroxide*, saturate with *sodium chloride*, acidify with *hydrochloric acid* and extract with successive 15 mL quantities of *ether* until complete extraction is effected. Wash the combined extracts with two 2 mL quantities of *water* and extract the

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combined washings with 10 mL of *ether*. Add the ether to the main ether layer, filter and wash the filter with *ether*. Evaporate the solvent and dry the residue to constant weight at 105°. Each g of residue is equivalent to 1.097 g of $C_{11}H_{17}N_2NaO_3$.

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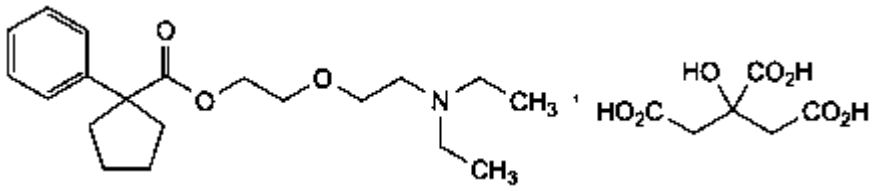
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Pentoxyverine Citrate

General Notices

(Pentoxyverine Hydrogen Citrate, Ph. Eur. monograph 1621)



$C_{26}H_{39}NO_{10}$ 525.6 *23142-01-0*

Action and use

Cough suppressant.

Ph Eur

DEFINITION

2-[2-(Diethylamino)ethoxy]ethyl 1-phenylcyclopentanecarboxylate dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very soluble in glacial acetic acid, freely soluble in methanol, soluble in ethanol (96 per cent) and in methylene chloride.

mp

About 93 °C.

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of pentoxyverine hydrogen citrate*.

B. Dissolve 0.25 g in 5 mL of *water R*. The solution gives the reaction of citrates (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

pH (2.2.3)

3.3 to 3.7 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution Introduce 5.0 mg of *pentoxyverine impurity A CRS* and 5.0 mg of *pentoxyverine impurity B CRS* in a conical flask, add 5.0 mL of the test solution and dilute to 100.0 mL with the mobile phase. Dilute 3.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm,

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 12 per cent,

— *temperature*: 50 °C.

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.5 g/L solution of *sodium heptanesulfonate R* adjusted to pH 3.0 with *dilute sulfuric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL.

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Run time 3 times the retention time of pentoxyverine.

Relative retention With reference to pentoxyverine (retention time = about 6 min): impurity B = about 0.8; impurity A = about 1.5.

System suitability Reference solution:

— *resolution*: minimum of 5.0 between the peaks due to pentoxyverine and to impurity A,

— *signal-to-noise ratio*: minimum of 100 for the peak due to pentoxyverine,

— *symmetry factor*: maximum of 2.0 for the peak due to pentoxyverine.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.3 per cent),

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.3 per cent),

— *any other impurity*: not more than one-third of the area of the peak due to pentoxyverine in the chromatogram obtained with the reference solution (0.1 per cent),

— *total of any other impurity*: not more than the area of the peak due to pentoxyverine in the chromatogram obtained with the reference solution (0.3 per cent),

— *disregard limit*: 0.1 times the area of the peak due to pentoxyverine in the chromatogram obtained with the reference solution (0.03 per cent); disregard any peak with a retention time less than or equal to 2.5 min.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 70 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 52.56 mg of $C_{26}H_{39}NO_{10}$.

STORAGE

Protected from light.

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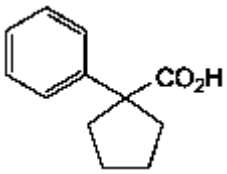
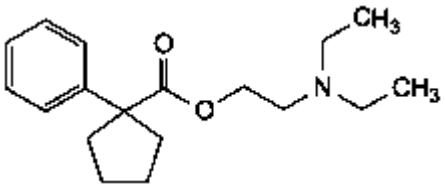
IMPURITIES



A. 1-phenylcyclopentanecarboxylic acid,



B. 2-(diethylamino)ethyl 1-phenylcyclopentanecarboxylate (caramiphen).

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Pepsin

General Notices

(Pepsin Powder, Ph. Eur. monograph 0682)

9001-75-6

Action and use

Proteolytic enzyme.

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DEFINITION

Powder prepared from the gastric mucosa of pigs, cattle or sheep. It contains gastric proteinases, active in acid medium (pH 1 to 5).

Activity Not less than 0.5 Ph. Eur. U./mg (dried substance).

PRODUCTION

The animals from which pepsin powder is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

Appearance

White or slightly yellow, crystalline or amorphous powder, hygroscopic.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

The solution in water may be slightly opalescent with a weak acidic reaction.

IDENTIFICATION

In a mortar, pound 30 mg of *fibrin blue R*. Suspend in 20 mL of *dilute hydrochloric acid R2*. Filter the suspension on a filter paper and wash with *dilute hydrochloric acid R2* until a colourless filtrate is obtained. Perforate the filter paper and wash the *fibrin blue R* through it into a conical flask using 20 mL of *dilute hydrochloric acid R2*. Shake before use. Dissolve a quantity of the substance to be examined, equivalent to not less than 20 Ph. Eur. U., in 2 mL of *dilute hydrochloric acid R2* and adjust to pH 1.6 ± 0.1. Add 1 mL of this solution to a test-tube containing 4 mL of the fibrin blue suspension, mix and place in a water-bath at 25 °C with gentle shaking. Prepare a blank solution at the

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same time and in the same manner using 1 mL of *water R*. After 15 min of incubation the blank solution is colourless and the test solution is blue.

TESTS

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 0.500 g by drying at 60 °C over *diphosphorus pentoxide R* at a pressure not exceeding 670 Pa for 4 h.

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

ASSAY

The activity of pepsin powder is determined by comparing the quantity of peptides, non-precipitable by *trichloroacetic acid solution R* and assayed using the *phosphomolybdotungstic reagent R*, which are released per minute from a substrate of *haemoglobin solution R*, with the quantity of such peptides released by *pepsin powder BRP* from the same substrate in the same conditions.

For the test solution and the reference solution, prepare the solution and carry out the dilution at 0 °C to 4 °C.

Avoid shaking and foaming during preparation of the test and reference solutions.

Test solution Immediately before use, prepare a solution of the substance to be examined expected to contain 0.5 Ph. Eur. U./mL in *dilute hydrochloric acid R2*; before dilution to volume, adjust to pH 1.6 ± 0.1, if necessary, using *1 M hydrochloric acid*.

Reference solution Less than 15 min before use, prepare a solution of *pepsin powder BRP* containing 0.5 Ph. Eur. U./mL in *dilute hydrochloric acid R2*; before dilution to volume, adjust to pH 1.6 ± 0.1, if necessary, using *1 M hydrochloric acid*.

Table 0682.-1

	Tubes								
	S_1	S_{1b}	S_2	S_{2b}	S_3	S_{3b}	T	T_b	B
Dilute hydrochloric acid R2 (mL)	0.5	0.5	0.25	0.25			0.25	0.25	1.0
Reference solution (mL)	0.5	0.5	0.75	0.75	1.0	1.0			
Test solution (mL)							0.75	0.75	

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	Tubes								
	S_1	S_{1b}	S_2	S_{2b}	S_3	S_{3b}	T	T_b	B
Trichloroacetic acid solution R (mL)		10.0		10.0		10.0		10.0	10.0
Mix		+		+		+		+	+
Water bath at 25 °C	+	+	+	+	+	+	+	+	+
Haemoglobin solution R (mL)		5.0		5.0		5.0		5.0	5.0
Mix		+		+		+		+	+
Haemoglobin solution R (mL)	5.0		5.0		5.0		5.0		
Mix	+		+		+		+		
Water bath at 25 °C, 10 min	+	+	+	+	+	+	+	+	+
Trichloroacetic acid solution R (mL)	10.0		10.0		10.0		10.0		
Mix	+		+		+		+		
Filter	+	+	+	+	+	+	+	+	+

Designate tubes in duplicate T, T_b, S_1, S_{1b}, S_2, S_{2b}, S_3, S_{3b}; designate a tube B.

Add *dilute hydrochloric acid R2* to the tubes as follows:

B: 1.0 mL

S_1 and S_{1b}: 0.5 mL

S_2, S_{2b} and T and T_b: 0.25 mL

Add the reference solution to the tubes as follows:

S_1 and S_{1b}: 0.5 mL

S_2 and S_{2b}: 0.75 mL

S_3 and S_{3b}: 1.0 mL

Add 0.75 mL of the test solution to tubes T and T_b.

Add 10.0 mL of *trichloroacetic acid solution R* to tubes S_{1b}, S_{2b}, S_{3b}, T_b and B. Mix by shaking.

Place the tubes and *haemoglobin solution R* in a water bath at 25 ± 0.1 °C. When temperature equilibrium is reached, add 5.0 mL of *haemoglobin solution R* to tubes B, S_{1b}, S_{2b}, S_{3b} and T_b. Mix.

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At time zero add 5.0 mL of *haemoglobin solution R* successively and at intervals of 30 s to tubes S_1, S_2, S_3 and T.

Mix immediately after each addition.

Exactly 10 min after adding the *haemoglobin solution R*, stop the reaction by adding, at intervals of 30 s, 10.0 mL of *trichloroacetic acid solution R* to tubes S_1, S_2, S_3 and T (the use of a fast-flowing or blow-out pipette is recommended) and mix.

Filter the contents of each tube (samples and blanks) twice through the same suitable filter paper previously washed with a 50 g/L solution of *trichloroacetic acid R*, then with *water R* and dried. Discard the first 5 mL of filtrate. Place 3.0 mL of each filtrate separately in a tube containing 20 mL of *water R*. Mix.

A suitable filter paper complies with the following test Filter 5 mL of a 50 g/L solution of *trichloroacetic acid R* through a 7 cm disc of white filter paper: the absorbance (*2.2.25*) of the filtrate, measured at 275 nm using unfiltered *trichloroacetic acid R* solution as the compensation liquid, is less than 0.04.

Add to each tube 1.0 mL of *sodium hydroxide solution R* and 1.0 mL of *phosphomolybdotungstic reagent R*, beginning with the blanks and then the samples of each set, in a known order.

A schematic presentation of the above operations is shown in Table 0682.-1.

After 15 min measure the absorbance (*2.2.25*) of solutions S_1, S_2, S_3, S_{1b}, S_{2b}, S_{3b} and T at 540 nm using the filtrate obtained from tube B as the compensation liquid. Correct the average absorbance values for the filtrates obtained from tubes S_1, S_2 and S_3 by subtracting the average values obtained for the filtrates from tubes S_{1b}, S_{2b}, S_{3b} respectively.

Draw a calibration curve of the corrected values against volume of reference solution used. Determine the activity of the substance to be examined using the corrected absorbance for the test solution ($T - T_b$) together with the calibration curve and taking into account the dilution factors.

STORAGE

Store in an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

LABELLING

The label states the activity in European Pharmacopoeia Units per milligram.

Ph Eur

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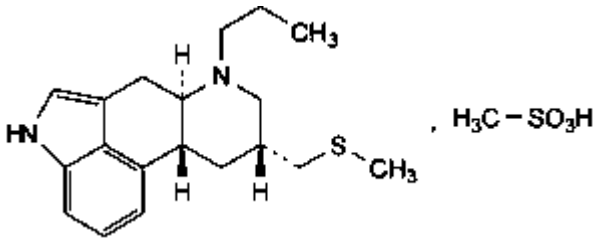
Pergolide Mesilate

General Notices

(Ph. Eur. monograph 1555)



$C_{20}H_{30}N_2O_3S_2$ 410.6 *66104-23-2*

Action and use

Dopamine receptor agonist; treatment of Parkinson's disease.

Ph Eur

DEFINITION

(6a*R*,9*R*,10a*R*)-9-[(Methylsulfanyl)methyl]-7-propyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline monomethanesulfonate.

Content

97.5 per cent to 102.0 per cent (dried substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in pergolide mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent) and in methylene chloride, very slightly soluble in acetone.

IDENTIFICATION

A. Specific optical rotation (2.2.7): -23 to -17 (dried substance).

Dissolve 0.25 g in *dimethylformamide R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *pergolide mesilate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 10 mg of *4,4'-dimethoxybenzophenone R* in *methanol R* and dilute to 10 mL with the same solvent. To 1 mL of the solution add 2 mL of the test solution and dilute to 100 mL with *methanol R*. Dilute 1 mL of this solution to 10 mL with *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 5.0 mL of *morpholine for chromatography R* with 995 mL of *water R* and adjust to pH 7.0 with *phosphoric acid R*; use within 24 h;

— *mobile phase B*: *acetonitrile R*, *methanol R*, *tetrahydrofuran R* (1:1:1 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	70 → 0	30 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
35 - 40	0 → 70	100 → 30
40 - 50	70	30

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to 4,4′-dimethoxybenzophenone (1st peak) and pergolide (2nd peak).

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C for 1 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Solution A Dissolve 5.0 mg of *DL-methionine R* in 500 mL of *0.01 M hydrochloric acid*. Add 500 mL of *methanol R* and mix.

Test solution Dissolve 65.0 mg of the substance to be examined in solution A and dilute to 100.0 mL with solution A. Dilute 10.0 mL of this solution to 100.0 mL with solution A.

Reference solution Dissolve 65.0 mg of *pergolide mesilate CRS* in solution A and dilute to 100.0 mL with solution A. Dilute 10.0 mL of this solution to 100.0 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

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— *temperature*: 40 °C.

Mobile phase Mix 1 volume of *acetonitrile R*, 1 volume of *methanol R* and 2 volumes of a mixture prepared as follows: dissolve 2.0 g of *sodium octanesulfonate R* in *water R*, add 1.0 mL of *anhydrous acetic acid R* and dilute to 1000 mL with *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Retention time Pergolide = about 9 min.

System suitability Reference solution:

— *symmetry factor*: maximum 1.5 for the peak due to pergolide.

Calculate the percentage content of $C_{20}H_{30}N_2O_3S_2$ from the assigned content of *pergolide mesilate CRS*.

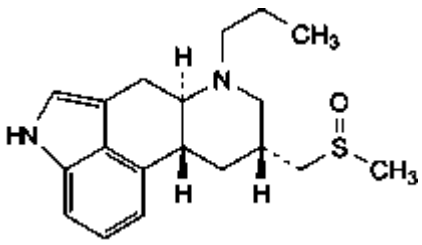
STORAGE

Protected from light.

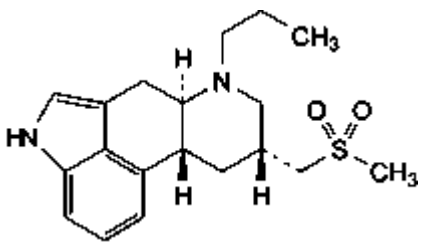
IMPURITIES

Specified impurities *A*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B*.



A. (6a*R*,9*R*,10a*R*)-9-[(methylsulfinyl)methyl]-7-propyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline (pergolide sulfoxide),



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B. (6a*R*,9*R*,10a*R*)-9-[(methylsulfonyl)methyl]-7-propyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline (pergolide sulfone).

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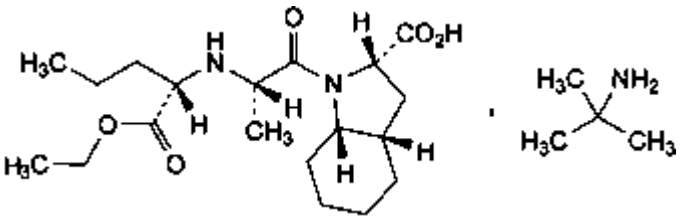
Perindopril Erbumine

General Notices

(Perindopril tert-Butylamine, Ph. Eur. monograph 2019)



$C_{23}H_{43}N_3O_5$ 441.6 *107133-36-8*

Action and use

Angiotensin converting enzyme inhibitor.

Preparation

Perindopril Erbumine Tablets

Ph Eur

DEFINITION

2-Methylpropan-2-amine (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), soluble or sparingly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

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A. Specific optical rotation (2.2.7): -69 to -66 (anhydrous substance).

Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *perindopril tert-butylamine CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

C. Examine the chromatograms obtained in the test for impurity A.

Results In the chromatogram obtained with the test solution a spot is observed with the same R_F as the spot with the higher R_F in the chromatogram obtained with reference solution (c) (*tert*-butylamine).

TESTS

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *perindopril impurity A CRS* in *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 20.0 mL with *methanol R*.

Reference solution (c) To 5 mL of reference solution (a) add 5 mL of a 20 g/L solution of *1,1-dimethylethylamine R* in *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *toluene R*, *methanol R* (1:40:60 *V/V/V*).

Application 10 µL of the test solution and reference solutions (b) and (c).

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Expose to iodine vapour for at least 20 h.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent).

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Stereochemical purity

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in ethanol (96 per cent) R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with ethanol (96 per cent) R. Dilute 1.0 mL of this solution to 10.0 mL with ethanol (96 per cent) R.

Reference solution (b) Dissolve 10 mg of perindopril for stereochemical purity CRS (containing impurity I) in ethanol (96 per cent) R and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 50 °C for the column and the tubing preceding the column (the method has been developed with a temperature of 50 °C for at least 30 cm of the tubing preceding the column).

Mobile phase Mix, in the following order, 21.7 volumes of acetonitrile R1, 0.3 volumes of pentanol R, and 78 volumes of a 1.50 g/L solution of sodium heptanesulfonate R previously adjusted to pH 2.0 with a mixture of equal volumes of perchloric acid R and water for chromatography R.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 215 nm.

Equilibration Minimum 4 h.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with perindopril for stereochemical purity CRS and the chromatogram obtained with reference solution (b) to identify the peak due to impurity I.

Run time 1.5 times the retention time of perindopril.

Relative retention With reference to perindopril (retention time = about 100 min): impurity I = about 0.9.

System suitability:

— the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with perindopril for stereochemical purity CRS;

— signal-to-noise ratio: minimum 3 for the principal peak in the chromatogram obtained with reference solution (a);

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— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to perindopril in the chromatogram obtained with reference solution (b).

Limits:

— *impurity I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *disregard limit*: disregard any peak with a relative retention with reference to perindopril of less than 0.6 or more than 1.4.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or maintain them at a temperature below 10 °C*.

Test solution Dissolve 60 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dissolve 3 mg of *perindopril for peak identification CRS* (containing impurities B, E, F, H and K) in 1 mL of mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 200.0 mL with mobile phase A.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 60 °C for the column and the tubing preceding the column.

Mobile phase:

— *mobile phase A*: *water for chromatography R* adjusted to pH 2.5 with a mixture of equal volumes of *perchloric acid R*; and *water for chromatography R*;

— *mobile phase B*: 0.03 per cent *V/V* solution of *perchloric acid R* in *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 60	95 → 40	5 → 60

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *perindopril for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, E, F, H and K.

Relative retention With reference to perindopril (retention time = about 25 min): impurity B = about 0.68; impurity K = about 0.72; impurity E = about 1.2; impurity F = about 1.6; impurity H = about 1.8 (impurity H may be eluted as 1 or 2 peaks).

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity K.

Limits:

— *impurity E*: not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity B*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities F, H*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.50 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.160 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 22.08 mg of $C_{23}H_{43}N_3O_5$.

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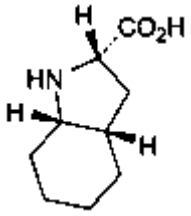
STORAGE

In an airtight container.

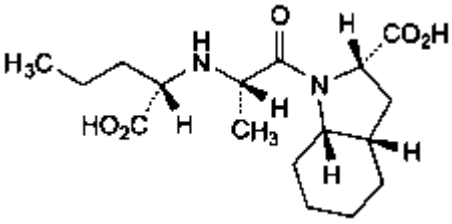
IMPURITIES

Specified impurities *A, B, E, F, H, I.*

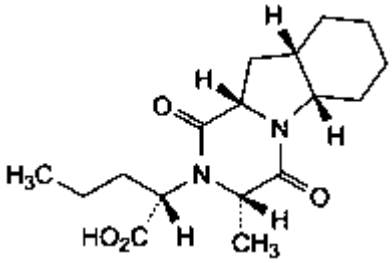
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, G, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z, AA, BB, CC.*



A. (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid,



B. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxybutyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (perindoprilat),



C. (2*S*)-2-[(3*S*,5a*S*,9a*S*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]pentanoic acid,

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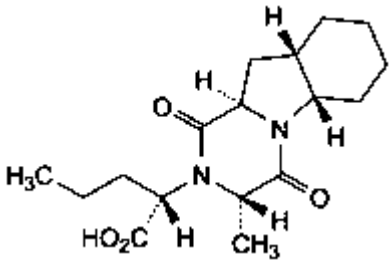
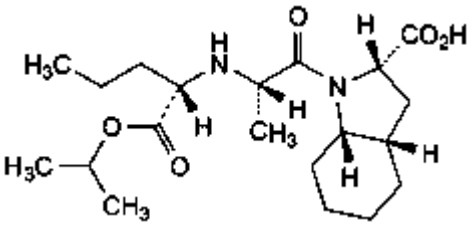
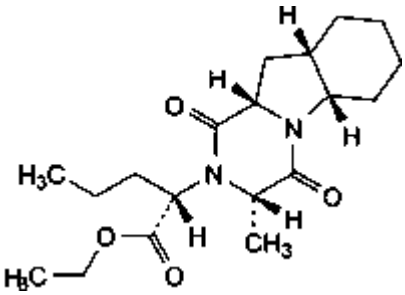


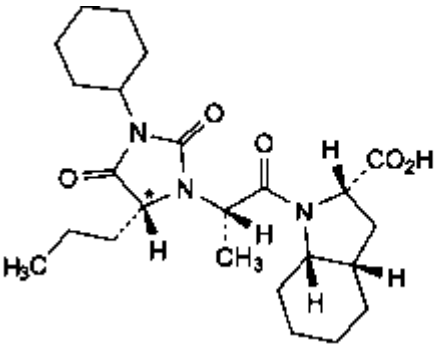
D. (2*S*)-2-[(3*S*,5a*S*,9a*S*,10a*R*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]pentanoic acid,



E. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-[(1-methylethoxy)carbonyl]butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,



F. ethyl (2*S*)-2-[(3*S*,5a*S*,9a*S*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]pentanoate,



G. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[(5*RS*)-3-cyclohexyl-2,4-dioxo-5-propylimidazolidin-1-yl]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,

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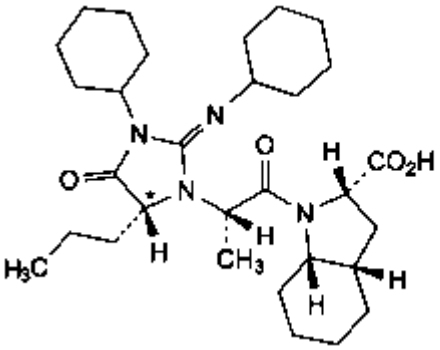
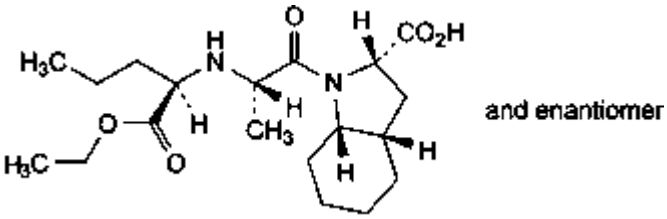
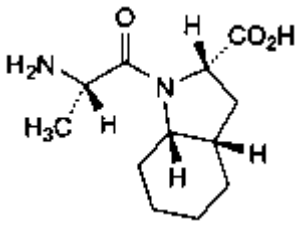


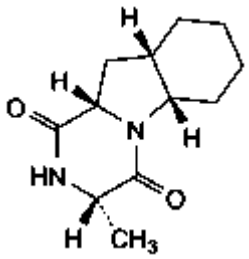
H. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[(5*RS*)-3-cyclohexyl-2-(cyclohexylimino)-4-oxo-5-propylimidazolidin-1-yl]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,



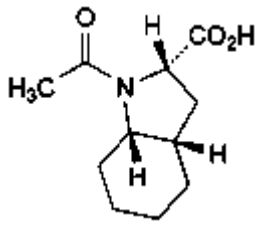
I. (2*RS*,3a*RS*,7a*RS*)-1-[(2*RS*)-2-[[(1*SR*)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid ((±)-1″-*epi*-perindopril),



J. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-aminopropanoyl]octahydro-1*H*-indole-2-carboxylic acid,



K. (3*S*,5a*S*,9a*S*,10a*S*)-3-methyldecahydropyrazino[1,2-*a*]indole-1,4-dione,



L. (2*S*,3a*S*,7a*S*)-1-acetyloctahydro-1*H*-indole-2-carboxylic acid,

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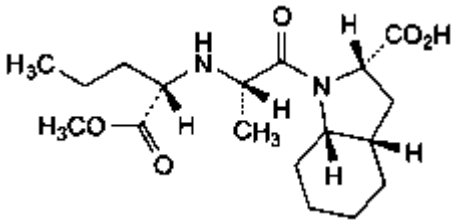
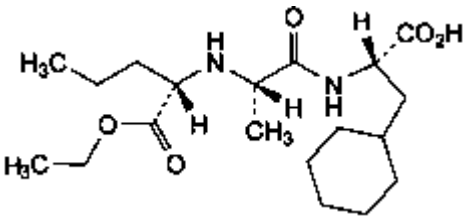
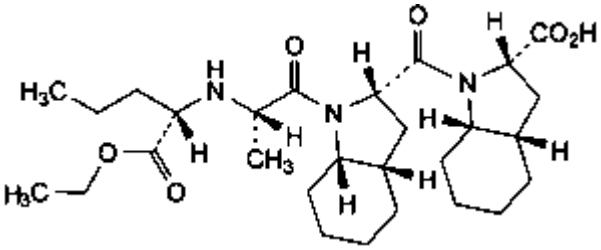


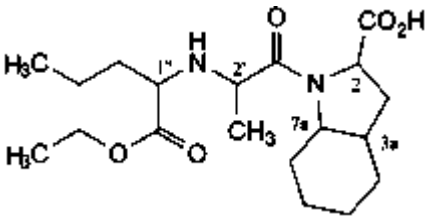
M. (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(methoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,



N. (2*S*)-3-cyclohexyl-2-[[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)butyl]amino]propanoyl]amino]propanoic acid,



O. (2*S*,3a*S*,7a*S*)-1-[[(2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indol-2-yl]carbonyl]octahydro-1*H*-indole-2-carboxylic acid,



1-[2-[[1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid,

P. (2*RS*,3a*RS*,7a*RS*)-, (2′*SR*)-, (1″*RS*)-:
(±)-2′-*epi*-perindopril,

Q. (2*RS*,3a*RS*,7a*SR*)-, (2′*RS*)-, (1″*RS*)-:
(±)-7a-*epi*-perindopril,

R. (2*RS*,3a*SR*,7a*RS*)-, (2′*RS*)-, (1″*RS*)-:
(±)-3a-*epi*-perindopril,

S. (2*SR*,3a*RS*,7a*RS*)-, (2′*RS*)-, (1″*RS*)-:
(±)-2-*epi*-perindopril,

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T. (2*RS*,3a*RS*,7a*RS*)-, (2′*SR*)-, (1″*SR*)-:

(±)-1″,2′-di-*epi*-perindopril,

U. (2*RS*,3a*RS*,7a*SR*)-, (2′*RS*)-, (1″*SR*)-:

(±)-1″,7a-di-*epi*-perindopril,

V. (2*SR*,3a*SR*,7a*RS*)-, (2′*RS*)-, (1″*RS*)-:

(±)-2,3a-di-*epi*-perindopril,

W. (2*SR*,3a*RS*,7a*RS*)-, (2′*RS*)-, (1″*SR*)-:

(±)-1″,2-di-*epi*-perindopril,

X. (2*SR*,3a*RS*,7a*SR*)-, (2′*RS*)-, (1″*RS*)-:

(±)-2,7a-di-*epi*-perindopril,

Y. (2*SR*,3a*RS*,7a*RS*)-, (2′*SR*)-, (1″*RS*)-:

(±)-2,2′-di-*epi*-perindopril,

Z. (2*RS*,3a*SR*,7a*RS*)-, (2′*RS*)-, (1″*SR*)-:

(±)-1″,3a-di-*epi*-perindopril,

AA. (2*RS*,3a*SR*,7a*SR*)-, (2′*RS*)-, (1″*RS*)-:

(±)-3a,7a-di-*epi*-perindopril,

BB. (2*RS*,3a*SR*,7a*RS*)-, (2′*SR*)-, (1″*RS*)-:

(±)-2′,3a-di-*epi*-perindopril,

CC. (2*RS*,3a*RS*,7a*SR*)-, (2′*SR*)-, (1″*RS*)-:

(±)-2′,7a-di-*epi*-perindopril.

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Perindopril Erbumine Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Perindopril Erbumine Tablets contain Perindopril Erbumine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of perindopril erbumine, $C_{19}H_{32}N_2O_5,C_4H_{11}N$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powdered tablets containing 50 mg of Perindopril Erbumine in 10 mL of *dichloromethane* and centrifuge for 5 minutes. Filter the supernatant liquid (Whatman GF/C is suitable), extract the filtrate with 10 mL of *water* and wash the upper aqueous layer with two 10-mL quantities of *hexane*. Evaporate the aqueous layer to dryness on a water bath and dry the residue at 60° at a pressure not exceeding 0.7 kPa, taking care to avoid excessive heating. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *infrared absorption spectrum* of *perindopril erbumine BPCRS*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of 0.05M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute with 0.05M *hydrochloric acid*, if necessary, to produce a solution expected to contain 0.0004% w/v of Perindopril Erbumine.

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(2) 0.0004% w/v of *perindopril erbumine BPCRS* in 0.05M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil 3 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

34 volumes of *acetonitrile* and 66 volumes of *water*, adjusted to pH 2.0 with a mixture of equal volumes of *perchloric acid* and *water*.

DETERMINATION OF CONTENT

Calculate the total content of perindopril erbumine, $C_{19}H_{32}N_2O_5,C_4H_{11}N$, in the medium from the chromatograms obtained and using the declared content of $C_{19}H_{32}N_2O_5,C_4H_{11}N$, in *perindopril erbumine BPCRS*.

LIMITS

The amount of perindopril erbumine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) To a quantity of the powdered tablets containing 16 mg of Perindopril Erbumine, add 7 mL and mix with the aid of ultrasound. Dilute to 10 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.16% w/v of *perindopril for peak identification EPCRS*.

(4) 0.01% w/v of *perindopril impurity standard BPCRS*.

(5) Dilute 2 volumes of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.0 mm) packed with spherical *octylsilyl silica gel for chromatography* (5 µm) (Inertsil C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A *water* adjusted to pH 2.5 with a mixture of equal volumes of *perchloric acid* and *water*.

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Mobile phase B 0.03% v/v solution of *perchloric acid* in *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-(5 - t)	95	5	isocratic
(5 - t)-(60 - t)	95→40	5→60	linear gradient
(60 – t)-(65 - t)	40→95	60→5	linear gradient

Use the chromatogram supplied with *perindopril for peak identification EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities B, E, F, H and K. When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to perindopril (retention time = about 25 minutes) are: impurity B = about 0.68; impurity K = about 0.72; impurity E = about 1.2; impurity F = about 1.6; impurity H = about 1.8 (impurity H may be eluted as 1 or 2 peaks).

Use the chromatogram supplied with *perindopril impurity standard BPCRS* and the chromatogram obtained with solution (4) to identify the peaks due to impurities C and D. When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to perindopril (retention time = about 25 minutes) are: impurity C = about 1.25; impurity D = about 1.3.

The isocratic step is described for a chromatographic system with a dwell volume (*D*) of 2 mL. If *D* is different from 2 mL, correct the gradient times with the value t, calculated using the following expression:

$$\frac{D-2}{flowrate}$$

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *perindopril for peak identification EPCRS* and the *peak-to-valley* ratio is at least 3, where H_p is the height above the baseline of the peak due to impurity B and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity K.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B or F is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity C or D is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

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the area of any peak corresponding to impurity E is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of all the *secondary peaks* excluding any peaks corresponding to impurities B, C, D, E and F is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) To a quantity of the powdered tablets add sufficient of the mobile phase to produce a solution containing 0.004% w/v of Perindopril Erbumine, mix with the aid of ultrasound and filter.
(2) 0.004% w/v of *perindopril erbumine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but with an injection volume of 20 µL.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{32}N_2O_5,C_4H_{11}N$ in the tablets using the declared content of $C_{19}H_{32}N_2O_5,C_4H_{11}N$ in *perindopril erbumine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Perindopril Erbumine.

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Peritoneal Dialysis Solutions

General Notices

(Solutions for Peritoneal Dialysis, Ph. Eur. monograph 0862)

Ph Eur

DEFINITION

Preparations for intraperitoneal use containing electrolytes with a concentration close to the electrolytic composition of plasma. They contain glucose in varying concentrations or other suitable osmotic agents.

Solutions for peritoneal dialysis are supplied in:

— rigid or semi-rigid plastic containers;

— flexible plastic containers fitted with a special connecting device; these are generally filled to a volume below their nominal capacity and presented in closed protective envelopes;

— glass containers.

The containers and closures comply with the requirements for containers for preparations for parenteral administration (*3.2*).

Several formulations are used. The concentrations of the components per litre of solution are usually in the following range (see Table 0862.-1).

Table 0862.-1.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	125 - 150	125 - 150
Potassium	0 - 4.5	0 - 4.5
Calcium	0 - 2.5	0 - 5.0
Magnesium	0.25 - 1.5	0.50 - 3.0
Acetate and/or lactate and/or hydrogen carbonate	30 - 60	30 - 60
Chloride	90 - 120	90 - 120
Glucose	25 - 250	

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When hydrogen carbonate is present, the solution of sodium hydrogen carbonate is supplied in a container or a separate compartment and is added to the electrolyte solution immediately before use.

Unless otherwise justified and authorised, antioxidants are not added to the solutions.

IDENTIFICATION

According to the stated composition, the solution to be examined gives the following identification reactions (*2.3.1*):

— potassium: reaction (b);

— calcium: reaction (a);

— sodium: reaction (b);

— chlorides: reaction (a);

— acetates: to 5 mL of the solution to be examined add 1 mL of *hydrochloric acid R* in a test-tube fitted with a stopper and a bent tube, heat and collect a few millilitres of distillate; carry out reaction (b) of acetates on the distillate;

— lactates, hydrogen carbonates: the identification is carried out together with the assay;

— magnesium: to 0.1 mL of *titan yellow solution R* add 10 mL of *water R*, 2 mL of the solution to be examined and 1 mL of *1 M sodium hydroxide*; a pink colour is produced;

— glucose: to 5 mL of the solution to be examined, add 2 mL of *dilute sodium hydroxide solution R* and 0.05 mL of *copper sulfate solution R*; the solution is blue and clear; heat to boiling; an abundant red precipitate is formed.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_4 (*2.2.2, Method I*).

pH (*2.2.3*)

5.0 to 6.5. If the solution contains hydrogen carbonate, the pH is 6.5 to 8.0.

Hydroxymethylfurfural

Carry out the test only if glucose is added to the preparation. To a volume of the solution to be examined containing the equivalent of 25 mg of glucose, add 5.0 mL of a 100 g/L solution of *p-toluidine R* in *2-propanol R* containing 10 per cent *V/V* of *glacial acetic acid R*, then add 1.0 mL of a 5 g/L solution of *barbituric acid R*. The absorbance (*2.2.25*) determined at 550 nm after allowing the mixture to stand for 2-3 min is not greater than that of a standard prepared at the same time and in the same manner using a solution containing 10 µg of *hydroxymethylfurfural R* in the same volume as the solution to be examined (400 ppm expressed with reference to the glucose concentration). If the solution contains hydrogen carbonate, use as the standard a solution containing 20 µg of *hydroxymethylfurfural R* (800 ppm expressed with reference to the glucose concentration).

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Aluminium

Maximum 10 µg/L.

Atomic absorption spectrometry (*2.2.23, Method I or II*). Use a matrix modifier (for example *nitric acid R* and *magnesium nitrate R* in *water R*) in the same quantity for the test solution, the reference solutions and the blank solution.

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions. Method I – direct calibration.

Prepare the reference solutions by diluting, for example *aluminium standard solution (10 ppm Al) R* with acidified *water R*.

Reference solutions. Method II – standard additions.

Prepare at least 3 reference solutions in the test solution, in a range spanning the expected aluminium concentration of the test solution, for example by diluting *aluminium standard solution (10 ppm Al) R* with the test solution.

Blank solution *water R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Graphite furnace.

Particulate contamination (*2.9.19, Method I*)

Use 50 mL of the solution to be examined.

Extractable volume (*2.9.17*)

The solution complies with the test prescribed for parenteral infusions.

Sterility (*2.6.1*)

The solution complies with the test.

Bacterial endotoxins (*2.6.14*)

Less than 0.05 IU/mL, unless otherwise justified and authorised.

Pyrogens (*2.6.8*)

Solutions for which a validated test for bacterial endotoxins cannot be carried out comply with the test for pyrogens. Inject per kilogram of the rabbit's mass 10 mL of the solution.

ASSAY

Sodium

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97.5 per cent to 102.5 per cent of the content of sodium (Na) stated on the label.

Atomic emission spectrometry (2.2.22, Method I).

Test solution If necessary, dilute the solution to be examined with water R to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using sodium standard solution (200 ppm Na) R.

Wavelengths 589.0 nm or 589.6 nm (sodium emits as a doublet).

Potassium

95.0 per cent to 105.0 per cent of the content of potassium (K) stated on the label.

Atomic absorption spectrometry (2.2.23, Method I).

Test solution If necessary, dilute the solution to be examined with water R to a concentration suitable for the instrument to be used. To 100 mL of the solution add 10 mL of a 22 g/L solution of sodium chloride R.

Reference solutions Prepare the reference solutions using potassium standard solution (100 ppm K) R. To 100 mL of each reference solution add 10 mL of a 22 g/L solution of sodium chloride R.

Source Potassium hollow-cathode lamp.

Wavelength 766.5 nm.

Atomisation device Air-propane or air-acetylene flame.

Calcium

95.0 per cent to 105.0 per cent of the content of calcium (Ca) stated on the label.

Atomic absorption spectrometry (2.2.23, Method I).

Test solution If necessary, dilute the solution to be examined with water R to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using calcium standard solution (400 ppm Ca) R.

Source Calcium hollow-cathode lamp.

Wavelength 422.7 nm.

Atomisation device Air-propane or air-acetylene flame.

Magnesium

95.0 per cent to 105.0 per cent of the content of magnesium (Mg) stated on the label.

Atomic absorption spectrometry (2.2.23, Method I).

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Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using *magnesium standard solution (100 ppm Mg) R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285.2 nm.

Atomisation device Air-propane or air-acetylene flame.

Total chloride

95.0 per cent to 105.0 per cent of the content of chloride (Cl) stated on the label.

Dilute an accurately measured volume of the solution to be examined containing the equivalent of about 0.68 mEq of chloride with an appropriate volume of *water R* in order to immerse the electrode. Carry out a potentiometric titration (*2.2.20*), using *0.1 M silver nitrate*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Acetate

95.0 per cent to 105.0 per cent of the content of acetate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of acetate, add 10.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of acetate.

Lactate

95.0 per cent to 105.0 per cent of the content of lactate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of lactate, add 10.0 mL of *0.1 M hydrochloric acid*. Add 50 mL of *acetonitrile R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of lactate.

Sodium hydrogen carbonate

95.0 per cent to 105.0 per cent of the content of sodium hydrogen carbonate stated on the label.

Titrate with *0.1 M hydrochloric acid*, a volume of the solution to be examined corresponding to about 0.1 g of sodium hydrogen carbonate, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 8.40 mg of $NaHCO_3$.

Lactate and hydrogen carbonate

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95.0 per cent to 105.0 per cent of the content of lactates and hydrogen carbonates stated on the label.

Liquid chromatography (2.2.29).

Test solution The solution to be examined.

Reference solution Dissolve in 100 mL of *water for chromatography R* quantities of lactates and hydrogen carbonates, accurately weighed, in order to obtain solutions having concentrations representing about 90 per cent, 100 per cent and 110 per cent of the concentrations stated on the label.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *cation-exchange resin R* (9 µm);

— *temperature*: 60 °C.

Mobile phase *0.005 M sulfuric acid* previously degassed with *helium for chromatography R*.

Flow rate 0.6 mL/min.

Detection Differential refractometer.

Injection 20 µL, twice.

Order of elution Lactates, hydrogen carbonates.

Determine the concentration of lactate and hydrogen carbonates in the test solution by interpolating the peak area for lactate and the peak height for hydrogen carbonate from the linear regression curve obtained with the reference solutions.

Reducing sugars

(expressed as glucose): 95.0 per cent to 105.0 per cent of the content of glucose stated on the label.

Transfer a volume of the solution to be examined containing the equivalent of 25 mg of glucose to a 250 mL conical flask with a ground-glass neck and add 25.0 mL of *cupri-citric solution R*. Add a few grains of pumice, fit a reflux condenser, heat so that boiling occurs within 2 min and boil for exactly 10 min. Cool and add 3 g of *potassium iodide R* dissolved in 3 mL of *water R*. Carefully add, in small amounts, 25 mL of a 25 per cent *m/m* solution of *sulfuric acid R*. Titrate with *0.1 M sodium thiosulfate* using *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration using 25.0 mL of *water R*.

Calculate the content of reducing sugars expressed as glucose ($C_6H_{12}O_6$), using Table 0862.-2.

Table 0862.-2.

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Volume of *0.1 M sodium thiosulfate* (mL)	Glucose (mg)
8	19.8
9	22.4
10	25.0
11	27.6
12	30.3
13	33.0
14	35.7
15	38.5
16	41.3

STORAGE

At 4 °C or above.

LABELLING

The label states:

— the formula of the solution for peritoneal dialysis, expressed in grams per litre and in millimoles per litre;

— the calculated osmolarity, expressed in milliosmoles per litre;

— the nominal volume of the solution for peritoneal dialysis in the container;

— that the solution is free from bacterial endotoxins, or where applicable, that it is apyrogenic;

— the storage conditions;

— that the solution is not to be used for intravenous infusion;

— that any unused portion of the solution is to be discarded.

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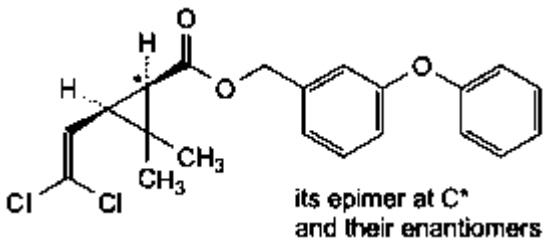
Permethrin (25:75)

General Notices

(Ph. Eur. monograph 1762)



$C_{21}H_{20}Cl_2O_3$ 391.3 Undefined *cis/trans* ratio *52645-53-1*

Action and use

Insecticide.

Ph Eur

DEFINITION

Mixture of the *cis* and *trans* isomers of (3-phenoxyphenyl)methyl (1*RS*,2*RS*)-2-(2,2-dichloroethenyl)-3,3-dimethylcyclopropane-1-carboxylate.

Content

— *total*: 98.0 per cent to 102.0 per cent (anhydrous substance);

— *cis isomer*: 23.0 per cent to 27.0 per cent (anhydrous substance);

— *trans isomer*: 73.0 per cent to 77.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Colourless or slightly brownish viscous liquid, semi-solid or crystalline solid.

Solubility

Practically insoluble in water, very soluble in heptane, freely soluble in anhydrous ethanol, sparingly soluble in ethylene glycol.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *permethrin (25:75) CRS*.

B. Examine the chromatograms obtained in the assay.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time and in *cis/trans* ratio to the 2 principal peaks in the chromatogram obtained with the reference solution (*cis/trans* ratio = about 0.3).

TESTS

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Warm the substance to be examined at 70-85 °C for 20 min. Dissolve 1.0 g of this substance in *heptane R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *permethrin for system suitability CRS* (containing impurities B, C and G) in *heptane R* and dilute to 1.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *heptane R*. Dilute 1.0 mL of this solution to 20.0 mL with *heptane R*.

Column:

— *material*: fused silica;

— *size*: *l* = 15 m, Ø = 0.53 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 1.5 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 12.0 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	45
	2 - 26.5	45 → 290
	26.5 - 40.5	290

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	Time (min)	Temperature (°C)
Injection port		250
Detector		290

Detection Flame ionisation.

Injection 1 µL.

Identification of impurities Use the chromatogram supplied with *permethrin for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, C and G.

Relative retention With reference to permethrin (retention time = about 24 min): impurity B = about 0.5; impurity C = about 0.7; impurity G = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity G and permethrin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.5;

— *impurities B, C*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Water (*2.5.32*)

Maximum 0.25 per cent, determined on 0.100 g using the evaporation technique:

— *temperature*: 110 °C;

— *heating time*: 3 min.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*).

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Test solution Warm the substance to be examined at 70-85 °C for 20 min. Dissolve 0.100 g of this substance in the mobile phase using sonication and dilute to 50.0 mL with the mobile phase.

Reference solution Warm *permethrin (25:75) CRS* at 70-85 °C for 20 min. Dissolve 0.100 g of this substance in the mobile phase using sonication and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *dioxan R*, *heptane R* (1.1:98.9 *V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time Twice the retention time of *cis*-permethrin.

Retention time *cis*-permethrin = about 6 min.

Elution order *cis*-permethrin, *trans*-permethrin.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to *cis*-permethrin and *trans*-permethrin.

Calculation of percentage contents:

— calculate the percentage content of *cis*-permethrin and *trans*-permethrin by normalisation;

— calculate the percentage content of $C_{21}H_{20}Cl_2O_3$ taking into account the assigned content of *permethrin (25:75) CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *B, C*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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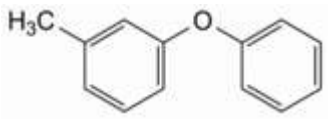
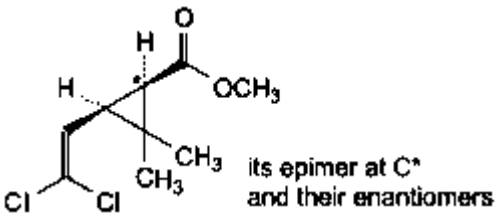
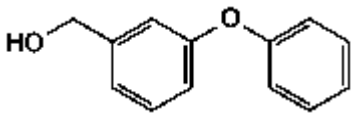
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, D, E, F, G, H.



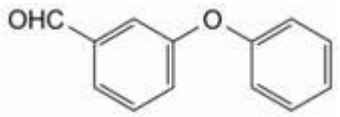
A. 1-methyl-3-phenoxybenzene,



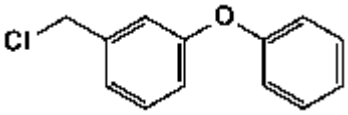
B. methyl (1*RS*,2*RS*)-2-(2,2-dichloroethenyl)-3,3-dimethylcyclopropane-1-carboxylate,



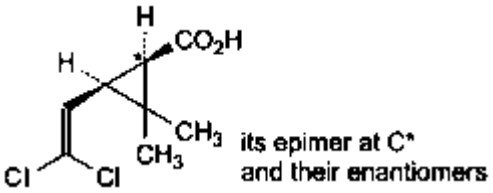
C. (3-phenoxyphenyl)methanol,



D. 3-phenoxybenzaldehyde,



E. 1-(chloromethyl)-3-phenoxybenzene,



F. (1*RS*,2*RS*)-2-(2,2-dichloroethenyl)-3,3-dimethylcyclopropane-1-carboxylic acid,

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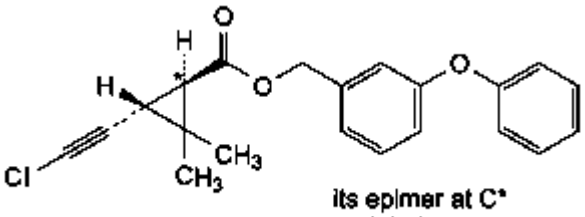
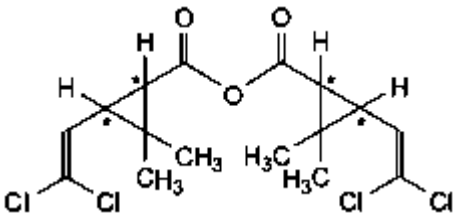


G. 3-(phenoxyphenyl)methyl (1*RS*,2*RS*)-2-(chloroethynyl)-3,3-dimethylcyclopropane-1-carboxylate,



H. 2-(2,2-dichloroethenyl)-3,3-dimethylcyclopropane-1-carboxylic anhydride.

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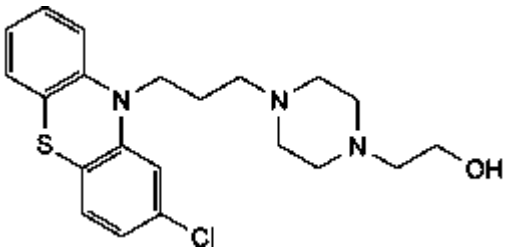
Perphenazine

General Notices

(Ph. Eur. monograph 0629)



$C_{21}H_{26}ClN_3OS$ 404.0 *58-39-9*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

2-[4-[3-(2-Chloro-10*H*-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent). It dissolves in dilute solutions of hydrochloric acid.

IDENTIFICATION

A. Melting point (*2.2.14*): 96 °C to 100 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *perphenazine CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*).

Dissolve 0.20 g in 10 mL of *methanol R*.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use. Carry out the test protected from light.*

Test solution Dissolve 20 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 2 mg of *perphenazine for system suitability CRS* (containing impurities A and B) in 1.0 mL of mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *base-deactivated octylsilyl silica gel for chromatography R* (4 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 35 volumes of *acetonitrile R* and 65 volumes of a 7 g/L solution of *sodium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 10	100 → 80	0 → 20
10 - 33	80 → 30	20 → 70
33 - 48	30 → 100	70 → 0

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 245 nm.

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Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *perphenazine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to perphenazine (retention time = about 12 min): impurity A = about 0.3; impurity B = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity B and perphenazine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.6;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 65 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 20.20 mg of $C_{21}H_{26}ClN_3OS$.

STORAGE

Protected from light.

IMPURITIES

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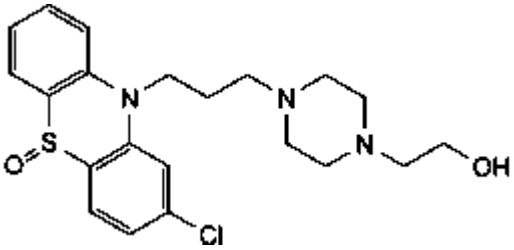
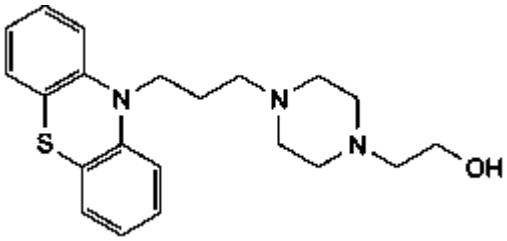
Specified impurities *A, B.*



A. 2-[4-[3-(2-chloro-5-oxido-10*H*-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol,



B. 2-[4-[3-(10*H*-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol.

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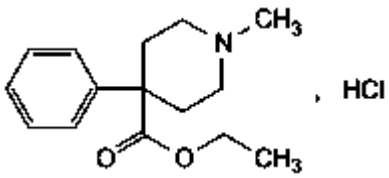
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Pethidine Hydrochloride

General Notices

(Ph. Eur. monograph 0420)



$C_{15}H_{22}ClNO_2$ 283.8 *50-13-5*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Pethidine Injection

Pethidine Tablets

Ph Eur

DEFINITION

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

If intended for use in the manufacture of parenteral preparations, the manufacturing process is validated to show that the content of impurity B is not more than 0.1 ppm.

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 187 °C to 190 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of pethidine hydrochloride*.

C. Dissolve 0.1 g in 10 mL of *ethanol R* and add 10 mL of *picric acid solution R*. A crystalline precipitate is formed which, when washed with *water R* and dried at 100-105 °C, melts (2.2.14) at 186 °C to 193 °C. Mix equal quantities of the precipitate and the substance to be examined and determine the melting point of the mixture. The melting point is at least 20 °C lower than that of the precipitate.

D. To 5 mL of solution S (see Tests) add 5 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.3 mL of *0.01 M hydrochloric acid*. The solution is red.

Impurity B

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.100 g of the substance to be examined in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 25.0 mL with the same mixture of solvents.

Test solution (b) Dissolve 0.125 g of the substance to be examined in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 10.0 mL with the same mixture of solvents.

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Reference solution (a) Dilute 0.5 mL of test solution (a) to 100.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Reference solution (b) Dissolve 10.0 mg of *pethidine impurity A CRS* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (c) Dissolve 12.5 mg of *1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine R* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 10.0 mL with the same mixture of solvents. Dilute 1.0 mL of the solution to 100.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Reference solution (d) Dilute 5.0 mL of reference solution (b) and 1.0 mL of reference solution (c) to 100.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm,

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 340 m^2/g, a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase:

— *mobile phase A*: mix equal volumes of a 42.0 g/L solution of *sodium perchlorate R* and of a 11.6 g/L solution of *phosphoric acid R*, adjust to pH 2.0 with *triethylamine R*,

— *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	80 → 75	20 → 25
15 - 31	75 → 55	25 → 45
31 - 40	55	45

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL; inject test solution (b) and reference solution (d).

Relative retention With reference to pethidine (retention time = about 24 min): impurity B = about 0.66; impurity A = about 0.68.

System suitability Reference solution (d):

— *signal-to-noise ratio*: minimum 10 for the first peak,

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— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity B, and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (10 ppm) if intended for non-parenteral administration.

Related substances

Liquid chromatography (*2.2.29*) as described in the test for impurity B with the following modifications.

Injection 20 µL; inject test solution (a) and reference solution (a).

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.220 g in 50 mL of *alcohol R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.38 mg of $C_{15}H_{22}ClNO_2$.

STORAGE

In an airtight container, protected from light.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

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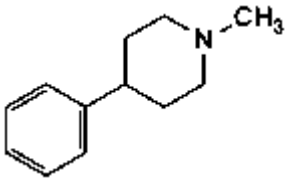
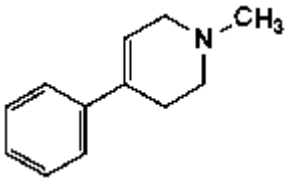
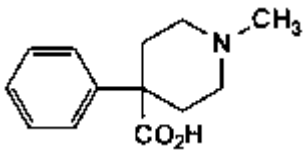


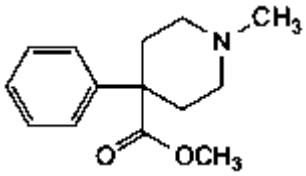
A. 1-methyl-4-phenylpiperidine (MPP),



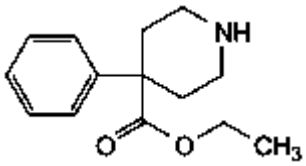
B. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),



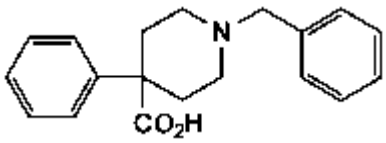
C. 1-methyl-4-phenylpiperidine-4-carboxylic acid,



D. methyl 1-methyl-4-phenylpiperidine-4-carboxylate,



E. ethyl 4-phenylpiperidine-4-carboxylate,



F. 1-benzyl-4-phenylpiperidine-4-carboxylic acid,

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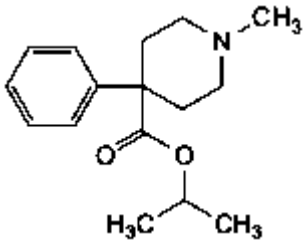
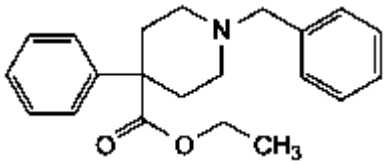
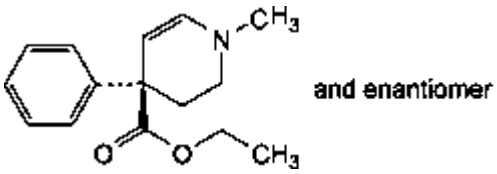


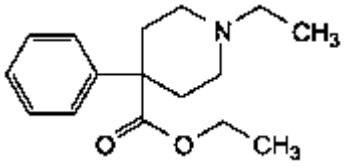
G. 1-methylethyl 1-methyl-4-phenylpiperidine-4-carboxylate,



H. ethyl 1-benzyl-4-phenylpiperidine-4-carboxylate,



I. ethyl (4*RS*)-1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine-4-carboxylate,



J. ethyl 1-ethyl-4-phenylpiperidine-4-carboxylate.

Ph Eur

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Pethidine Injection

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Pethidine Injection is a sterile solution of Pethidine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

PRODUCTION

The manufacturing process of Pethidine Hydrochloride, used in the formulation of Pethidine Injection, is validated to show that the content of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine is not more than 0.1 ppm.

Content of pethidine hydrochloride, $C_{15}H_{21}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume containing 50 mg of Pethidine Hydrochloride add sufficient 1M *sodium hydroxide* to make strongly alkaline to *litmus paper* and extract with two 10 mL quantities of *chloroform*. Wash the combined extracts with 5 mL of *water*, dry over *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. Remove the last traces of chloroform by drying the residual oil at 60° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of pethidine (*RS 266*).

B. Yields the reactions characteristic of *chlorides*, Appendix VI.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection containing 0.1 g of Pethidine Hydrochloride to 25 mL with a mixture of 20 volumes of *acetonitrile R1* and 80 volumes of *water*.

(2) Dilute 0.5 volumes of solution (1) to 100 volumes with a mixture of 20 volumes of *acetonitrile R1* and 80 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *spherical end-capped octadecylsilyl silica gel for chromatography* (5 µm) with a specific surface area of 340 m^2/g, a pore size of 10 nm and a carbon loading of 19% (Kromasil C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Mix equal volumes of a 4.2% w/v solution of *sodium perchlorate* and a 1.2% w/v solution of *orthophosphoric acid*. Adjust the pH to 2.0 with *triethylamine*.

Mobile phase B *acetonitrile R1*.

Time	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0–15	80 → 75	20 → 25
15–31	75 → 55	25 → 45
31–40	55	45
40–41	55 → 80	45 → 20
41–50	80	20

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than 0.1 times the area of the peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection, if necessary, with sufficient *water* to produce a solution containing 0.1% w/v of Pethidine Hydrochloride and further dilute 3 volumes of the resulting solution to 25 volumes with the mobile phase.

(2) Dilute 3 volumes of a 0.10% w/v solution of *pethidine hydrochloride BPCRS* to 25 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

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(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

11 volumes of *acetonitrile* and 9 volumes of a mixture prepared in the following manner: dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water*, add 10 mL *triethylamine*, mix well and adjust the solution to pH 7.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The *column efficiency*, determined on the peak due to pethidine in the chromatogram obtained with solution (2), should be at least 8000 *theoretical plates* per metre.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{21}NO_2$,HCl in the injection using the declared content of $C_{15}H_{21}NO_2$,HCl in *pethidine hydrochloride BPCRS*.

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Pethidine Tablets

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Pethidine Tablets contain Pethidine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pethidine hydrochloride, $C_{15}H_{21}NO_2$,HCl

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Pethidine Hydrochloride with 20 mL of *chloroform*, filter, evaporate the filtrate to dryness and dry the residue at a pressure of 2 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pethidine hydrochloride (*RS 267*).

B. Shake a quantity of the powdered tablets containing 0.2 g of Pethidine Hydrochloride with 20 mL of *water* and filter. To 5 mL of the filtrate add 10 mL of *picric acid solution R1*. The *melting point* of the crystals so obtained, after washing with *water*, is about 190°, Appendix V A.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *kieselguhr G* as the coating substance but allowing the solvent front to ascend 12 cm above the line of application. Impregnate the dry plate by placing it in a closed tank containing a mixture of 10 volumes of *2-phenoxyethanol* and 90 volumes of *acetone* so that the plate dips about 5 mm beneath the surface of the liquid, allowing the impregnation solvent to ascend at least 15 cm, removing the plate from the tank and drying in a current of air. Use immediately, with the flow of the mobile phase in the same direction as the impregnation. Use as the mobile phase the upper layer obtained by shaking together 1 volume of *diethylamine*, 8 volumes of *2-phenoxyethanol* and 100 volumes of *petroleum spirit* (*boiling range, 50° to 70°*) and allowing it to settle.

Apply separately to the plate 5 µL of each of the following solutions. For solution (1) use the upper layer obtained by shaking a quantity of the powdered tablets containing 0.1 g of Pethidine Hydrochloride with 5 mL of *water*, filtering, shaking the filtrate with 0.5 mL of 5M *sodium hydroxide* and 2 mL of *ether* and allowing the layers to separate. For solution (2) dilute 0.5 mL of solution (1) to 50 mL with *ether*.

After removal of the plate, allow it to dry in air for 10 minutes, return the plate to the tank and repeat the development. Remove the plate, allow it to dry in air for 10 minutes and spray with a 0.2% w/v solution of *2,7-dichlorofluorescein* in *methanol*. Allow the plate to stand for 5

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minutes and spray with *water* until the background is white to pale yellow. Examine in daylight. The chromatograms show red or orange spots. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%). Examine without delay under *ultraviolet light* (*365 nm*). The chromatograms show spots with intense yellow fluorescence. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.5 g of Pethidine Hydrochloride in 40 mL of *water*, add 2 mL of 5M *sodium hydroxide* and extract immediately with quantities of 25, 10 and 10 mL of *chloroform*. Wash each extract with the same 15 mL of *water* and filter into a dry flask. Titrate the combined extracts, which should be clear and free from droplets of *water*, with *0.05M perchloric acid VS* using 0.15 mL of *1-naphtholbenzein solution* as indicator. Each mL of *0.05M perchloric acid VS* is equivalent to 14.19 mg of $C_{15}H_{21}NO_2$,HCl.

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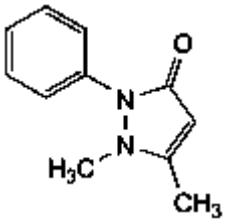
Phenazone

General Notices

(Ph. Eur. monograph 0421)



$C_{11}H_{12}N_2O$ 188.2 *60-80-0*

Action and use

Analgesic; used to test hepatic drug-metabolizing activity.

Ph Eur

DEFINITION

1,5-Dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

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A. Melting point (2.2.14): 109 °C to 113 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison phenazone CRS.

C. To 1 mL of solution S (see Tests) add 4 mL of water R and 0.25 mL of dilute sulfuric acid R. Add 1 mL of sodium nitrite solution R; a green colour develops.

D. To 1 mL of solution S add 4 mL of water R and 0.5 mL of ferric chloride solution R2. A red colour develops which is discharged on the addition of dilute sulfuric acid R.

TESTS

Solution S

Dissolve 2.5 g in carbon dioxide-free water R and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of phenolphthalein solution R; the solution is colourless. Add 0.2 mL of 0.01 M sodium hydroxide; the solution is red. Add 0.25 mL of methyl red solution R and 0.4 mL of 0.01 M hydrochloric acid; the solution is red or yellowish-red.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of phenazone impurity A CRS in the mobile phase, add 10 mL of the test solution and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 5.0 mg of phenazone impurity A CRS in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 6.0 mm;

— *stationary phase*: spherical octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Dissolve 6.8 g of potassium dihydrogen phosphate R in water R and dilute to 1000 mL with the same solvent. Add 2 mL of triethylamine R and adjust to pH 7.0 with sodium hydroxide solution R. Add 430 mL of methanol R.

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Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 3 times the retention time of phenazone.

Relative retention With reference to phenazone (retention time = about 13 min): impurity A = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity A and phenazone.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.05 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Chlorides (2.4.4)

Maximum 100 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 100 ppm.

Dissolve 1.5 g in *distilled water R* and dilute to 15 mL with the same solvent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 6 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 20 mL of *water R*. Add 2 g of *sodium acetate R*, 1 mL of *dilute acetic acid R* and 25.0 mL of *0.05 M iodine*. Allow to stand protected from light for 30 min. Add 25 mL of *methylene chloride R* and shake until the precipitate dissolves. Titrate with *0.1 M*

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sodium thiosulfate, using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration.

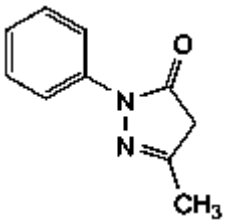
1 mL of *0.05 M iodine* is equivalent to 9.41 mg of $C_{11}H_{12}N_2O$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A.*



A. 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one.

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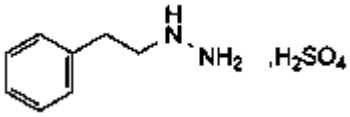
Phenelzine Sulfate

General Notices

Phenelzine Sulphate



234.3 *156-51-4*

Action and use

Monoamine oxidase inhibitor; antidepressant.

Preparation

Phenelzine Tablets

DEFINITION

Phenelzine Sulfate is phenethylhydrazine hydrogen sulfate. It contains not less than 98.0% and not more than 102.0% of $C_8H_{12}N_2,H_2SO_4$, calculated with reference to the dried substance.

CHARACTERISTICS

A white powder or pearly platelets.

Freely soluble in *water*; practically insoluble in *ethanol (96%)* and in *ether*.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.1% w/v solution in 0.05M *sulfuric acid* exhibits three well-defined maxima, at 252, 258 and 263 nm. The *absorbances* at the maxima are about 0.62, about 0.77 and about 0.58, respectively.

B. Dissolve 0.1 g in 5 mL of *water*, make alkaline with 5M *sodium hydroxide* and add 1 mL of *cupri-tartaric solution* R1. A red precipitate is produced.

C. Yields reaction A characteristic of *sulfates*, Appendix VI.

TESTS

Melting point

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164° to 168°, Appendix V A.

Loss on drying

When dried over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 24 hours, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.026% w/v of the substance to be examined in the mobile phase.

(2) 0.026% w/v *phenelzine sulfate BPCRS* *in the mobile phase*.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *methanol R2* and 60 volumes of a solution of 0.216% w/v *sodium octanesulfonate* and 0.68% w/v *potassium dihydrogen phosphate* previously adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the principal peak is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{12}N_2,H_2SO_4$ in the substance being examined using the declared content of $C_8H_{12}N_2,H_2SO_4$ in *phenelzine sulfate BPCRS*.

STORAGE

Phenelzine Sulfate should be protected from light.

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Phenelzine Tablets

General Notices

Action and use

Monoamine oxidase inhibitor; antidepressant.

DEFINITION

Phenelzine Tablets contain Phenelzine Sulfate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of phenelzine, $C_8H_{12}N_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 30 mg of phenelzine with 25 mL of *water* for 5 minutes and filter. Make the filtrate alkaline with 5M *sodium hydroxide* and extract with two 25 mL quantities of *chloroform*. Extract the combined chloroform layers with two 25 mL quantities of 0.05M *sulfuric acid* and dilute the combined extracts to 100 mL with 0.05M *sulfuric acid*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits three well-defined maxima, at 252, 258 and 263 nm.

B. Extract a quantity of the powdered tablets containing the equivalent of 30 mg of phenelzine with 10 mL of *water* and filter. Make 5 mL of the filtrate alkaline with 5M *sodium hydroxide* and add 1 mL of *cupri-tartaric solution R1*. A red precipitate is produced.

C. Extract a quantity of the powdered tablets containing the equivalent of 45 mg of phenelzine with 5 mL of *water* and filter. The filtrate yields the reactions characteristic of *sulfates*, Appendix VI.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 0.1 g of phenelzine add 20 mL of *water* and 2 mL of 2M *hydrochloric acid*, heat to boiling and boil for 30 seconds, stirring constantly. Add 25 mL of *water*, cool, add 2 g of *sodium hydrogen carbonate* and 50 mL of *0.05M iodine VS*, stopper the flask and allow to stand for 90 minutes. Add 15 mL of 2M *hydrochloric acid* and titrate with 0.1M *sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the powder. The difference between the titrations represents the amount of iodine required. Each mL of *0.05M iodine VS* is equivalent to 3.405 mg of $C_8H_{12}N_2$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of phenelzine.

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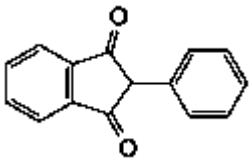
Phenindione

General Notices



$C_{15}H_{10}O_2$ 222.2 *83-12-5*

Action and use

Oral anticoagulant (indanedione).

Preparation

Phenindione Tablets

DEFINITION

Phenindione is 2-phenylindane-1,3-dione. It contains not less than 98.0% and not more than 102.0% of $C_{15}H_{10}O_2$, calculated with reference to the dried substance.

CHARACTERISTICS

Soft, white or creamy white crystals.

Very slightly soluble in *water*; slightly soluble in *ethanol (96%)* and in *ether*. Solutions are yellow to red.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of phenindione *(RS 268)*.

TESTS

Melting point

148° to 151°, Appendix V A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

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(1) 0.25% w/v of the substance being examined in *methanol*.

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

(3) 0.0005% w/v each of *phenindione BPCRS*, *phenylacetic acid* (impurity 3), *benzalphthalide* (impurity 4) and *phthalic acid* (impurity 5) in *methanol*.

(4) Dilute 1 volume of solution (2) to 10 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (X-bridge shield C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a chilled auto-sampler temperature of 4°.

(f) Use a detection wavelength of 220 nm.

(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes *acetonitrile*, 10 volumes of a 1.36% w/v *dipotassium hydrogen phosphate* solution previously adjusted to pH 3.0 with *orthophosphoric acid*, and 80 volumes of *water*.

Mobile phase B 10 volumes *water* and 90 volumes *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-0.5	80	20	isocratic
0.5-10	80→50	20→50	linear gradient
10-13	50	50	isocratic
13-21	50→30	50→70	linear gradient
21-22	30→80	70→20	linear gradient
22-25	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenindione (retention time about 7 minutes) are: impurity 5, about 0.2; impurity 3, about 0.4; impurity 1, about 0.6; impurity 4, about 1.8 and impurity 2, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to impurity 5 and impurity 3 is at least 4.6.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak due to impurity 1 or 2 is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Loss on drying

When dried at 105° for 2 hours, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A 2% v/v *glacial acetic acid* in *acetonitrile*.

(1) Mix with the aid of ultrasound 25 mg of Phenindione in 20 mL of 0.01M *sodium hydroxide* and add 50 mL of solution A. Dilute to 100 mL with solution A.
(2) 25 mg of *phenindione BPCRS* in 20 mL of 0.01M *sodium hydroxide* and 30 mL of solution A. Make up to 100 mL with solution A.
(3) 5 mg each of *phenindione BPCRS* and *phenylacetic acid* (impurity 3) in 5 mL of 0.01M *sodium hydroxide* and 5 mL of solution A. Make up to 20 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 250 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes *acetonitrile* and 60 volumes of 0.68 % w/v *potassium dihydrogen phosphate* previously adjusted to pH 3.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

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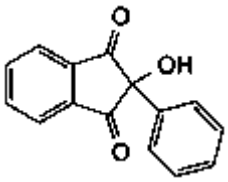
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 3 and phenindione is at least 6.0.

DETERMINATION OF CONTENT

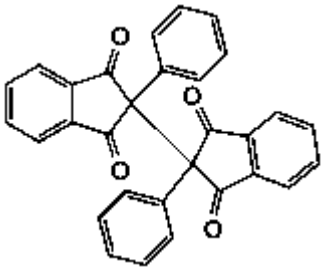
Calculate the content of $C_{15}H_{10}O_2$ using the declared content of $C_{15}H_{10}O_2$ in *phenindione BPCRS*.

IMPURITIES

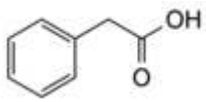
The impurities limited by the requirements of this monograph include:



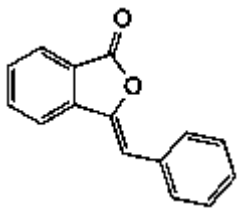
1. 2-hydroxy-2-phenyl-1*H*-indene-1,3(2*H*)-dione



2. 2′-diphenyl-1*H*,1′*H*-[2,2′-bi-indene]-1,1′,3,3′(2*H*,2′*H*)-tetrone



3. phenylacetic acid



4. 3-benzylidene-2-benzofuran-1(3*H*)-one (benzalphthalide)

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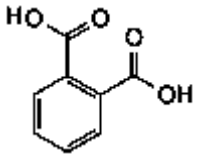

5. phthalic acid

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Phenindione Tablets

General Notices

Action and use

Oral anticoagulant (indanedione).

DEFINITION

Phenindione Tablets contain Phenindione.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of phenindione, $C_{15}H_{10}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.2 g of Phenindione with 50 mL of *dichloromethane*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of phenindione (*RS 268*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(2) Use 900 mL of a solution containing 0.68% w/v of *potassium dihydrogen phosphate* and 0.18% w/v of *sodium hydroxide*, pH adjusted to 8.0, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter through a 0.45-µm nylon filter. Measure the absorbance of the filtrate, suitably diluted with the dissolution medium if necessary, at the maximum at 328 nm, Appendix II B using dissolution medium in the reference cell.
(2) Measure the absorbance of a suitable solution of *phenindione BPCRS* using dissolution medium in the reference cell, at the maximum at 328 nm.

DETERMINATION OF CONTENT

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Calculate the total content of Phenindione, $C_{15}H_{10}O_2$, in the medium from the absorbances obtained and using the declared content of $C_{15}H_{10}O_2$ in *phenindione BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 25 mg of Phenindione in *methanol*. Add sufficient *methanol* to produce a solution expected to contain 0.25% w/v of Phenindione, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) 0.00375% w/v of *phenindione impurity 1 BPCRS* in *methanol*.

(4) 0.0005% w/v of *phenindione BPCRS*, *phenylacetic acid* (impurity 3), *benzalphthalide* (impurity 4) and *phthalic acid* (impurity 5) in *methanol*.

(5) Dilute 1 volume of solution (2) to 10 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (X-bridge shield C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use an autosampler temperature of 4°.

(f) Use a detection wavelength of 220 nm.

(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A

10 volumes of *acetonitrile*, 10 volumes of a 1.36% w/v *dipotassium hydrogen phosphate* solution previously adjusted to pH 3.0 with *orthophosphoric acid* and 80 volumes of *water*.

Mobile phase B

10 volumes of *water* and 90 volumes of *acetonitrile*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-0.5	80	20	isocratic
0.5-10	80→50	20→50	linear gradient
10-13	50	50	isocratic
13-21	50→30	50→70	linear gradient
21-22	30→80	70→20	linear gradient
22-25	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenindione (retention time, about 7 minutes) are: impurity 5, about 0.2; impurity 3, about 0.4; impurity 1, about 0.6; impurity 4, about 1.7; impurity 2, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to impurity 3 and phenindione is at least 6.0;

the *resolution* between the peaks due to phenindione and impurity 4 is at least 8.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1.5%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the total impurity content is not greater than 2.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A 2% v/v *glacial acetic acid* in *acetonitrile*.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 25 mg of Phenindione in 20 mL of 0.01M *sodium hydroxide* and 50 mL of solution A. Dilute to 100 mL with solution A, centrifuge and use the supernatant liquid.

(2) 0.025% w/v of *phenindione BPCRS* in a mixture of 20 volumes of 0.01M *sodium hydroxide* and 80 volumes of solution A.

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(3) 0.025% w/v *phenindione BPCRS* and *phenylacetic acid* (impurity 3) in a mixture of 20 volumes of 0.01M *sodium hydroxide* and 80 volumes of solution A.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 4°.

(f) Use a detection wavelength of 250 nm.

(g) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes *acetonitrile* and 60 volumes of 0.68 % w/v *potassium dihydrogen phosphate* previously adjusted to pH 3.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 3 and phenindione is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{10}O_2$ in the tablets using the declared content of $C_{15}H_{10}O_2$ in *phenindione BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenindione.

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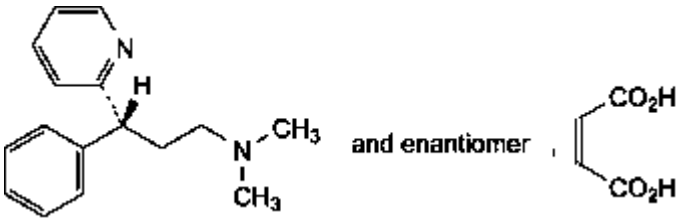
Pheniramine Maleate

General Notices

(Ph. Eur. monograph 1357)



$C_{20}H_{24}N_2O_4$ 356.4 *132-20-7*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

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DEFINITION

(3*RS*)-*N*,*N*-Dimethyl-3-phenyl-3-(pyridin-2-yl)propan-1-amine (*Z*)-butenedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), in methanol and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

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A. Melting point (2.2.14): 106 °C to 109 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 40.0 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 5.0 mL of the solution to 50.0 mL with *0.1 M hydrochloric acid*.

Spectral range 220-320 nm.

Absorption maximum At 265 nm.

Shoulder At 261 nm.

Specific absorbance at the absorption maximum 200 to 220.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *pheniramine maleate CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 65 mg of *maleic acid R* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 0.10 g of *pheniramine maleate CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *anhydrous formic acid R*, *methanol R*, *di-isopropyl ether R* (3:7:20:70 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

Results The chromatogram obtained with the test solution shows 2 clearly separated spots; the upper spot is similar in position and size to the spot in the chromatogram obtained with reference solution (a); the lower spot is similar in position and size to the lower spot in the chromatogram obtained with reference solution (b).

TESTS

Solution S

Dissolve 2.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

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pH (*2.2.3*)

4.5 to 5.5.

Dissolve 0.20 g in 20 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, mobile phase A (10:90 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 10.0 mg of *pheniramine impurity A CRS* and 10 mg of *4-benzylpyridine R* (impurity B) in 10.0 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the solvent mixture.

Reference solution (d) Dilute 1.0 mL of the test solution to 10.0 mL with reference solution (a). Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.30 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase:

— *mobile phase A*: dissolve 5.056 g of *sodium heptanesulfonate R* in 900 mL of *water R*, adjust to pH 2.5 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 37	90 → 62	10 → 38

Flow rate 1 mL/min.

Detection Spectrophotometer at 264 nm.

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Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B.

Relative retention With reference to pheniramine (retention time = about 31 min): maleic acid = about 0.1; impurity A = about 0.9; impurity B = about 0.97.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity B and pheniramine.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: maximum 1.0 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to maleic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.130 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 17.82 mg of $C_{20}H_{24}N_2O_4$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B.*

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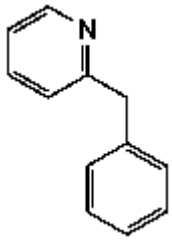
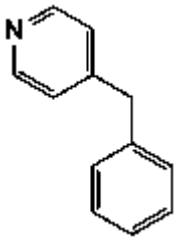


A. 2-benzylpyridine,



B. 4-benzylpyridine.

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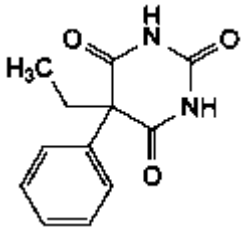
Phenobarbital

General Notices

(Ph. Eur. monograph 0201)



$C_{12}H_{12}N_2O_3$ 232.2 *50-06-6*

Action and use

Barbiturate.

Preparations

Phenobarbital Elixir

Phenobarbital Tablets

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DEFINITION

5-Ethyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent).

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It forms water-soluble compounds with alkali hydroxides, carbonates and ammonia.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Determine the melting point (2.2.14) of the substance to be examined. Mix equal parts of the substance to be examined and phenobarbital CRS and determine the melting point of the mixture. The difference between the melting points (which are about 176 °C) is not greater than 2 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison phenobarbital CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in ethanol (96 per cent) R and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 10 mg of phenobarbital CRS in ethanol (96 per cent) R and dilute to 10.0 mL with the same solvent.

Plate TLC silica gel GF_{254} plate R.

Mobile phase concentrated ammonia R, ethanol (96 per cent) R, methylene chloride R (5:15:80 *V/V/V*); use the lower layer.

Application 10 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives the reaction of non-nitrogen substituted barbiturates (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 1.0 g in a mixture of 4 mL of dilute sodium hydroxide solution R and 6 mL of water R.

Acidity

Boil 1.0 g with 50 mL of water R for 2 min, allow to cool and filter. To 10 mL of the filtrate add 0.15 mL of methyl red solution R. The solution is orange-yellow. Not more than 0.1 mL of 0.1 M sodium hydroxide is required to produce a pure yellow colour.

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Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.125 g of the substance to be examined in 5.0 mL of *methanol R* and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Mix 1.0 mL of the test solution and 20.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase. Mix 1.0 mL of this solution with 2.0 mL of *methanol R* and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *phenobarbital impurity A CRS* and 5.0 mg of *phenobarbital impurity B CRS* in 2.0 mL of *methanol R* and dilute to 10.0 mL with the mobile phase. Mix 1.0 mL of this solution with 20.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 6.60 g of *sodium acetate R* in 900 mL of *water R*, add 3 mL of *glacial acetic acid R*, adjust to pH 4.5 with *glacial acetic acid R* and dilute to 1000 mL with *water R*. Mix 60 volumes of this solution with 40 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 2.1 times the retention time of phenobarbital.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to phenobarbital (retention time = about 14 min): impurity A = about 0.2; impurity B = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B.

Limits:

— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity B*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

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— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

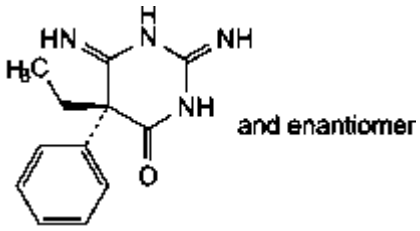
Dissolve 0.200 g in 40 mL of *ethanol (96 per cent) R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 23.22 mg of $C_{12}H_{12}N_2O_3$.

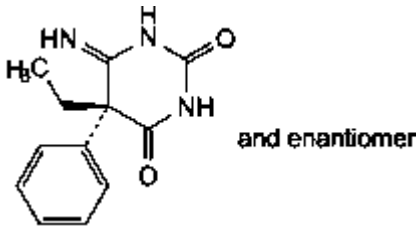
IMPURITIES

Specified impurities A, B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. (5*RS*)-5-ethyl-2,6-diimino-5-phenyltetrahydropyrimidin-4(1*H*)-one,



B. (5*RS*)-5-ethyl-6-imino-5-phenyldihydropyrimidine-2,4(1*H*,3*H*)-dione,

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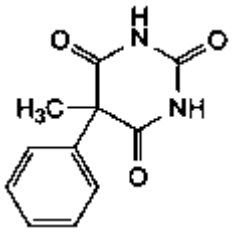

C. 5-methyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione.

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Phenobarbital Elixir

General Notices

Phenobarbital Oral Solution

Phenobarbital Elixir from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Barbiturate.

DEFINITION

Phenobarbital Elixir is an *oral solution* containing 0.3% w/v of Phenobarbital in a suitable flavoured vehicle containing a sufficient volume of *ethanol (96 %)* or of an appropriate Dilute Ethanol to give a final concentration of 38% v/v of ethanol.

The elixir complies with the requirements stated under Oral Liquids and with the following requirements.

Content of phenobarbital, $C_{12}H_{12}N_2O_3$

0.285 to 0.315% w/v.

IDENTIFICATION

Extract 50 mL with three 50-mL quantities of ether, wash the combined ether extracts with 20 mL of water, discard the washings, extract the ether solution with a mixture of 5 mL of 2M *sodium hydroxide* and 25 mL of *water* and then with two 5-mL quantities of *water*. Acidify the combined aqueous extracts to *litmus paper* with *2M hydrochloric acid*, extract with four 25-mL quantities of *ether*, wash the combined ether extracts with two 2-mL quantities of *water*, wash the combined aqueous washings with 10 mL of *ether*, add the ether washings to the combined ether extracts, evaporate the ether and dry the residue of phenobarbital to constant weight at 105°. The *infrared absorption spectrum* of the residue Appendix II A, is concordant with the reference spectrum of phenobarbital *(RS 270)*.

TESTS

Ethanol content

36 to 40% v/v, Appendix VIII F.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the elixir containing 100 mg of Phenobarbital in 100 mL of the mobile phase.

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(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase. Dilute 1 volume of the resulting solution to 50 volumes with the mobile phase.

(3) 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb S5 ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the run time of phenobarbital.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution containing 0.66% w/v of *sodium acetate* in *water*, adjusted to pH 4.5 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to phenobarbital (retention time, about 9 minutes) are: impurity A, about 0.4; impurity B, about 0.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a weighed quantity of the elixir containing 100 mg of Phenobarbital in 100 mL of the mobile phase. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(2) 0.01% of *phenobarbital BPCRS* in the mobile phase.

(3) A solution of 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under the test for Related substances.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Determine the weight per mL of the elixir, Appendix V G, and calculate the content of $C_{12}H_{12}N_2O_3$, weight in volume, using the declared content of $C_{12}H_{12}N_2O_3$ in *phenobarbital BPCRS*.

STORAGE

Phenobarbital Elixir should be protected from light.

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Phenobarbital Injection

General Notices

Action and use

Barbiturate.

DEFINITION

Phenobarbital Injection is a sterile solution containing Phenobarbital Sodium in a suitable vehicle.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phenobarbital sodium, $C_{12}H_{11}N_2NaO_3$

95.0 to 105.0% w/v.

IDENTIFICATION

To a quantity of the injection containing 1 g of Phenobarbital Sodium, add 15 mL of *water*, make slightly acidic with 1M *sulfuric acid*, filter and retain the residue. Wash the residue with *water* and dry at 105°. The *infrared absorption spectrum* of the residue Appendix II A, is concordant with the reference spectrum of phenobarbital *(RS 270)*.

TESTS

Alkalinity

pH, 10.0 to 11.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the injection containing 100 mg of Phenobarbital in 100 mL of the mobile phase.

(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase. Dilute 1 volume of the resulting solution to 50 volumes with the mobile phase.

(3) 0.0005% w/v each of *phenobarbital impurity A EPCRS* and *phenobarbital impurity B EPCRS*.

(4) 0.0015% w/v of *2-phenylbutanoic acid* in the mobile phase.

(5) 0.002% w/v of *(2-phenylbutanoyl) urea* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb S5 ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of phenobarbital.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution containing 0.66% w/v of *sodium acetate* in *water*, adjusted to pH 4.5 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to phenobarbital (retention time, about 9 minutes) are: impurity A, about 0.4; impurity B, about 0.5; 2-phenylbutanoic acid, about 2.0; (2-phenylbutanoyl) urea, about 2.30.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-phenylbutanoic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1.5%);

the area of any peak corresponding to (2-phenylbutanoyl) urea (impurity E) is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (2.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of *secondary peaks*, excluding any peaks corresponding to 2-phenylbutanoic acid or (2-phenylbutanoyl) urea, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the injection containing 100 mg of Phenobarbital in 100 mL of the mobile phase. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(2) 0.01% w/v of *phenobarbital BPCRS* in the mobile phase.

(3) 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under the test for Related substances.

SYSTEM SUITABILITY

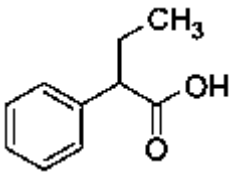
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

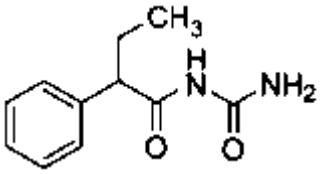
Calculate the content of $C_{12}H_{11}N_2NaO_3$ in the injection from the chromatograms obtained using the declared content of $C_{12}H_{12}N_2O_3$ in *phenobarbital BPCRS*. Each mg of *phenobarbital BPCRS* is equivalent to 1.095 mg of phenobarbital sodium.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenobarbital Sodium and:



1. 2-phenylbutanoic acid



E. (2*RS*)-*N*-carbamimidoyl-2-phenylbutanamide; (2-Phenylbutanoyl)urea

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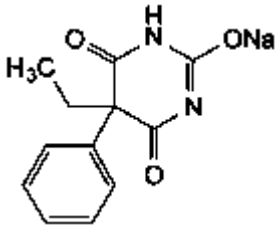
Phenobarbital Sodium

General Notices

(Ph. Eur. monograph 0630)



$C_{12}H_{11}N_2NaO_3$ 254.2 *57-30-7*

Action and use

Barbiturate.

Preparations

Phenobarbital Injection

Paediatric Phenobarbital Oral Solution

Phenobarbital Sodium Tablets

Ph Eur

DEFINITION

Sodium derivative of 5-ethyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

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Freely soluble in carbon dioxide-free water (a small fraction may be insoluble), soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E.

A. Acidify 10 mL of solution S (see Tests) with *dilute hydrochloric acid R* and shake with 20 mL of *ether R*. Separate the ether layer, wash with 10 mL of *water R*, dry over *anhydrous sodium sulfate R* and filter. Evaporate the filtrate to dryness and dry the residue at 100-105 °C (test residue). Determine the melting point (2.2.14) of the test residue. Mix equal parts of the test residue and *phenobarbital CRS* and determine the melting point of the mixture. The difference between the melting points (which are about 176 °C) is not greater than 2 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Use the test residue obtained in identification test A.

Comparison *phenobarbital CRS*.

If the spectra obtained in the solid state show differences, dissolve the test residue and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *ethanol (50 per cent V/V) R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 9 mg of *phenobarbital CRS* in *ethanol (50 per cent V/V) R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *ethanol (96 per cent) R*, *methylene chloride R* (5:15:80 *V/V/V*); use the lower layer.

Application 10 µL.

Development Over 2/3 of the plate.

Detection Examine immediately in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives the reaction of non-nitrogen substituted barbiturates (2.3.1).

E. It gives reaction (a) of sodium (2.3.1).

TESTS

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Solution S

Dissolve 5.0 g in *ethanol (50 per cent V/V) R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

Maximum 10.2.

Dissolve 5.0 g as completely as possible in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 55.0 mg of the substance to be examined in 2.0 mL of *methanol R* and dilute to 10.0 mL with the mobile phase.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in 10.0 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Mix 1.0 mL of test solution (b) and 20.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *phenobarbital impurity A CRS* and 5.0 mg of *phenobarbital impurity B CRS* in 2.0 mL of *methanol R* and dilute to 10.0 mL with the mobile phase. Mix 1.0 mL of the solution and 20.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25.0 mg of *phenobarbital CRS* in 10.0 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 6.6 g of *sodium acetate R* in 900 mL of *water R*, add 3 mL of *glacial acetic acid R*, adjust to pH 4.5 with *glacial acetic acid R* and dilute to 1000 mL with *water R*. Mix 60 volumes of this solution and 40 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 2.5 times the retention time of phenobarbital.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

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Relative retention With reference to phenobarbital (retention time = about 13 min): impurity A = about 0.29; impurity B = about 0.32.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurity B, use the concentration of impurity B in reference solution (b);

— for impurities other than A and B, use the concentration of phenobarbital sodium in reference solution (a).

Limits:

— *impurities A, B*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 7.0 per cent, determined on 0.500 g by drying in an oven at 150 °C for 4 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection 10 µL of test solution (b) and reference solution (c).

Run time 1.5 times the retention time of phenobarbital.

Calculate the percentage content of $C_{12}H_{11}N_2NaO_3$ taking into account the assigned content of *phenobarbital CRS* and a conversion factor of 1.095.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A, B*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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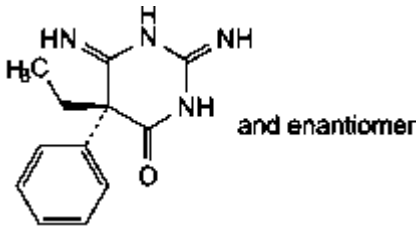
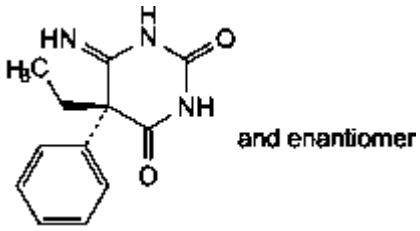
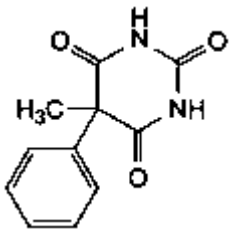
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, E.



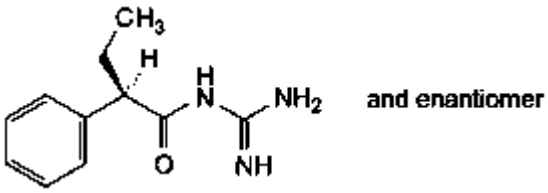
A. (5*RS*)-5-ethyl-2,6-diimino-5-phenyltetrahydropyrimidin-4(1*H*)-one,



B. (5*RS*)-5-ethyl-6-imino-5-phenyldihydropyrimidine-2,4(1*H*,3*H*)-dione,



C. 5-methyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione,



E. (2*RS*)-*N*-carbamimidoyl-2-phenylbutanamide.

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Phenobarbital Tablets

General Notices

Phenobarbital Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Barbiturate.

DEFINITION

Phenobarbital Tablets contain Phenobarbital.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of phenobarbital, $C_{12}H_{12}N_2O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Weigh and powder 20 tablets. Extract a quantity of the powder containing 0.3 g of Phenobarbital in a continuous extraction apparatus with *ether* until complete extraction is achieved. Remove the ether and dry the residue of phenobarbital to constant weight at 105°. Heat 0.2 g of the residue on a water bath with 15 mL of *ethanol (25%)* until dissolved, filter while hot and allow the filtrate to cool. Filter, wash the crystals with a small quantity of *ethanol (25%)* and dry at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of phenobarbital *(RS 270)*. If the spectra obtained are not concordant, heat the residue in a sealed tube at 105° for 1 hour and prepare a new spectrum of the residue.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered tablets containing 100 mg of Phenobarbital with 100 mL of the mobile phase and filter.

(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase. Dilute 1 volume of the resulting solution to 50 volumes with the mobile phase.

(3) 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5µm) (Spherisorb ODS 2 is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of phenobarbital.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution of 0.66% w/v of *sodium acetate* in *water*, adjusted to pH 4.5 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to phenobarbital (retention time, about 9 minutes) are: impurity A, about 0.4; impurity B, about 0.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered tablets containing 100 mg of Phenobarbital with 80 mL of the mobile phase, dilute to 100 mL with the mobile phase and filter. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(2) 0.01% of *phenobarbital BPCRS* in the mobile phase.

(3) 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

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DETERMINATION OF CONTENT

Calculate the content of $C_{12}H_{12}N_2O_3$ in the tablets from the chromatograms obtained using the declared content of $C_{12}H_{12}N_2O_3$ in *phenobarbital BPCRS*.

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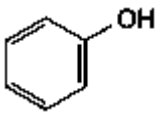
Phenol

General Notices

(Ph. Eur. monograph 0631)



C_6H_6O 94.1 *108-95-2*

Action and use

Antiseptic; antimicrobial preservative; antipruritic.

Preparations

Aqueous Phenol Injection

Oily Phenol Injection

Phenol and Glycerol Injection

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

Colourless or faintly pink or faintly yellowish, crystals or crystalline masses, deliquescent.

Solubility

Soluble in water, very soluble in ethanol (96 per cent), in glycerol and in methylene chloride.

IDENTIFICATION

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A. Dissolve 0.5 g in 2 mL of *concentrated ammonia R*. The substance dissolves completely. Dilute to about 100 mL with *water R*. To 2 mL of this solution add 0.05 mL of *strong sodium hypochlorite solution R*. A blue colour develops and becomes progressively more intense.

B. To 1 mL of solution S (see Tests) add 10 mL of *water R* and 0.1 mL of *ferric chloride solution R1*. A violet colour is produced which disappears on addition of 5 mL of *2-propanol R*.

C. To 1 mL of solution S add 10 mL of *water R* and 1 mL of *bromine water R*. A white precipitate is formed.

TESTS

Solution S

Dissolve 1.0 g in *water R* and dilute to 15 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

Acidity

To 2 mL of solution S add 0.05 mL of *methyl orange solution R*. The solution is yellow.

Freezing point (*2.2.18*)

Minimum 39.5 °C.

Residue on evaporation

Maximum 0.05 per cent.

Evaporate 5.000 g to dryness on a water-bath and dry at 100-105 °C for 1 h. The residue weighs a maximum of 2.5 mg.

ASSAY

Dissolve 2.000 g in *water R* and dilute to 1000.0 mL with the same solvent. Transfer 25.0 mL of the solution to a ground-glass-stoppered flask and add 50.0 mL of *0.0167 M bromide-bromate* and 5 mL of *hydrochloric acid R*, close the flask, allow to stand with occasional swirling for 30 min. Then allow to stand for 15 min. Add 5 mL of a 200 g/L solution of *potassium iodide R*, shake and titrate with *0.1 M sodium thiosulfate* until a faint yellow colour remains. Add 0.5 mL of *starch solution R* and 10 mL of *chloroform R* and continue the titration with vigorous shaking. Carry out a blank titration.

1 mL of *0.0167 M bromide-bromate* is equivalent to 1.569 mg of C_6H_6O.

STORAGE

In an airtight container, protected from light.

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Phenol and Glycerol Injection

General Notices

DEFINITION

Phenol and Glycerol Injection is a sterile solution containing 5% w/v of Phenol in Glycerol that has been previously dried at 120° for 1 hour.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phenol, C_6H_6O

4.75 to 5.25% w/v.

CHARACTERISTICS

A pale straw-coloured, viscous solution.

IDENTIFICATION

A. Add *bromine water* to a 1% w/v solution. A white precipitate is produced, which, on the continued addition of *bromine water*, at first dissolves then reappears and becomes permanent.

B. To 0.5 mL add 5 mL of *water* and 0.05 mL of *sodium nitrite solution* and carefully pour on to the surface of *sulfuric acid*. A coloured zone, red above and green below, appears at the junction of the two layers.

C. When heated on a borax bead in a naked flame, it imparts a green colour to the flame.

ASSAY

Dissolve 2 g in sufficient *water* to produce 50 mL, transfer 25 mL to a 500 mL glass-stoppered flask and add 50 mL of 0.05M *bromine VS* and 5 mL of *hydrochloric acid*, stopper, swirl occasionally during 30 minutes and allow to stand for a further 15 minutes. Add 5 mL of a 20% w/v solution of *potassium iodide*, taking care to avoid loss of bromine, shake thoroughly and titrate with 0.1M *sodium thiosulfate VS* until only a faint yellow colour remains. Add 0.1 mL of *starch mucilage* and 10 mL of *chloroform* and complete the titration with vigorous shaking. Repeat the operation without the injection. The difference between the titrations represents the amount of bromine required. Each mL of 0.05M *bromine VS* is equivalent to 1.569 mg of C_6H_6O. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of C_6H_6O.

STORAGE

Phenol and Glycerol Injection should be protected from light.

LABELLING

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The strength is stated as the percentage w/v of Phenol.

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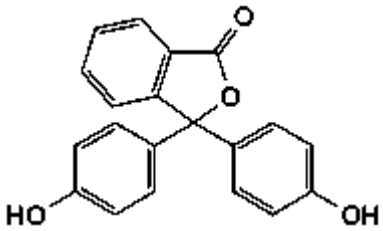
Phenolphthalein

General Notices

(Ph. Eur. monograph 1584)



$C_{20}H_{14}O_4$ 318.3 *77-09-8*

Action and use

Stimulant laxative.

Ph Eur

DEFINITION

Phenolphthalein contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 3,3-bis(4-hydroxyphenyl)isobenzofuran-1(3*H*)-one, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, practically insoluble in water, soluble in ethanol (96 per cent).

It melts at about 260 °C.

IDENTIFICATION

A. Dissolve 25.0 mg in *alcohol R* and dilute to 100.0 mL with the same solvent (solution A). To 2.0 mL of solution A add 5.0 mL of *1 M hydrochloric acid*and dilute to 50.0 mL with *alcohol R* (solution A_1). To 10.0 mL of solution A add 5.0 mL of *1 M hydrochloric acid* and dilute to 50.0 mL with *alcohol R* (solution A_2). To 2.0 mL of solution A add 5.0 mL of *1 M sodium hydroxide* and dilute to 50.0 mL with *alcohol R* (solution B). Examined between 220 nm and 250 nm (*2.2.25*), solution A_1 shows an absorption maximum at 229 nm. The specific absorbance at the maximum at 229 nm is 922 to 1018. Examined between 250 nm and 300 nm, solution A_2 shows an absorption maximum

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at 276 nm. The specific absorbance at the maximum at 276 nm is 142 to 158. Examined between 230 nm and 270 nm, solution B shows an absorption maximum at 249 nm. The specific absorbance at the maximum at 249 nm is 744 to 822.

B. Dissolve about 10 mg in *alcohol R*. Add 1 mL of *dilute sodium hydroxide solution R*. The solution is red. Add 5 mL of *dilute sulfuric acid R*. The colour disappears.

TESTS

Solution S

To 2.0 g add 40 mL of *distilled water R* and heat to boiling. Cool and filter.

Appearance of solution

Dissolve 0.20 g in 5 mL of *alcohol R*. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.15 mL of *bromothymol blue solution R1*. Add 0.05 mL of *0.01 M hydrochloric acid*, the solution is yellow. Add 0.10 mL of *0.01 M sodium hydroxide*, the solution is blue.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel F_{254} plate R*.

Test solution Dissolve 0.5 g of the substance to be examined in *alcohol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 10 mL with *alcohol R*. Dilute 5 mL of this solution to 100 mL with *alcohol R*.

Reference solution (b) Dissolve 25 mg of *fluorene R* in *alcohol R*, add 0.5 mL of the test solution and dilute to 10 mL with *alcohol R*.

Apply to the plate 5 µL of the test solution and 5 µL of each of the reference solutions. Develop over a path corresponding to two-thirds of the plate height using a mixture of 50 volumes of *acetone R* and 50 volumes of *methylene chloride R*. Allow the plate to dry in air. Examine in ultraviolet light at 254 nm and re-examine after exposure to ammonia vapour. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Chlorides (*2.4.4*)

Dilute 10 mL of solution S to 15 mL with *water R*. The solution complies with the limit test for chlorides (100 ppm).

Sulfates (*2.4.13*)

15 mL of solution S complies with the limit test for sulfates (200 ppm).

Loss on drying (*2.2.32*)

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Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 5 mL of *dimethylformamide R*. Add 5 mL of *sodium carbonate solution R*, 10 mL of *sodium hydrogen carbonate solution R*, 35 mL of *water R* and 50.0 mL of *0.05 M iodine*. Add 10 mL of *methylene chloride R* and 20 mL of *dilute sulfuric acid R*. Titrate the excess of iodine with *0.1 M sodium thiosulfate*, using 0.3 mL of *starch solution R* added towards the end of the titration, as indicator. Carry out a blank titration.

1 mL of *0.05 M iodine* is equivalent to 3.979 mg of $C_{20}H_{14}O_4$.

STORAGE

Store protected from light.

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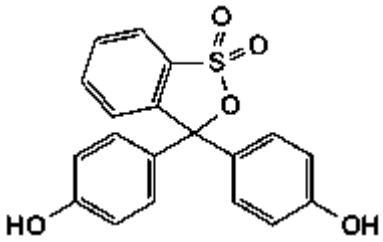
Phenolsulfonphthalein

General Notices

Phenolsulphonphthalein

(Ph. Eur. monograph 0242)



$C_{19}H_{14}O_5S$ 354.4 *143-74-8*

Action and use

Measurement of renal function; marker in drug absorption studies.

Ph Eur

DEFINITION

Phenolsulfonphthalein (phenol red) contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 3,3-bis(4-hydroxyphenyl)-3*H*-2,1-benzoxathiole 1,1-dioxide, calculated with reference to the dried substance.

CHARACTERS

A bright-red to dark-red, crystalline powder, very slightly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 10 mg in a 10 g/L solution of *sodium carbonate R* and dilute to 200.0 mL with the sodium carbonate solution. Dilute 5.0 mL of the solution to 100.0 mL with a 10 g/L solution of *sodium carbonate R*. Examined between 400 nm and 630 nm (*2.2.25*), the solution shows an absorption maximum at 558 nm. The specific absorbance at the maximum is 1900 to 2100.

B. Dissolve about 10 mg in 1 mL of *dilute sodium hydroxide solution R* and add 9 mL of *water R*. The solution is deep red. To 5 mL of the solution add a slight excess of *dilute sulfuric acid R*. The colour becomes orange.

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C. To 5 mL of the solution prepared for identification test B add 1 mL of *0.0167 M bromide-bromate* and 1 mL of *dilute hydrochloric acid R*, shake and allow to stand for 15 min. Make alkaline with *dilute sodium hydroxide solution R*. An intense violet-blue colour is produced.

TESTS

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 0.1 g of the substance to be examined in *0.1 M sodium hydroxide* and dilute to 5 mL with the same solvent.

Reference solution Dilute 0.5 mL of the test solution to 100 mL with *0.1 M sodium hydroxide*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 25 volumes of *glacial acetic acid R*, 25 volumes of *water R* and 100 volumes of *tert-pentyl alcohol R*. Allow the plate to dry in air until the solvent has evaporated and expose the plate to the vapour from *concentrated ammonia R*. Examine in ultraviolet light at 254 nm. Not more than one spot, apart from the principal spot, appears in the chromatogram obtained with the test solution and this spot is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Insoluble matter

To 1.0 g of the finely powdered substance to be examined add 12 mL of *sodium hydrogen carbonate solution R*. Allow to stand for 1 h, shaking frequently. Dilute to 100 mL with *water R* and allow to stand for 15 h. Centrifuge at 2000 *g* to 3000 *g*, for 30 min, decant the supernatant and wash the residue with 25 mL of a 10 g/L solution of *sodium hydrogen carbonate R* and then 25 mL of *water R*. Dry at 100 °C to 105 °C. The residue weighs not more than 5 mg (0.5 per cent).

Loss on drying (*2.2.32*)

Not more than 1.0 per cent, determined on 1.00 g of the powdered substance to be examined by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.2 per cent, determined on 0.5 g.

ASSAY

Dissolve 0.900 g in 15 mL of *1 M sodium hydroxide* and dilute to 250.0 mL with *water R*. To 10.0 mL of the solution in a glass-stoppered flask add 25 mL of *glacial acetic acid R*, 20.0 mL of *0.0167 M potassium bromate*, 5 mL of a 100 g/L solution of *potassium bromide R* and 5 mL of *hydrochloric acid R*. Allow to stand protected from light for 15 min, add 10 mL of a 100 g/L solution of *potassium iodide R* and titrate immediately with *0.1 M sodium thiosulfate*, using 0.1 mL of *starch solution R* as indicator.

1 mL of *0.0167 M potassium bromate* is equivalent to 4.43 mg of $C_{19}H_{14}O_5S$.

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Phenoxybenzamine Capsules

General Notices

Action and use

Alpha-adrenoceptor antagonist; treatment of hypertension in phaeochromocytoma.

DEFINITION

Phenoxybenzamine Capsules contain Phenoxybenzamine Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of phenoxybenzamine hydrochloride, $C_{18}H_{22}ClNO,HCl$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared in *methanol*.

(1) Shake a quantity of the powdered capsule contents containing 10 mg of Phenoxybenzamine Hydrochloride with 5 mL with *methanol*. Dilute to 10 mL and filter (a Whatman GF/C filter is suitable).

(2) 0.1% w/v of *phenoxybenzamine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F* (Merck silica gel 60 plates are suitable) .

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

20 volumes of *dichloromethane* and 80 volumes of *acetone*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

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Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 500 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.01M *hydrochloric acid* if necessary, to produce a solution expected to contain 0.002% w/v of Phenoxybenzamine Hydrochloride.

(2) 0.002% w/v of *phenoxybenzamine hydrochloride BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Kromasil C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 268 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

45 volumes of a 0.22% w/v solution of *anhydrous sodium dihydrogen orthophosphate*, previously adjusted to pH 3.0 with *orthophosphoric acid*, and 55 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions, the retention time of phenoxybenzamine is about 11 minutes.

DETERMINATION OF CONTENT

Calculate the total content of phenoxybenzamine hydrochloride, $C_{18}H_{22}ClNO,HCl$, in the medium from the chromatograms obtained and using the declared content of $C_{18}H_{22}ClNO,HCl$ in *phenoxybenzamine hydrochloride BPCRS*.

LIMITS

The amount of phenoxybenzamine hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *acetonitrile*.

(1) Shake a quantity of the capsule contents containing 80 mg of Phenoxybenzamine Hydrochloride with 50 mL and dilute to 100 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) Add 0.5 mL of 0.1M *sodium hydroxide* to 10 mL of 0.08% w/v of *phenoxybenzamine hydrochloride BPCRS* in *acetonitrile* (generation of impurity B and impurity 1).

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a flow rate of 0.6 mL per minute. For solution (1), allow the chromatography to proceed for 1.5 times the retention time of phenoxybenzamine.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenoxybenzamine (retention time about 35 minutes) are: impurity B, about 0.1 and impurity 1, about 0.15.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity B and impurity 1 is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (3) (0.4%);

the sum of the areas of any other *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *acetonitrile*.

(1) Mix, with the aid of ultrasound and occasional swirling, a quantity of the capsule contents containing 50 mg of Phenoxybenzamine Hydrochloride with 30 mL of *acetonitrile*. Dilute to produce 50 mL and filter. Dilute 1 volume of the filtrate to 5 volumes.
(2) 0.02% w/v of *phenoxybenzamine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{22}ClNO,HCl$ in the capsules using the declared content of $C_{18}H_{22}ClNO,HCl$ in *phenoxybenzamine hydrochloride BPCRS*.

IMPURITIES

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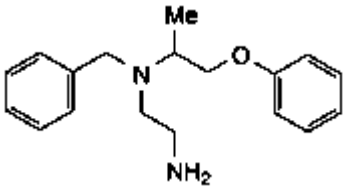
The impurities limited by the requirements of this monograph include those listed under Phenoxybenzamine Hydrochloride and:



1. 2-(benzyl-[1-phenoxypropan-2-yl]amino)amine.

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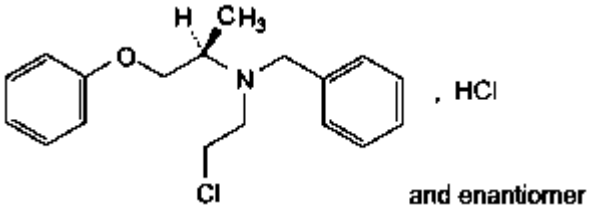
Phenoxybenzamine Hydrochloride

General Notices

(Ph. Eur. monograph 2983)



$C_{18}H_{23}Cl_2NO$ 340.3 *63-92-3*

Action and use

Alpha-adrenoceptor antagonist

Preparation

Phenoxybenzamine Capsules

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DEFINITION

(2*RS*)-*N*-Benzyl-*N*-(2-chloroethyl)-1-phenoxypropan-2-amine hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *phenoxybenzamine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in *acetonitrile R*, using sonication if necessary, and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *phenoxybenzamine impurity B CRS* in *acetonitrile R*, using sonication if necessary, and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 25.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 5 mg of *phenoxybenzamine for system suitability CRS* (containing impurity A) in *acetonitrile R* and dilute to 5 mL with the same solvent.

Reference solution (c) Dissolve 25.0 mg of *phenoxybenzamine hydrochloride CRS* in *acetonitrile R*, using sonication if necessary, and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 0.95 g of *potassium dihydrogen phosphate R* and 2.2 g of *dipotassium hydrogen phosphate R* in 1000 mL of *water for chromatography R* and adjust to pH 7.5 with *dipotassium hydrogen phosphate R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	40 → 25	60 → 75
6 - 22	25	75

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

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Identification of impurities Use the chromatogram supplied with *phenoxybenzamine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to phenoxybenzamine (retention time = about 20 min): impurity B = about 0.4; impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and phenoxybenzamine.

Calculation of percentage contents:

— for each impurity, use the concentration of impurity B in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at a pressure not exceeding 0.7 kPa for 24 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{18}H_{23}Cl_2NO$ taking into account the assigned content of *phenoxybenzamine hydrochloride CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.

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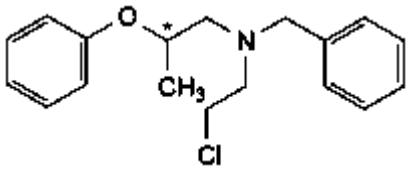
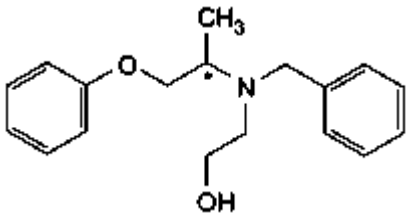
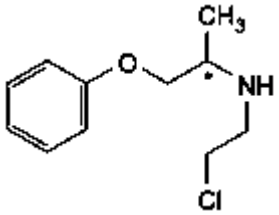


A. (2Ξ)-*N*-benzyl-*N*-(2-chloroethyl)-2-phenoxypropan-1-amine,



B. 2-[benzyl[(2Ξ)-1-phenoxypropan-2-yl]amino]ethan-1-ol,



C. (2Ξ)-*N*-(2-chloroethyl)-1-phenoxypropan-2-amine.

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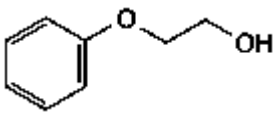
Phenoxyethanol

General Notices

(Ph. Eur. monograph 0781)



$C_8H_{10}O_2$ 138.2 *122-99-6*

Action and use

Antimicrobial preservative; also used topically in treatment of bacterial infections.

Ph Eur

DEFINITION

2-Phenoxyethanol.

Content

99.0 per cent *m/m* to 100.5 per cent *m/m*.

CHARACTERS

Appearance

Colourless, slightly viscous liquid.

Solubility

Slightly soluble in water, in arachis oil and in olive oil, miscible with acetone, with ethanol (96 per cent) and with glycerol.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Refractive index (2.2.6): 1.537 to 1.539.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

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Test solution Dissolve 80.0 mg in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Spectral range 240-350 nm.

Absorption maxima At 269 nm and 275 nm.

Specific absorbances at the absorption maxima:

— at 269 nm: 95 to 105;

— at 275 nm: 75 to 85.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *phenoxyethanol CRS*.

D. Shake 2 mL with a mixture of 4 g of *potassium permanganate R*, 5.4 g of *sodium carbonate R* and 75 mL of *water R* for 30 min. Add 25 g of *sodium chloride R* and stir continuously for 60 min, filter and acidify with *hydrochloric acid R* to about pH 1.7. The melting point of the precipitate, after recrystallisation from *water R*, is 96 °C to 99 °C (*2.2.14*).

TESTS

Relative density (*2.2.5*)

1.105 to 1.110.

Related substances

Gas chromatography (*2.2.28*).

Test solution Dilute 5.0 g of the substance to be examined to 20.0 mL with *anhydrous ethanol R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *anhydrous ethanol R*.

Reference solution (b) Dissolve 25.0 mg of *phenol R* (impurity A) in *anhydrous ethanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (c) Mix 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) and dilute to 10.0 mL with *anhydrous ethanol R*.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *anhydrous ethanol R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 R* (0.25 µm).

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Carrier gas helium for chromatography R.

Flow rate 1.0 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 13	90 → 220
	13 - 23	220
Injection port		250
Detector		270

Detection Flame ionisation.

Injection 1 µL of the test solution and reference solutions (c) and (d).

Elution order Impurity A, phenoxyethanol.

Retention time Phenoxyethanol = about 13 min.

System suitability Reference solution (c):

— *resolution*: minimum 15 between the peaks due to impurity A and phenoxyethanol.

Calculation of percentage contents:

— for each impurity, use the concentration of phenoxyethanol in reference solution (d).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

ASSAY

To 2.000 g in an acetylation flask fitted with an air condenser, add 10.0 mL of freshly prepared *acetic anhydride solution R1* and heat with frequent shaking in a water-bath for 45 min. Cool and carefully add 10 mL of *water R*. Heat for a further 2 min. Cool, add 10 mL of *butanol R*, shake vigorously and titrate the excess of acetic acid with *1 M sodium hydroxide* using 0.2 mL of *phenolphthalein solution R* as indicator. Repeat the procedure without the substance to be examined. The difference between the volumes used in the titrations represents the amount of acetic anhydride required for the acetylation of the substance to be examined.

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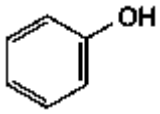
1 mL of *1 M sodium hydroxide* is equivalent to 0.1382 g of $C_8H_{10}O_2$.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



A. phenol.

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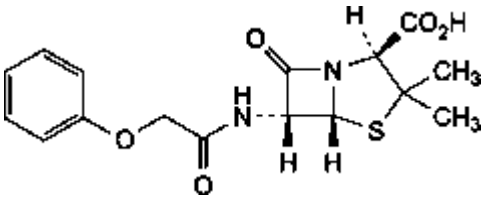
Phenoxymethylpenicillin

General Notices

(Ph. Eur. monograph 0148)



$C_{16}H_{18}N_2O_5S$ 350.4 *87-08-1*

Action and use

Penicillin antibacterial.

Ph Eur

DEFINITION

(2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-[(2-phenoxyacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Substance produced by the growth of certain strains of *Penicillium notatum* or related microorganisms.

Content

95.0 per cent to 102.0 per cent for the sum of the percentage contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Very slightly soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

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Second identification: A, C, D.

A. pH (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *phenoxymethylpenicillin CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *acetone R*.

Reference solution (a) Dissolve 25 mg of *phenoxymethylpenicillin CRS* in 5 mL of *acetone R*.

Reference solution (b) Dissolve 25 mg of *benzylpenicillin potassium CRS* and 25 mg of *phenoxymethylpenicillin potassium CRS* in 5 mL of *water R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is reddish-brown. Place the test-tube on a water-bath for 1 min; a dark reddish-brown colour develops.

TESTS

pH (2.2.3)

2.4 to 4.0.

Suspend 50 mg in 10 mL of *carbon dioxide-free water R*.

Related substances

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Liquid chromatography (2.2.29).

Solution A To 250 mL of 0.2 M potassium dihydrogen phosphate R add 500 mL of water R, adjust to pH 6.5 with an 8.4 g/L solution of sodium hydroxide R and dilute to 1000 mL with water R.

Test solution (a) Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Test solution (b) *Prepare immediately before use*. Dissolve 80.0 mg of the substance to be examined in solution A and dilute to 20.0 mL with solution A.

Reference solution (a) Dissolve 55.0 mg of phenoxymethylpenicillin potassium CRS in solution A and dilute to 50.0 mL with solution A.

Reference solution (b) Dissolve 9 mg of phenoxymethylpenicillin for system suitability CRS (containing impurities B, D, E and F) in 2 mL of solution A.

Reference solution (c) Dilute 1.0 mL of test solution (b) to 100.0 mL with solution A.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 20.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: phosphate buffer solution pH 3.4 R, methanol R, water for chromatography R (10:30:60 *V/V/V*);

— *mobile phase B*: phosphate buffer solution pH 3.4 R, methanol R, water for chromatography R (5:60:35 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 5	85 → 70	15 → 30
5 - 17	70 → 0	30 → 100
17 - 22	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (c) and (d).

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Identification of impurities Use the chromatogram supplied with *phenoxymethylpenicillin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, D, E and F.

Relative retention With reference to phenoxymethylpenicillin (retention time = about 11 min): impurity B = about 0.29; impurity D = about 0.38; impurity E = about 0.55 and 0.61; impurity F = about 0.88 and 0.95.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to the epimers of impurity F in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 20 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.5; impurity E = 1.3;

— for each impurity, use the concentration of phenoxymethylpenicillin in reference solution (c).

Limits:

— *impurity E (sum of isomers), impurity F (sum of epimers)*: for each impurity, maximum 1.0 per cent;

— *impurity B*: maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *sum of impurities other than D*: maximum 3.0 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity D (4-hydroxyphenoxymethylpenicillin)

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculation of percentage content:

— *correction factor*: multiply the peak area of impurity D by 1.7;

— use the concentration of phenoxymethylpenicillin in reference solution (c).

Limit Maximum 1.0 per cent (anhydrous substance).

Water

(*2.5.12*): maximum 0.5 per cent, determined on 1.00 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (a) and reference solution (a).

Calculate the percentage content of $C_{16}H_{18}N_2O_5S$ taking into account the assigned content of *phenoxymethylpenicillin potassium CRS* and a conversion factor of 0.902.

Calculate the sum of the percentage contents of phenoxymethylpenicillin and of 4-hydroxyphenoxymethylpenicillin.

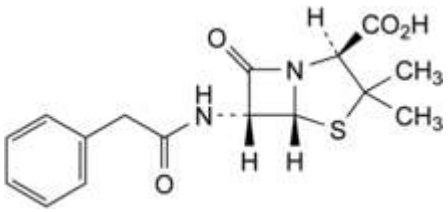
STORAGE

In an airtight container.

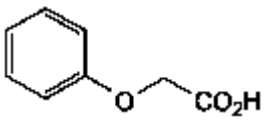
IMPURITIES

Specified impurities *B, D, E, F.*

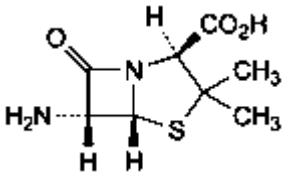
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*



A. (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(2-phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (benzylpenicillin),



B. phenoxyacetic acid,



C. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),

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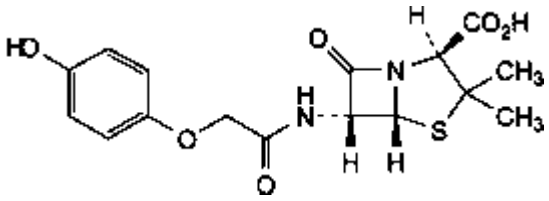
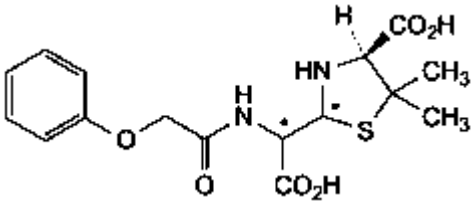
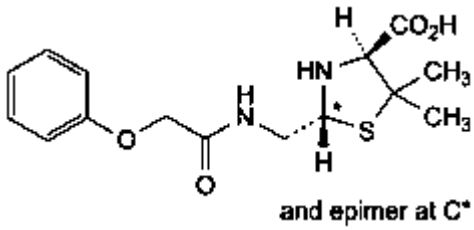


D. (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[[2-(4-hydroxyphenoxy)acetyl]amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (4-hydroxyphenoxymethylpenicillin),



E. (4*S*)-2-[carboxy[(2-phenoxyacetyl)amino]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of phenoxymethylpenicillin),



F. (2*RS*,4*S*)-5,5-dimethyl-2-[[(2-phenoxyacetyl)amino]methyl]-1,3-thiazolidine-4-carboxylic acid (penilloic acids of phenoxymethylpenicillin).

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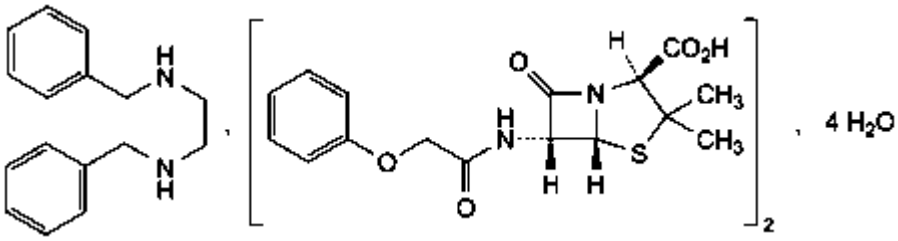
Phenoxymethylpenicillin (Benzathine) Tetrahydrate

General Notices

(Ph. Eur. monograph 2636)



$C_{48}H_{56}N_6O_{10}S_2,4H_2O$ 1013 *2113728-41-7*

Action and use

Penicillin antibacterial.

Ph Eur

DEFINITION

N^1,N^2-Dibenzylethane-1,2-diamine bis[(2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-(2-phenoxyacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] tetrahydrate.

Salt of a substance produced by the growth of certain strains of *Penicillium notatum* or related micro-organisms.

Content

— 94.0 per cent to 102.0 per cent for the sum of benzathine phenoxymethylpenicillin and benzathine 4-hydroxyphenoxymethylpenicillin (anhydrous substance) with correction for dispersing or suspending agents;

— *benzathine*: 23.0 per cent to 26.0 per cent (anhydrous substance).

Dispersing or suspending agents (e.g. lecithin) may be added.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Very slightly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *benzathine phenoxymethylpenicillin CRS*.

TESTS

pH (*2.2.3*)

4.0 to 6.5.

Suspend 0.600 g in 20 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Solution A To 250 mL of *0.2 M potassium dihydrogen phosphate R* add 500 mL of *water R*, adjust to pH 6.5 with an 8.4 g/L solution of *sodium hydroxide R* and dilute to 1000 mL with *water R*.

Test solution (a) Dissolve 40.0 mg of the substance to be examined in 10 mL of *methanol R* and dilute to 100.0 mL with solution A.

Test solution (b) *Prepare immediately before use*. Dissolve 80.0 mg of the substance to be examined in 10 mL of *methanol R* and dilute to 20.0 mL with solution A.

Reference solution (a) Dissolve 40.0 mg of *benzathine phenoxymethylpenicillin CRS* in 10 mL of *methanol R* and dilute to 100.0 mL with solution A.

Reference solution (b) Dissolve 8 mg of *benzathine phenoxymethylpenicillin for system suitability CRS* (containing impurities B, D, E, F, G, H and I) in 1 mL of *methanol R* and dilute to 2 mL with solution A.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 10.0 mL with a mixture of equal volumes of *methanol R* and solution A.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 25.0 mL with a mixture of equal volumes of *methanol R* and solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 3.4 R*, *methanol R*, *water for chromatography R* (10:30:60 *V/V/V*);

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— *mobile phase B*: *phosphate buffer solution pH 3.4 R*, *water for chromatography R*, *methanol R* (2.5:27.5:70 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 5	90 → 75	10 → 25
5 - 17	75 → 0	25 → 100
17 - 24	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *benzathine phenoxymethylpenicillin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, D, E, F, G, H and I.

Relative retention With reference to phenoxymethylpenicillin (retention time = about 10 min): benzathine = about 0.2; impurity B = about 0.3; impurity D = about 0.4; impurity E = about 0.60 and 0.64; impurity F = about 0.91 and 0.97; impurity H = about 1.36; impurity G = about 1.39; impurity I = about 2.4.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to the epimers of impurity F in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.5; impurity D = 1.7; impurity E = 1.3;

— for each impurity, use the concentration of phenoxymethylpenicillin in reference solution (c).

Limits:

— *impurity G*: maximum 2.0 per cent;

— *impurity E (sum of isomers), impurity F (sum of epimers)*: for each impurity, maximum 1.0 per cent;

— *impurities D, H, I*: for each impurity, maximum 0.5 per cent;

— *impurity B*: maximum 0.2 per cent;

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— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *sum of impurities other than D*: maximum 4.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to benzathine.

Water (*2.5.12, Method B*)

5.0 per cent to 8.0 per cent, determined on 0.200 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (a) and reference solution (a).

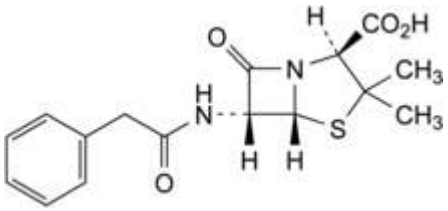
Calculate the percentage contents of benzathine ($C_{16}H_{20}N_2$) and benzathine phenoxymethylpenicillin ($C_{48}H_{56}N_6O_{10}S_2$) taking into account the assigned content of *benzathine phenoxymethylpenicillin CRS*.

Calculate the sum of the percentage contents of benzathine phenoxymethylpenicillin and of benzathine 4-hydroxyphenoxymethylpenicillin.

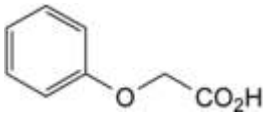
IMPURITIES

Specified impurities *B, D, E, F, G, H, I.*

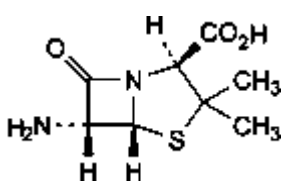
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*



A. (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (benzylpenicillin),



B. phenoxyacetic acid,



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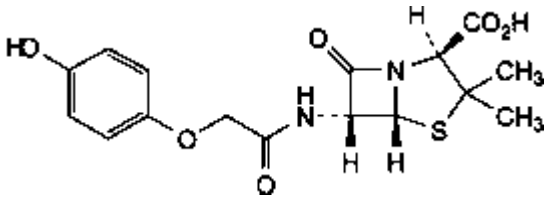
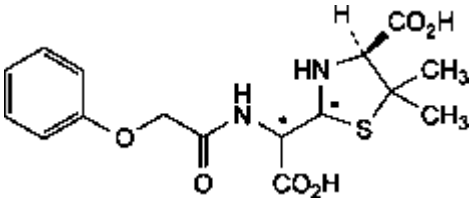
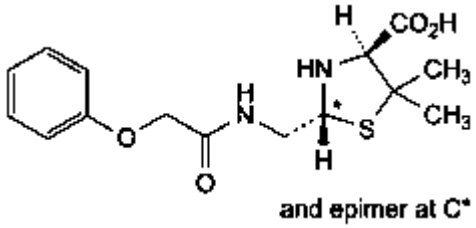
C. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



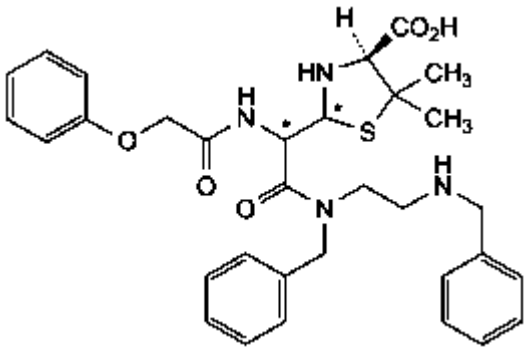
D. (2*S*,5*R*,6*R*)-6-[2-(4-hydroxyphenoxy)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (4-hydroxyphenoxymethylpenicillin),



E. (2Ξ,4*S*)-2-[(Ξ)-carboxy(2-phenoxyacetamido)methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of phenoxymethylpenicillin),



F. (2*RS*,4*S*)-5,5-dimethyl-2-[(2-phenoxyacetamido)methyl]-1,3-thiazolidine-4-carboxylic acid (penilloic acids of phenoxymethylpenicillin),



G. (2Ξ,4*S*)-2-[(1Ξ)-2-[benzyl[2-(benzylamino)ethyl]amino]-2-oxo-1-(2-phenoxyacetamido)ethyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid,

H. unknown structure,

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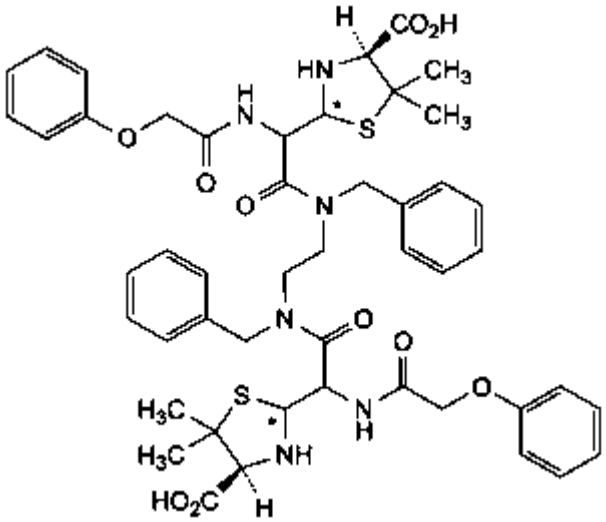

I. (2Ξ,2′Ξ,4*S*,4′*S*)-2,2′-[ethane-1,2-diylbis[(benzylazanediyl)[2-oxo-1-(2-phenoxyacetamido)ethane-2,1-diyl]]]bis(5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid).

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Phenoxymethylpenicillin Oral Solution

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Phenoxymethylpenicillin Oral Solution is a solution of Phenoxymethylpenicillin Potassium in a suitable flavoured vehicle. It is prepared by dissolving the dry ingredients in the specified volume of water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Suspensions stated under Oral Liquids.

For the following tests prepare the Oral Solution as directed on the label. The solution, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of phenoxymethylpenicillin, $C_{16}H_{18}N_2O_5S$, calculated as the sum of the contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin

When freshly constituted, not more than 120.0% of the stated amount of phenoxymethylpenicillin. When stored at the temperature and for the period stated on the label during which the Oral Solution may be expected to be satisfactory for use, not less than 80.0% of the stated amount of phenoxymethylpenicillin.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the oral solution containing the equivalent of 0.1 g of phenoxymethylpenicillin to 100 mL with *mixed phosphate buffer pH 5.4*.

(2) 0.11% w/v of *phenoxymethylpenicillin potassium BPCRS* in *mixed phosphate buffer pH 5.4*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with 0.1M *sodium hydroxide*, heat at 50° for 10 minutes, allow to cool and spray with a mixture of 100 volumes of *starch mucilage*, 6 volumes of *glacial acetic acid* and 2 volumes of a 1% w/v solution of *iodine* in a 4% w/v solution of *potassium iodide*.

MOBILE PHASE

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20 volumes of *acetone* and 80 volumes of *mixed phosphate buffer pH 5.4*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Dilute a volume containing the equivalent of 25 mg of phenoxymethylpenicillin to 20 mL with *water*. To 10 mL add 0.5 mL of *neutral red solution* and sufficient 0.01M *sodium hydroxide* to produce a permanent orange colour and then add 1.0 mL of *penicillinase solution*. The colour changes rapidly to red.

TESTS

Related substances

Carry out the method for *liquid chromatography Appendix III D*, using the following solutions in solution A. *Prepare immediately before use*.

Solution A To 250 volumes of 0.2 M *potassium dihydrogren phosphate* add 500 volumes of *water*, adjust to pH 6.5 with a 0.84% w/v solution of *sodium hydroxide*, dilute to 1000 volumes with *water*.

Solution B A 6.8% w/v solution of *potassium dihydrogen orthophosphate* in *water*, adjusted to pH 3.4 using *orthophosphoric acid*.

(1) Dilute a quantity of the oral solution with *solution A* to produce a solution containing the equivalent of 0.4% w/v of phenoxymethylpenicillin.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.4% w/v of *phenoxymethylpenicillin for system suitability EPCRS* and 0.04% w/v of *sodium benzoate*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temparature of 50°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile Phase A 10 volumes of solution B, 30 volumes of *methanol*, and 60 volumes of *water*.

Mobile phase B 5 volumes of solution B, 35 volumes of *water*, and 60 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-5	85→70	15→30	linear gradient

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
5-17	70→0	30→100	linear gradient
17-22	0	100	isocratic
22-23	0→85	100→15	linear gradient
23-35	85	15	re-equillibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenoxymethylpenicillin (retention time, about 11 minutes) are: impurity B, about 0.3; impurity D, about 0.4; impurity E, about 0.55 and 0.61; impurity F, about 0.88 and 0.95.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to the epimers of impurity F is at least 3.0;

the *resolution* between the peaks due to sodium benzoate and impurity E1 is at least 3.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B, D, E, and F using the chromatogram supplied with *phenoxymethylpenicillin for system suitability EPCRS*, and the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1):

multiply the area of any peak corresponding to impurity B, D, and E by the following correction factors respectively: 0.6, 1.7, and 1.3;

the area of any peak corresponding to impurity D is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

the sum of the areas of any peaks corresponding to the isomers of impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%)

the sum of the areas of any peaks corresponding to the epimers impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity B is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any secondary peaks, excluding impurity D, is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

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Disregard any peak that elutes before impurity B, after Phenoxymethylpenicillin and any peak with an area less than 0.75 times the area of the principal peak in the chromatogram obtained with solution (4) (0.15%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A, as described in Related substances, prepared immediately before use.

(1) Dilute a weighed quantity of the oral solution, if necessary, with solution A to produce a solution containing the equivalent of 0.05% w/v of phenoxymethylpenicillin.
(2) 0.055% w/v of *phenoxymethylpenicillin potassium BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and Calculate the content of $C_{16}H_{18}N_2O_5S$ in the oral solution using the declared content of $C_{16}H_{18}N_2O_5S$ in *phenoxymethylpenicillin potassium BPCRS*.

Using the value obtained in the related substances for impurity D (4-hydroxyphenoxymethylpenicillin), calculate the sum of the percentage contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin.

Repeat the procedure using a portion of the oral solution that has been stored at the temperature and for the period of time stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The Oral Solution should be stored at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of phenoxymethylpenicillin.

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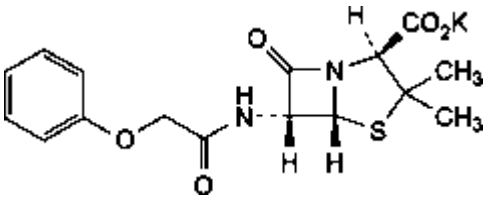
Phenoxymethylpenicillin Potassium

General Notices

(Ph. Eur. monograph 0149)



$C_{16}H_{17}KN_2O_5S$ 388.5 *132-98-9*

Action and use

Penicillin antibacterial.

Preparations

Phenoxymethylpenicillin Oral Solution

Phenoxymethylpenicillin Tablets

Ph Eur

DEFINITION

Potassium (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(2-phenoxyacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Substance produced by the growth of certain strains of *Penicillium notatum* or related microorganisms.

Content

95.0 per cent to 102.0 per cent for the sum of the percentage contents of phenoxymethylpenicillin potassium and 4-hydroxyphenoxymethylpenicillin potassium (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *phenoxymethylpenicillin potassium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a) Dissolve 25 mg of *phenoxymethylpenicillin potassium CRS* in 5 mL of *water R*.

Reference solution (b) Dissolve 25 mg of *benzylpenicillin potassium CRS* and 25 mg of *phenoxymethylpenicillin potassium CRS* in 5 mL of *water R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is reddish-brown. Place the test-tube on a water-bath for 1 min; a dark reddish-brown colour develops.

D. It gives reaction (a) of potassium (2.3.1).

TESTS

pH (2.2.3)

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5.5 to 7.5.

Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solution A To 250 mL of *0.2 M potassium dihydrogen phosphate R* add 500 mL of *water R*, adjust to pH 6.5 with an 8.4 g/L solution of *sodium hydroxide R* and dilute to 1000 mL with *water R*.

Test solution (a) Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Test solution (b) *Prepare immediately before use*. Dissolve 80.0 mg of the substance to be examined in solution A and dilute to 20.0 mL with solution A.

Reference solution (a) Dissolve 50.0 mg of *phenoxymethylpenicillin potassium CRS* in solution A and dilute to 50.0 mL with solution A.

Reference solution (b) Dissolve 8 mg of *phenoxymethylpenicillin for system suitability CRS* (containing impurities B, D, E and F) in 2 mL of solution A.

Reference solution (c) Dilute 1.0 mL of test solution (b) to 100.0 mL with solution A.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 20.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 3.4 R*, *methanol R*, *water for chromatography R* (10:30:60 *V/V/V*);

— *mobile phase B*: *phosphate buffer solution pH 3.4 R*, *methanol R*, *water for chromatography R* (5:60:35 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 5	85 → 70	15 → 30
5 - 17	70 → 0	30 → 100
17 - 22	0	100

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Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *phenoxymethylpenicillin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, D, E and F.

Relative retention With reference to phenoxymethylpenicillin (retention time = about 11 min): impurity B = about 0.29; impurity D = about 0.38; impurity E = about 0.55 and 0.61; impurity F = about 0.88 and 0.95.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to the epimers of impurity F in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 20 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.6; impurity E = 1.3;

— for each impurity, use the concentration of phenoxymethylpenicillin potassium in reference solution (c).

Limits:

— *impurity E (sum of isomers), impurity F (sum of epimers)*: for each impurity, maximum 1.0 per cent;

— *impurity B*: maximum 0.3 per cent;

— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *sum of impurities other than D*: maximum 3.0 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity D (4-hydroxyphenoxymethylpenicillin)

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculation of percentage content:

— *correction factor*: multiply the peak area of impurity D by 1.7;

— use the concentration of phenoxymethylpenicillin potassium in reference solution (c).

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Limit Maximum 4.0 per cent (anhydrous substance).

Water

(2.5.12): maximum 1.0 per cent, determined on 1.00 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (a) and reference solution (a).

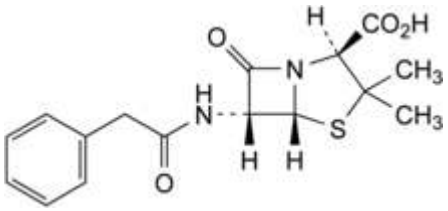
Calculate the percentage content of $C_{16}H_{17}KN_2O_5S$ taking into account the assigned content of *phenoxymethylpenicillin potassium CRS*.

Calculate the sum of the percentage contents of phenoxymethylpenicillin potassium and of 4-hydroxyphenoxymethylpenicillin potassium.

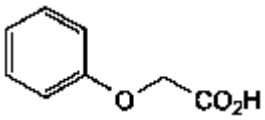
IMPURITIES

Specified impurities *B, D, E, F.*

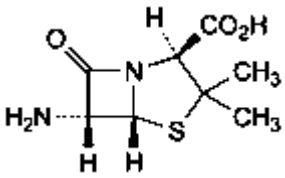
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*



A. (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(2-phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (benzylpenicillin),



B. phenoxyacetic acid,



C. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),

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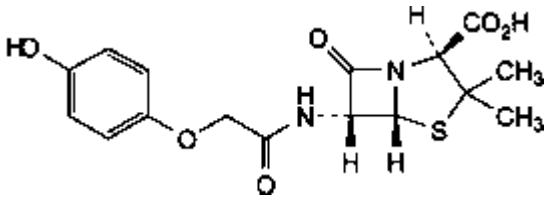
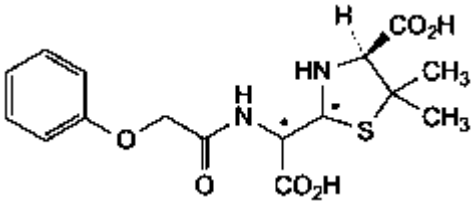
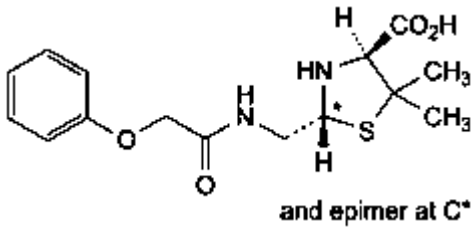


D. (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[[2-(4-hydroxyphenoxy)acetyl]amino]-4-thia- 1-azabicyclo[3.2.0]heptane-2-carboxylic acid (4-hydroxyphenoxymethylpenicillin),



E. (4*S*)-2-[carboxy[(2-phenoxyacetyl)amino]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of phenoxymethylpenicillin),



F. (2*RS*,4*S*)-5,5-dimethyl-2-[[(2-phenoxyacetyl)amino]methyl]-1,3-thiazolidine-4-carboxylic acid (penilloic acids of phenoxymethylpenicillin).

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Phenoxymethylpenicillin Tablets

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Phenoxymethylpenicillin Tablets contain Phenoxymethylpenicillin Potassium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of phenoxymethylpenicillin, $C_{16}H_{18}N_2O_5S$, calculated as the sum of the contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin.

92.5 to 107.5% of the stated amount of phenoxymethylpenicillin.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 80 mg of phenoxymethylpenicillin with *water*, dilute to 250 mL with *water* and filter. The *light absorption* of the filtrate, Appendix II B, exhibits maxima at 268 nm and 274 nm and a minimum at 272 nm.

B. Shake a quantity of the powdered tablets containing the equivalent of 10 mg of phenoxymethylpenicillin with 10 mL of *water*, filter and add 0.5 mL of *neutral red solution*. Add sufficient 0.01M *sodium hydroxide* to produce a permanent orange colour and then add 1.0 mL of *penicillinase solution*. The colour changes rapidly to red.

C. Ignite 0.5 g of the powdered tablets, add 5 mL of 2M *hydrochloric acid*, boil, cool and filter. The filtrate yields reaction B characteristic of *potassium salts*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 6.8 by the addition of 1M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

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(1) After 45 minutes withdraw a 10-mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 268 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *phenoxymethylpenicillin potassium BPCRS* in dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of phenoxymethylpenicillin, $C_{16}H_{18}N_2O_5S$, in the medium from the absorbances obtained and from the declared content of $C_{16}H_{18}N_2O_5S$ in *phenoxymethylpenicillin potassium BPCRS*.

LIMITS

The amount of phenoxymethylpenicillin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. *Prepare immediately before use*.

Solution A To 250 volumes of 0.2 M *potassium dihydrogren phosphate* add 500 volumes of *water*, adjust to pH 6.5 with a 0.84% w/v solution of *sodium hydroxide*, dilute to 1000 volumes with *water*.

Solution B A 6.8% w/v solution of *potassium dihydrogen orthophosphate* in *water*, adjusted to pH 3.4 using *orthophosphoric acid*.

(1) Dissolve a quantity of the powdered tablets in solution A to produce a solution containing the equivalent of 0.4% w/v of phenoxymethylpenicillin.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.4% w/v of *phenoxymethylpenicillin for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of solution B, 30 volumes of *methanol*, and 60 volumes of *water*

Mobile phase B 5 volumes of solution B, 35 volumes of *water*, and 60 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
2-5	85→70	15→30	linear gradient
5-17	70→0	30→100	linear gradient
17-22	0	100	isocratic
22-23	0→85	100→15	linear gradient
23-35	85	15	re-equillibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenoxymethylpenicillin (retention time, about 11 minutes) are: impurity B, about 0.3; impurity D, about 0.4; impurity E, about 0.55 and 0.61; impurity F, about 0.88 and 0.95

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to the epimers of impurity F is at least 3.0

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B, D, E, and F using the chromatogram supplied with *phenoxymethylpenicillin for system suitability EPCRS*, and the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1):

multiply the area of any peak corresponding to impurity B, D, and E by the following correction factors respectively: 0.6, 1.7, and 1.3;

the area of any peak corresponding to impurity D is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

the sum of the areas of any peaks corresponding to the isomers of impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%)

the sum of the areas of any peaks corresponding to the epimers impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity B is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any secondary peak, excluding impurity D, is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than 0.75 times the area of the principal peak in the chromatogram obtained with solution (4) (0.15%).

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ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A, as described under Related substances, *prepared immediately before use*.

(1) Dissolve a quantity of the powdered tablets in solution A to produce a solution containing the equivalent of 0.05% w/v of phenoxymethylpenicillin.
(2) 0.055% w/v of *phenoxymethylpenicillin potassium BPCRS*

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under Related substances

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{18}N_2O_5S$ in the tablets using the declared content of $C_{16}H_{18}N_2O_5S$ in *phenoxymethylpenicillin potassium BPCRS*.

Using the value obtained in the related substances for impurity D (4-hydroxyphenoxymethylpenicillin), calculate the sum of the percentage contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of phenoxymethylpenicillin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Phenoxymethylpenicillin Potassium*.

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Phentolamine Injection

General Notices

Action and use

Alpha-adrenoceptor antagonist.

DEFINITION

Phentolamine Injection is a sterile solution of Phentolamine Mesilate in Water for Injections with or without excipients.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phentolamine mesilate, $C_{17}H_{19}N_3O,CH_4SO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the injection, if necessary, with *ethanol* (*96%*) to give a solution containing 0.1% w/v of Phentolamine Mesilate.

(2) 0.1% w/v of *phentolamine mesilate BPCRS* in *ethanol* (*96%*).

(3) 1 volume of solution (1) and 1 volume of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

5 volumes of 13.5M *ammonia*, 15 volumes of *acetone* and 85 volumes of *butan-2-one*.

SYSTEM SUITABILITY

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The test is not valid unless the chromatogram obtained with solution (3) shows one compact spot.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 5.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the injection with the mobile phase to give a solution containing 0.05% w/v of Phentolamine Mesilate.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) Dilute 1 volume of solution (2) to 20 volumes with the mobile phase.
(4) 0.05% w/v of *phentolamine impurity standard BPCRS* in the mobile phase.
(5) Heat a 0.01% w/v solution of *phentolamine impurity standard BPCRS* in 0.05M *sodium acetate*, previously adjusted to pH 4.0 with *glacial acetic acid*, at 60° for 4 hours (generation of phentolamide).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-Phenyl is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

33 volumes of *acetonitrile* and 67 volumes of a 0.05% w/v solution of *ammonium acetate* previously adjusted to pH 5.9 with *dilute acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between phentolamine and impurity C is at least 3.0.

LIMITS

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Identify any peaks in the chromatogram obtained with solution (1) due to impurity A using the chromatogram obtained with solution (4) and phentolamide using the chromatogram obtained with solution (5) and the reference chromatogram supplied with *phentolamine impurity standard BPCRS*. Multiply the area of any peak corresponding to impurity A by a correction factor of 1.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 2.2 times the area of the principal peak in the chromatogram obtained with solution (2) (2.2%);

the area of any peak corresponding to phentolamide is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than 4.2 times the area of the principal peak in the chromatogram obtained with solution (2) (4.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the injection to give a solution containing 0.01% w/v of Phentolamine Mesilate.
(2) 0.01% w/v of *phentolamine mesilate BPCRS*.
(3) 0.05% w/v of *phentolamine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between phentolamine and impurity C is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O,CH_4SO_3$ in the injection using the declared content of $C_{17}H_{19}N_3O,CH_4SO_3$ in *phentolamine mesilate BPCRS*.

STORAGE

Phentolamine Injection should be protected from light.

IMPURITIES

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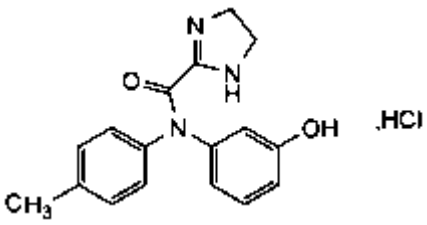
The impurities limited by the requirements of this monograph include those listed in the monograph for Phentolamine Mesilate and the following:



1. Phentolamide Hydrochloride.

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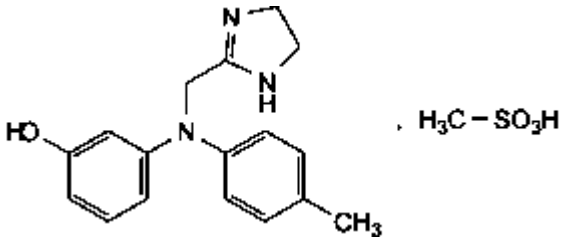
Phentolamine Mesilate

General Notices

(Ph. Eur. monograph 1138)



$C_{18}H_{23}N_3O_4S$ 377.5 *65-28-1*

Action and use

Alpha-adrenoceptor antagonist.

Preparation

Phentolamine Injection

Ph Eur

DEFINITION

3-[[(4,5-Dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol methanesulfonate.

Content

98.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in phentolamine mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

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White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: C, E.

Second identification: A, B, D, E.

A. Melting point (2.2.14): 178 °C to 182 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 60.0 mg in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *water R*.

Spectral range 230-350 nm.

Absorption maximum At 278 nm.

Specific absorbance at the absorption maximum 220 to 245.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *phentolamine mesilate CRS*.

D. Dissolve 0.5 g in a mixture of 5 mL of *ethanol (96 per cent) R* and 5 mL of a 10 g/L solution of *hydrochloric acid R* and add 0.5 mL of a 5 g/L solution of *ammonium vanadate R*. A light green precipitate is produced.

E. Mix 50 mg with 0.2 g of *sodium hydroxide R*, heat to fusion and continue heating for a few seconds. Allow to cool and add 0.5 mL of warm *water R*. Acidify with *dilute hydrochloric acid R* and heat. Sulfur dioxide is evolved, which turns moistened *starch iodate paper R* blue.

TESTS

Acidity

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.1 mL of *methyl red solution R*. If the solution is red, not more than 0.05 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 50.0 mL with the mobile phase.

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Reference solution (b) Dissolve 5 mg of *phentolamine for system suitability CRS* (containing impurities A and C) in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 33 volumes of *acetonitrile for chromatography R* and 67 volumes of a 0.5 g/L solution of *ammonium acetate R* previously adjusted to pH 5.9 with *dilute acetic acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Run time 1.5 times the retention time of phentolamine.

Identification of impurities Use the chromatogram supplied with *phentolamine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to phentolamine (retention time = about 15 min): impurity A = about 0.7; impurity C = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to phentolamine and impurity C.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.7;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 100 mL of *2-propanol R1*. Titrate under a stream of nitrogen with *0.1 M tetrabutylammonium hydroxide in 2-propanol*. Determine the end-point potentiometrically (*2.2.20*), using a glass indicator electrode and a suitable reference electrode. Carry out a blank titration.

1 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 37.75 mg of $C_{18}H_{23}N_3O_4S$.

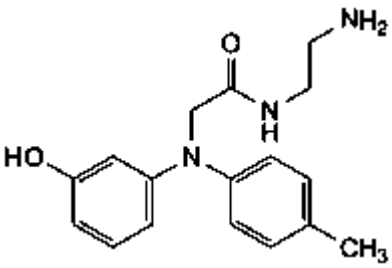
STORAGE

In an airtight container, protected from light.

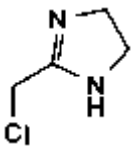
IMPURITIES

Specified impurities A.

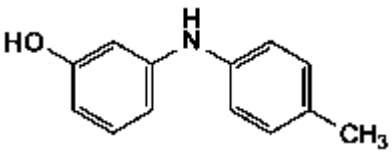
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. *N*-(2-aminoethyl)-2-[(3-hydroxyphenyl)(4-methylphenyl)amino]acetamide,



B. 2-(chloromethyl)-4,5-dihydro-1*H*-imidazole,



C. 3-[(4-methylphenyl)amino]phenol.

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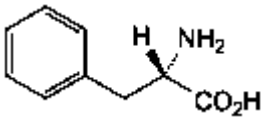
Phenylalanine

General Notices

(Ph. Eur. monograph 0782)



$C_9H_{11}NO_2$ 165.2 *63-91-2*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-phenylpropanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, or shiny, white flakes.

Solubility

Sparingly soluble in water, very slightly soluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *phenylalanine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of equal volumes of *glacial acetic acid R* and *water R* and dilute to 50 mL with the same mixture of solvents.

Reference solution Dissolve 10 mg of *phenylalanine CRS* in a mixture of equal volumes of *glacial acetic acid R* and *water R* and dilute to 50 mL with the same mixture of solvents.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. To about 10 mg add 0.5 g of *potassium nitrate R* and 2 mL of *sulfuric acid R*. Heat on a water-bath for 20 min. Allow to cool. Add 5 mL of a 50 g/L solution of *hydroxylamine hydrochloride R* and allow to stand in iced water for 10 min. Add 9 mL of *strong sodium hydroxide solution R*. A violet-red or violet-brown colour develops.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Dissolve 0.5 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 10 mL with the same solution.

Specific optical rotation (2.2.7)

-35.5 to -33.0 (dried substance).

Dissolve 0.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Ninhydrin-positive substances

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Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A dilute hydrochloric acid R1 or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of proline R in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of ammonium standard solution (100 ppm NH_4) R to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of isoleucine R and 30 mg of leucine R in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— resolution: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of phenylalanine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph Substances for pharmaceutical use (2034) do not apply.

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Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.25 g in 3 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*. The solution, without further addition of nitric acid, complies with the test.

Sulfates (2.4.13)

Maximum 300 ppm.

Dissolve 0.5 g in a mixture of 5 volumes of *dilute hydrochloric acid R* and 25 volumes of *distilled water R* and dilute to 15 mL with the same mixture of solvents.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (2.4.9)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 16.52 mg of $C_9H_{11}NO_2$.

STORAGE

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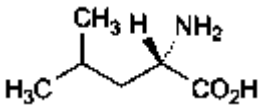
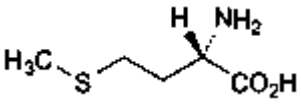
Protected from light.

IMPURITIES

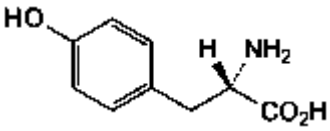
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



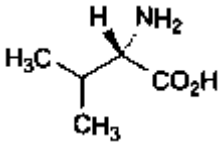
A. (2*S*)-2-amino-4-methylpentanoic acid (leucine),



B. (2*S*)-2-amino-4-(methylsulfanyl)butanoic acid (methionine),



C. (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid (tyrosine),



D. (2*S*)-2-amino-3-methylbutanoic acid (valine).

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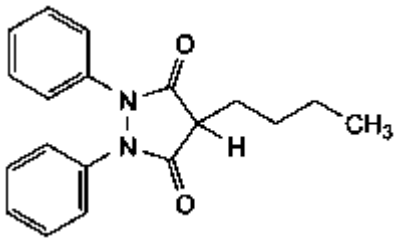
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Phenylbutazone

General Notices

(Ph. Eur. monograph 0422)



$C_{19}H_{20}N_2O_2$ 308.4 *50-33-9*

Action and use

Cyclo-oxygenase inhibitor; pyrazolone analgesic.

Ph Eur

DEFINITION

4-Butyl-1,2-diphenylpyrazolidine-3,5-dione.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent). It dissolves in alkaline solutions.

IDENTIFICATION

First identification: A, C.

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Second identification: A, B, D.

A. Melting point (2.2.14): 104 °C to 107 °C.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in a mixture of equal volumes of ethanol R and methylene chloride R and dilute to 25 mL with the same mixture of solvents.

Reference solution Dissolve 25 mg of phenylbutazone CRS in a mixture of equal volumes of ethanol R and methylene chloride R and dilute to 25 mL with the same mixture of solvents.

Plate TLC silica gel GF_{254} plate R.

Mobile phase acetone R, methylene chloride R (20:80 *V/V*).

Application 5 µL.

Development Over a path of 10 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison phenylbutazone CRS.

D. To 0.1 g add 1 mL of glacial acetic acid R and 2 mL of hydrochloric acid R and heat the mixture under a reflux condenser for 30 min. Cool, add 10 mL of water R and filter. To the filtrate add 3 mL of a 7 g/L solution of sodium nitrite R. A yellow colour is produced. To 1 mL of the solution add a solution of 10 mg of β-naphthol R in 5 mL of sodium carbonate solution R. A brownish-red to violet-red precipitate is formed.

TESTS

Solution S

Dissolve 1.0 g with shaking in 20 mL of dilute sodium hydroxide solution R and maintain the solution at 25 °C for 3 h.

Appearance of solution

Solution S is clear (2.2.1).

Acidity or alkalinity

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Heat to boiling 1.0 g in 50 mL of *water R*, cool with shaking in a closed flask and filter. To 25 mL of the filtrate add 0.5 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator. Add 0.6 mL of *0.01 M hydrochloric acid* and 0.1 mL of *methyl red solution R*; the solution is red or orange.

Absorbance (*2.2.25*)

Maximum 0.20 for solution S at 420 nm in a 4 cm cell.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 100.0 mg of the substance to be examined in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 5 mg of *phenylbutazone impurity B CRS* and 5 mg of *1,2-diphenylhydrazine R* in *acetonitrile R*, add 0.5 mL of the test solution and dilute to 50 mL with *acetonitrile R*. Dilute 2.5 mL to 10 mL with *acetonitrile R*.

Reference solution (c) Dissolve 1.0 mg of *benzidine R* in *acetonitrile R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL to 100.0 mL with *acetonitrile R*. Dilute 5.0 mL to 10.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.36 g of *sodium acetate R* in *water R*, adjust to pH 5.2 with a 52.5 g/L solution of *citric acid monohydrate R* and dilute to 1000 mL with *water R*,

— *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	70	30
10 - 20	70 → 40	30 → 60
20 - 35	40	60
35 - 40	40 → 70	60 → 30

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 240 nm.

Injection 20 µL; inject the test solution and reference solutions (a) and (b).

Relative retentions With reference to phenylbutazone (retention time = about 13 min): impurity E = about 0.2; impurity A = about 0.5; impurity B = about 1.2; impurity C = about 1.3; impurity D = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to phenylbutazone and to impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.55,

— *impurities A, B*: for each impurity, not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent),

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.20 per cent),

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.025 per cent); disregard any peak due to impurity E.

Impurity E

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 280 nm.

Injection Test solution and reference solution (c).

System suitability Reference solution (c):

— *signal-to-noise ratio*: minimum 10 for the principal peak.

Limit:

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (5 ppm).

Loss on drying (2.2.32)

Maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 4 h.

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

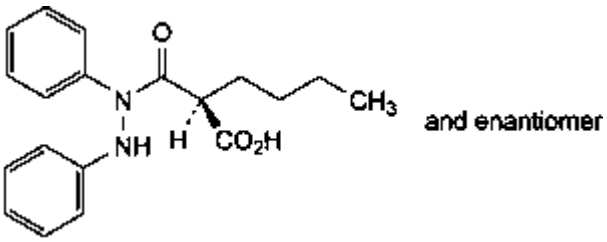
Dissolve 0.250 g in 25 mL of *acetone R* and add 0.5 mL of *bromothymol blue solution R1*. Titrate with *0.1 M sodium hydroxide* until a blue colour is obtained which persists for 15 s. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 30.84 mg of $C_{19}H_{20}N_2O_2$.

STORAGE

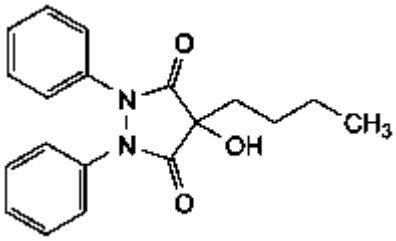
Protected from light.

IMPURITIES



and enantiomer

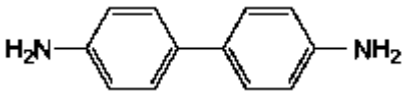
A. (2*RS*)-2-[(1,2-diphenyldiazanyl)carbonyl]hexanoic acid,



B. 4-butyl-4-hydroxy-1,2-diphenylpyrazolidine-3,5-dione,

C. C_6H_5-NH-NH-C_6H_5: 1,2-diphenyldiazane (1,2-diphenylhydrazine),

D. C_6H_5-N=N-C_6H_5: 1,2-diphenyldiazene,



E. biphenyl-4,4′-diamine (benzidine).

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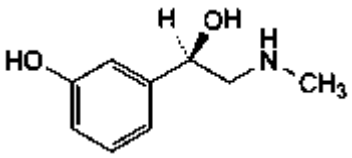
Phenylephrine

General Notices

(Ph. Eur. monograph 1035)



$C_9H_{13}NO_2$ 167.2 *59-42-7*

Action and use

Alpha-adrenoceptor agonist.

Ph Eur

DEFINITION

(1*R*)-1-(3-Hydroxyphenyl)-2-(methylamino)ethanol.

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

mp

About 174 °C.

IDENTIFICATION

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First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *phenylephrine CRS*.

C. Thin-layer chromatography (2.2.27).

Solvent mixture A mixture of equal volumes of *methylene chloride R* and methanolic hydrochloric acid (*hydrochloric acid R* diluted 10-fold with *methanol R*).

Test solution Dissolve 0.1 g of the substance to be examined in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution Dissolve 20 mg of *phenylephrine CRS* in the solvent mixture and dilute to 1 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (0.5:25:70 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In a current of cold air.

Detection Examine in ultraviolet light at 254 nm; spray with a 1 g/L solution of *fast red B salt R* in a 50 g/L solution of *sodium carbonate R* and examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in 1 mL of *1 M hydrochloric acid*, add 0.05 mL of *copper sulfate solution R* and 1 mL of a 200 g/L solution of *sodium hydroxide R*. A violet colour develops. Add 1 mL of *ether R* and shake. The upper layer remains colourless.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, Method II).

Dissolve 1 g in *1 M hydrochloric acid* and dilute to 10 mL with the same acid.

Specific optical rotation (2.2.7)

-53 to -57 (dried substance).

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Dissolve 1.250 g in *1 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *dilute hydrochloric acid R*, mobile phase B, mobile phase A (5:200:800 *V/V/V*).

Buffer solution pH 2.8 Dissolve 3.25 g of *sodium octanesulfonate monohydrate R* in 1000 mL of *water for chromatography R* by stirring for 30 min and adjust to pH 2.8 with *dilute phosphoric acid R*.

Test solution Dissolve 41.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *phenylephrine hydrochloride for peak identification CRS* (containing impurities C and E) in 2 mL of the solvent mixture.

Column:

— *size*: *l* = 0.055 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution pH 2.8 (10:90 *V/V*);

— *mobile phase B*: buffer solution pH 2.8, *acetonitrile R1* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	93	7
3 - 13	93 → 70	7 → 30
13 - 14	70 → 93	30 → 7

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL.

Identification of impurities Identify the peaks due to impurities C and E using the chromatogram obtained with reference solution (b).

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Relative retention With reference to phenylephrine (retention time = about 2.8 min): impurity C = about 1.3; impurity E = about 3.6.

System suitability:

— *symmetry factor*: maximum 1.9 for the principal peak in the chromatogram obtained with the test solution;

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to phenylephrine in the chromatogram obtained with reference solution (b).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.5; impurity E = 0.5;

— *impurities C, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.72 mg of $C_9H_{13}NO_2$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *C, E.*

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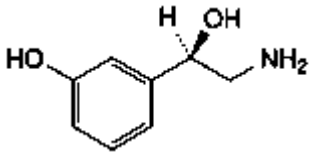
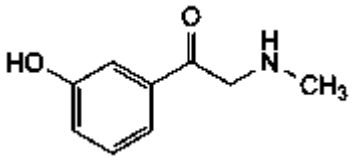
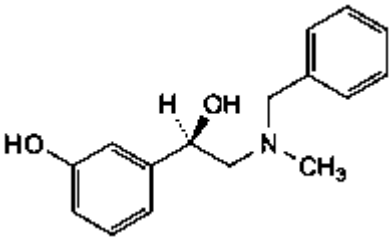
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, D.



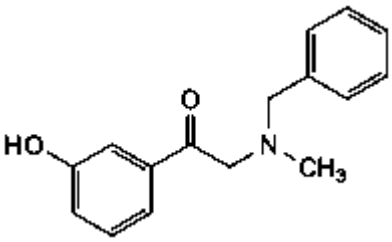
A. (1*R*)-2-amino-1-(3-hydroxyphenyl)ethanol (norphenylephrine),



C. 1-(3-hydroxyphenyl)-2-(methylamino)ethanone (phenylephrone),



D. (1*R*)-2-(benzylmethylamino)-1-(3-hydroxyphenyl)ethanol (benzylphenylephrine),



E. 2-(benzylmethylamino)-1-(3-hydroxyphenyl)ethanone (benzylphenylephrone).

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Phenylephrine Eye Drops

General Notices

Action and use

Alpha-adrenoceptor agonist.

DEFINITION

Phenylephrine Eye Drops are a sterile solution of Phenylephrine Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of phenylephrine hydrochloride $C_9H_{13}NO_2$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

To 350 mg of *4-nitroaniline* add 1.5 mL of *hydrochloric acid*, and mix. Dilute with water to 50 mL, mix, and allow to settle. Place 5 mL of the clear supernatant in a 100 mL volumetric flask, and immerse it in an ice bath. While it is in the ice bath, add 1 mL of *hydrochloric acid*, then add, in small portions, 2 mL of a 1% w/v *sodium nitrite* solution, dilute with *water* to volume, and mix (solution A).

(1) Dilute the eye drops with sufficient *water* to give a solution containing 1% w/v of Phenylephrine Hydrochloride.

(2) 1% w/v of *phenylephrine hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with 0.5M *ethanolic potassium hydroxide*, dry at 60° for 15 minutes and spray with solution A. Examine in daylight.

MOBILE PHASE

3 volumes of *ammonium hydroxide,* 25 volumes of *water* and 72 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to phenylephrine in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.0 to 5.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B A mixture of 20 volumes of mobile phase B and 80 volumes of mobile phase A.

(1) Dilute the eye drops, if necessary, with solution B to give a solution containing 0.1% w/v of Phenylephrine Hydrochloride.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution B. Dilute 1 volume to 5 volumes with solution B.
(3) 0.1% w/v of *phenylephrine hydrochloride for peak identification EPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (1.8 µm) (Zorbax Eclipse Plus C18).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 215 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *acetonitrile* R1 and 90 volumes of a 0.325% w/v solution of sodium octanesulfonate monohydrate in water adjusted to pH 2.8 with dilute orthophosphoric acid.

Mobile phase B 10 volumes of a 0.325% w/v solution of sodium octanesulfonate monohydrate in water adjusted to pH 2.8 with dilute orthophosphoric acid and 90 volumes *acetonitrile* R1.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	93	7	isocratic
3-13	93→70	7→30	linear gradient
13-14	70→93	30→7	linear gradient
14-20	93	7	re-equilibration

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When the chromatograms are recorded under the prescribed conditions, the retention times relative to phenylephrine (retention time about 3 minutes) are: impurity C, about 1.3; impurity E, about 3.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak to valley ratio* is at least 5, where H_p is the height above the baseline of the peak due to impurity C and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to phenylephrine.

LIMITS

Identify any peaks in solution (1) corresponding to impurities C and E using the chromatogram obtained with solution (3) and multiply the area of the each peak by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the eye drops with sufficient *water* to give a solution containing 0.1% w/v of Phenylephrine Hydrochloride.
(2) 0.1% w/v of *phenylephrine hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil C18 BDS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 273 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.10% w/v *sodium heptanesulfonate* in a mixture of 2 volumes of *glacial acetic acid*, 400 volumes of *methanol* and 600 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_2$,HCl using the declared content of $C_9H_{13}NO_2$,HCl in *phenylephrine hydrochloride BPCRS*.

STORAGE

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Phenylephrine Eye Drops should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and E listed under Phenylephrine Hydrochloride.

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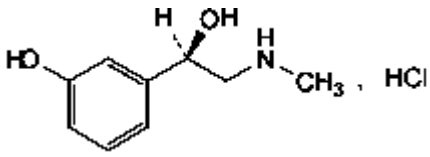
Phenylephrine Hydrochloride

General Notices

(Ph. Eur. monograph 0632)



$C_9H_{14}ClNO_2$ 203.7 *61-76-7*

Action and use

Alpha-adrenoceptor agonist.

Preparations

Phenylephrine Eye Drops

Phenylephrine Injection

Phenylephrine Intracameral Injection

Ph Eur

DEFINITION

(1*R*)-1-(3-Hydroxyphenyl)-2-(methylamino)ethanol hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

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About 143 °C.

IDENTIFICATION

First identification: A, C, E.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Melting point (2.2.14): 171 °C to 176 °C.

Dissolve 0.3 g in 3 mL of *water R*, add 1 mL of *dilute ammonia R1* and initiate crystallisation by scratching the wall of the tube with a glass rod. Wash the crystals with iced *water R* and dry at 105 °C for 2 h.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *phenylephrine hydrochloride CRS*.

D. Dissolve about 10 mg in 1 mL of *water R* and add 0.05 mL of a 125 g/L solution of *copper sulfate pentahydrate R* and 1 mL of a 200 g/L solution of *sodium hydroxide R*. A violet colour is produced. Add 1 mL of *ether R* and shake; the upper layer remains colourless.

E. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.00 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Specific optical rotation (2.2.7)

-43 to -47 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase B, mobile phase A (20:80 *V/V*).

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Buffer solution pH 2.8 Dissolve 3.25 g of *sodium octanesulfonate monohydrate R* in 1000 mL of *water for chromatography R* by stirring for 30 min and adjust to pH 2.8 with *dilute phosphoric acid R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *phenylephrine hydrochloride for peak identification CRS* (containing impurities C and E) in 2 mL of the solvent mixture.

Column:

— *size*: *l* = 0.055 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution pH 2.8 (10:90 *V/V*);

— *mobile phase B*: buffer solution pH 2.8, *acetonitrile R1* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	93	7
3 - 13	93 → 70	7 → 30
13 - 14	70 → 93	30 → 7

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL.

Identification of impurities Identify the peaks due to impurities C and E using the chromatogram obtained with reference solution (b).

Relative retention With reference to phenylephrine (retention time = about 2.8 min): impurity C = about 1.3; impurity E = about 3.6.

System suitability:

— *symmetry factor*: maximum 1.9 for the principal peak in the chromatogram obtained with the test solution;

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— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to phenylephrine in the chromatogram obtained with reference solution (b).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.5; impurity E = 0.5;

— *impurities C, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulfates (*2.4.13*)

Maximum 500 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in a mixture of 0.5 mL of *0.1 M hydrochloric acid* and 80 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*) using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 20.37 mg of $C_9H_{14}ClNO_2$.

IMPURITIES

Specified impurities C, E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, D.

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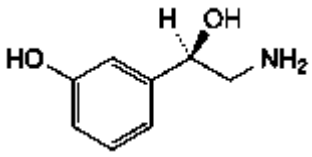
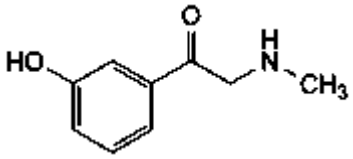
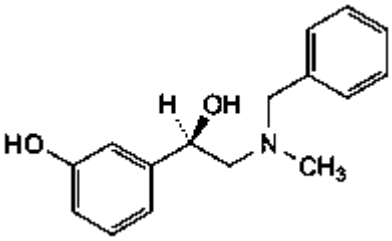


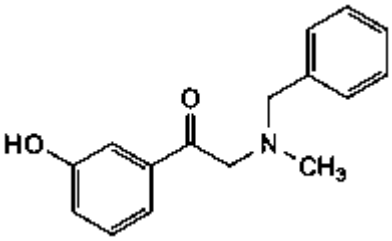
A. (1*R*)-2-amino-1-(3-hydroxyphenyl)ethanol (norphenylephrine),



C. 1-(3-hydroxyphenyl)-2-(methylamino)ethanone (phenylephrone),



D. (1*R*)-2-(benzylmethylamino)-1-(3-hydroxyphenyl)ethanol (benzylphenylephrine),



E. 2-(benzylmethylamino)-1-(3-hydroxyphenyl)ethanone (benzylphenylephrone).

Ph Eur

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Phenylephrine Injection

General Notices

Action and use

Alpha-adrenoceptor agonist.

DEFINITION

Phenylephrine Injection is a sterile solution of Phenylephrine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phenylephrine hydrochloride, $C_9H_{13}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

To 350 mg of *4-nitroaniline* add 1.5 mL of *hydrochloric acid*, and mix. Dilute with water to 50 mL, mix, and allow to settle. Place 5 mL of the clear supernatant in a 100 mL volumetric flask, and immerse it in an ice bath. While it is in the ice bath, add 1 mL of *hydrochloric acid*, then add, in small portions, 2 mL of a 1% w/v *sodium nitrite* solution, dilute with *water* to volume, and mix (solution A).

(1) Concentrate, or dilute a volume of the injection with sufficient *water*, if necessary, to produce a solution containing 1% w/v of Phenylephrine Hydrochloride.

(2) 1% w/v of *phenylephrine hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with 0.5M *ethanolic potassium hydroxide*, dry at 60° for 15 minutes and spray with solution A. Examine in daylight.

MOBILE PHASE

3 volumes of *ammonium hydroxide,* 25 volumes of *water* and 72 volumes of *methanol*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the test for Related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to phenylephrine in the chromatogram obtained with solution (4).

TESTS

Acidity

pH, 4.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B A mixture of 20 volumes of mobile phase B and 80 volumes of mobile phase A.

(1) Dilute the injection with sufficient solution B, if necessary, to produce a solution containing 0.005% w/v of Phenylephrine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes of solution B. Dilute 1 volume to 5 volumes of solution B.

(3) 0.1% w/v of *phenylephrine hydrochloride for peak identification EPCRS* in solution B.

(4) 0.005% w/v of *phenylephrine hydrochloride BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (1.8 µm) (Zorbax Eclipse Plus C18).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *acetonitrile* R1 and 90 volumes of a 0.325% w/v solution of sodium octanesulfonate monohydrate in water adjusted to pH 2.8 with dilute orthophosphoric acid.

Mobile phase B 10 volumes of a 0.325% w/v solution of sodium octanesulfonate monohydrate in water adjusted to pH 2.8 with dilute orthophosphoric acid and 90 volumes *acetonitrile* R1.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	93	7	isocratic
3-13	93→70	7→30	linear gradient
13-14	70→93	30→7	linear gradient
14-20	93	7	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to phenylephrine (retention time about 3 minutes) are: impurity C, about 1.3; impurity E, about 3.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak to valley ratio* is at least 5, where H_p is the height above the baseline of the peak due to impurity C and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to phenylephrine.

LIMITS

Identify any peaks in solution (1) corresponding to impurities C and E using the chromatogram obtained with solution (3) and multiply the area of the each peak by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

To a quantity containing 50 mg of Phenylephrine Hydrochloride add sufficient 0.5M *sulfuric acid* to produce 100 mL. Dilute 10 mL to 100 mL with 0.5M *sulfuric acid* and measure the *absorbance* of the resulting solution at the maximum at 273 nm, Appendix II B. Calculate the content of $C_9H_{13}NO_2$,HCl taking 90 as the value of A(1%, 1 cm) at the maximum at 273 nm.

STORAGE

Phenylephrine Injection should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and E listed under Phenylephrine Hydrochloride.

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Phenylephrine Intracameral Injection

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Alpha-adrenoceptor agonist.

DEFINITION

Phenylephrine Intracameral Injection is a sterile, isotonic solution of Phenylephrine Hydrochloride in a suitable diluent. It is supplied as a ready-to-use solution.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of phenylephrine hydrochloride, $C_9H_{13}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume containing 1.2 mg of Phenylephrine Hydrochloride add, if necessary, sufficient *water* to produce 1 mL and then add 0.05 mL of *weak copper sulfate solution* and 1 mL of 5M *sodium hydroxide*; a violet colour is produced. Add 1 mL of *ether* and shake; the ether layer remains colourless.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

Osmolality

The osmolality of the injection is 300 to 400 mosmol/kg, Appendix V N.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of mobile phase B and 80 volumes of mobile phase A.

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(1) Dilute a quantity of the injection, if necessary, to produce a solution containing 0.1% w/v of Phenylephrine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 20 volumes and then further dilute 1 volume to 50 volumes.

(3) 0.1% w/v of *phenylephrine hydrochloride for peak identification EPCRS* (contains Ph Eur impurities C and E).

(4) Dilute 1 volume of solution (2) to 2 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (1.8 µm) (Zorbax Eclipse Plus C18 is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with the same material (Phenomenex is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *acetonitrile R1* and 90 volumes of a pH 2.8 buffer prepared by dissolving 3.25 g of *sodium octanesulfonate monohydrate* in 1000 mL of *water*, stirring for 30 minutes and adjusting the pH to 2.8 with *dilute phosphoric acid*.

Mobile phase B 10 volumes of the pH 2.8 buffer and 90 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	93	7	isocratic
3-13	93→70	7→30	linear gradient
13-14	70→93	30→7	linear gradient
14-20	93	7	isocratic

When the chromatograms are recorded under the prescribed conditions the retention time of phenylephrine is about 2.8 minutes; the relative retention of impurity C is about 1.3 and that of impurity E is about 3.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (1), the *symmetry factor* of the principal peak is not more than 1.9;

in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 5 where H_p is the height above the baseline of the peak due to impurity C and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to

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phenylephrine.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities C and E using solution (3) and multiply the areas of these peaks by the following correction factors: impurity C, 0.5; impurity E, 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C or E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection containing 30 mg of Phenylephrine Hydrochloride to 50 mL with *water*.
(2) 0.06% w/v of *phenylephrine hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 273 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.10% w/v of *sodium heptanesulfonate* in a mixture of 2 volumes of *glacial acetic acid*, 400 volumes of *methanol* and 600 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_2$,HCl in the injection using the declared content of $C_9H_{13}NO_2$,HCl in *phenylephrine hydrochloride BPCRS*.

STORAGE

Phenylephrine Intracameral Injection should be protected from light.

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IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and E listed under Phenylephrine Hydrochloride.

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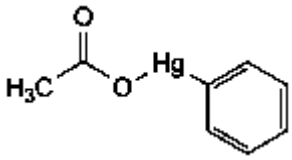
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Phenylmercuric Acetate

General Notices

(Ph. Eur. monograph 2042)



$C_8H_8HgO_2$ 336.7 *62-38-4*

Action and use

Antiseptic, antimicrobial preservative.

Ph Eur

DEFINITION

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder or small, colourless crystals.

Solubility

Slightly soluble in water, soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *Ph. Eur. reference spectrum of phenylmercuric acetate*.

B. To 5 mL of solution S (see Tests) add 5 mL of *water R* and 0.1 mL of *sodium sulfide solution R*. A white precipitate is formed that darkens slowly on heating.

C. To 10 mL of solution S add 2 mL of *potassium iodide solution R* and shake vigorously. Filter. The filtrate gives reaction (b) of acetates (*2.3.1*).

TESTS

Solution S

Dissolve 0.250 g in 40 mL of *water R* by heating to boiling. Allow to cool and dilute to 50 mL with *water R*. Prepare the solution immediately before use.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Ionised mercury

Maximum 0.2 per cent.

To 2 mL of solution S add 8 mL of *water R*, 2 mL of *potassium iodide solution R* and 3 mL of *dilute hydrochloric acid R*. Filter. The filtrate is not more coloured than the potassium iodide solution used. Wash the precipitate with 3 mL of *water R*. Combine the filtrate and the washings, add 2 mL of *dilute sodium hydroxide solution R* and dilute to 20 mL with *water R*. 12 mL of this solution complies with test A for heavy metals (*2.4.8*). Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Polymercuric benzene compounds

Maximum 1.5 per cent.

Shake 0.2 g with 10 mL of *acetone R*. Filter. Wash the residue twice with 5 mL of *acetone R*. Dry the residue at 105 °C for 1 h. The residue weighs a maximum of 3 mg.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 45 °C for 15 h.

ASSAY

Dissolve with heating 0.300 g in 100 mL of *water R*. Cool and add 3 mL of *nitric acid R*. Titrate with *0.1 M ammonium thiocyanate* using 2 mL of *ferric ammonium sulfate solution R2* as indicator, until a persistent reddish-yellow colour is obtained.

1 mL of *0.1 M ammonium thiocyanate* is equivalent to 33.67 mg of phenylmercuric acetate.

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Phenylmercuric Borate

General Notices

(Ph. Eur. monograph 0103)

Action and use

Antiseptic; antimicrobial preservative.

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DEFINITION

Compound consisting of equimolecular proportions of phenylmercuric orthoborate and phenylmercuric hydroxide ($C_{12}H_{13}BHg_2O_4$; M_r 633) or of the dehydrated form (metaborate, $C_{12}H_{11}BHg_2O_3$; M_r 615) or of a mixture of the 2 compounds.

Content

— *mercury* (Hg; A_r 200.6): 64.5 per cent to 66.0 per cent (dried substance),

— *borates expressed as* H_3BO_3: 9.8 per cent to 10.3 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder or colourless, shiny crystals.

Solubility

Slightly soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison *Ph. Eur. reference spectrum of phenylmercuric borate*.

B. To 2 mL of solution S (see Tests) add 8 mL of *water R* and 0.1 mL of *sodium sulfide solution R*. A white precipitate is formed that darkens slowly on heating.

C. Dissolve about 20 mg in 2 mL of *methanol R*. The solution is clear and colourless. Ignite; the solution burns with a green-edged flame.

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TESTS

Solution S

Dissolve 0.25 g by sprinkling it on the surface of 25 mL of boiling *water R*, cool and dilute to 25 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Ionised mercury

Maximum 0.01 per cent.

To 10 mL of solution S add 2 mL of *potassium iodide solution R* and 3 mL of *dilute hydrochloric acid R*. Filter. The filtrate is colourless. Wash the precipitate with 3 mL of *water R*. Combine the filtrate and the washings, add 2 mL of *dilute sodium hydroxide solution R* and dilute to 20 mL with *water R*. 12 mL of this solution complies with test A for heavy metals (*2.4.8*). Prepare the reference solution using a mixture of 2.5 mL of *lead standard solution (2 ppm Pb) R* and 7.5 mL of *water R*.

Loss on drying (*2.2.32*)

Maximum 3.5 per cent, determined on 0.50 g by drying in an oven at 45 °C for 15 h ± 30 min.

ASSAY

Mercury

Dissolve 0.300 g in 100 mL of *water R* and add 3 mL of *nitric acid R*. Titrate with *0.1 M ammonium thiocyanate*, using 2 mL of *ferric ammonium sulfate solution R2* as indicator, until a persistent reddish-yellow colour is obtained.

1 mL of *0.1 M ammonium thiocyanate* is equivalent to 20.06 mg of Hg.

Borates

Dissolve 0.600 g with heating in 25 mL of *water R*. Dissolve 10 g of *sorbitol R* in the hot solution and cool. Titrate with *0.1 M sodium hydroxide*, using 0.5 mL of *phenolphthalein solution R* as indicator, until a persistent pink colour is obtained. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 6.18 mg of H_3BO_3.

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Phenylmercuric Nitrate

General Notices

(Ph. Eur. monograph 0783)

Action and use

Antiseptic; antimicrobial preservative.

Ph Eur

DEFINITION

Mixture of phenylmercuric nitrate ($C_6H_5HgNO_3$; M_r 339.7) and phenylmercuric hydroxide (C_6H_5HgOH; M_r 294.7).

Content

62.5 per cent to 64.0 per cent of Hg (A_r 200.6) (dried substance).

CHARACTERS

Appearance

White or pale yellow powder.

Solubility

Very slightly soluble in water and in ethanol (96 per cent), slightly soluble in hot water. It dissolves in glycerol and in fatty oils.

IDENTIFICATION

A. To 5 mL of solution S (see Tests) add 8 mL of *water R* and 0.1 mL of *sodium sulfide solution R*. A white precipitate is formed that darkens slowly on heating.

B. To 1 mL of a saturated solution of the substance to be examined add 1 mL of *dilute hydrochloric acid R*. A white, flocculent precipitate is formed.

C. To 5 mL of solution S add 1 mL of *dilute hydrochloric acid R*, 2 mL of *methylene chloride R* and 0.2 mL of *dithizone solution R*. Shake. The lower layer is orange-yellow.

D. About 10 mg gives the reaction of nitrates (*2.3.1*).

TESTS

Solution S

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To 0.1 g add 45 mL of *water R* and heat to boiling with shaking. Cool, filter and dilute to 50 mL with *water R*.

Appearance of solution

Solution S is colourless (*2.2.2, Method II*).

Inorganic mercuric compounds

Maximum 0.1 per cent.

To 10 mL of solution S add 2 mL of *potassium iodide solution R* and 3 mL of *dilute hydrochloric acid R*. Filter. The filtrate is colourless. Wash the precipitate with 2 mL of *water R*. Combine the filtrate and washings, add 2 mL of *dilute sodium hydroxide solution R* and dilute to 20 mL with *water R*. 12 mL of the solution complies with test A for heavy metals (*2.4.8*). Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* for 24 h.

ASSAY

Dissolve 0.150 g in a mixture of 10 mL of *dilute nitric acid R* and 90 mL of *water R*, heating to boiling. Cool to 15-20 °C. Titrate with *0.1 M ammonium thiocyanate* using 2 mL of *ferric ammonium sulfate solution R2* as indicator, until a persistent reddish-yellow colour is obtained. Carry out a blank titration.

1 mL of *0.1 M ammonium thiocyanate* is equivalent to 20.06 mg of Hg.

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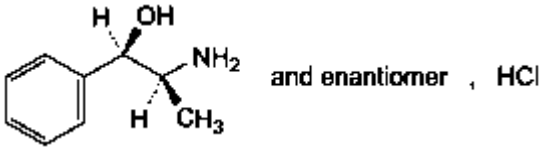
Phenylpropanolamine Hydrochloride

General Notices

(Ph. Eur. monograph 0683)



$C_9H_{14}ClNO$ 187.7 *154-41-6*

Action and use

Adrenoceptor agonist.

Ph Eur

DEFINITION

(1*RS*,2*SR*)-2-Amino-1-phenylpropan-1-ol hydrochloride.

Content

99.0 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 194 °C to 197 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *phenylpropanolamine hydrochloride CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 20 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *phenylpropanolamine hydrochloride CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Pretreatment Spray with a 20 g/L solution of *disodium tetraborate R*, using 8 mL for a plate 100 mm x 200 mm and dry in a stream of cold air for 30 min.

Mobile phase *concentrated ammonia R*, *ethanol (96 per cent) R*, *butanol R* (6:24:70 *V/V/V*).

Application 10 µL as bands of 10 mm by 3 mm.

Development Over 1/2 of the plate.

Drying In a current of warm air.

Detection Allow to cool, then spray with a 2 g/L solution of *ninhydrin R* in *ethanol (96 per cent) R* and heat at 110 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.25 g in *water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Related substances

Liquid chromatography (*2.2.29*).

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Buffer solution Dissolve 3.4 g of *potassium dihydrogen phosphate R* in 500 mL of *water for chromatography R* and adjust to pH 2.5 with *phosphoric acid R*.

Test solution Dissolve 25.0 mg of the substance to be examined in *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *cathine hydrochloride R* (1*S*,2*S*-enantiomer of impurity A) in *methanol R* and dilute to 50 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R*. Dilute 1 mL of this solution to 10 mL with the test solution.

Column:

— *size*: *l* = 0.075 m, Ø = 3.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (1.8 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution (2:98 *V/V*);

— *mobile phase B*: *water for chromatography R*, *acetonitrile R1* (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	100	0
6 - 14	100 → 48	0 → 52
14 - 18	48	52

Flow rate 0.56 mL/min.

Detection Spectrophotometer at 206 nm.

Injection 1 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to phenylpropanolamine (retention time = about 3 min): impurity A = about 1.2.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to phenylpropanolamine.

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Calculation of percentage contents:

— for each impurity, use the concentration of phenylpropanolamine hydrochloride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

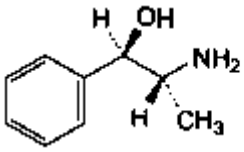
ASSAY

Dissolve 0.150 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.77 mg of $C_9H_{14}ClNO$.

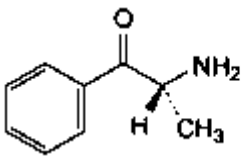
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E.*



and enantiomer

A. (1*RS*,2*RS*)-2-amino-1-phenylpropan-1-ol (racemic cathine, racemic norpseudoephedrine),



and enantiomer

B. (2*RS*)-2-amino-1-phenylpropan-1-one (racemic cathinone),

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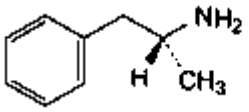
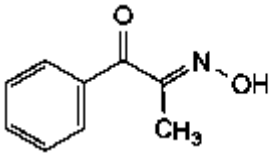


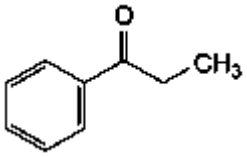
and enantiomer

C. (2*RS*)-1-phenylpropan-2-amine (amfetamine),



and (*Z*)-isomer

D. (2*EZ*)-2-(hydroxyimino)-1-phenylpropan-1-one (α-isonitrosopropiophenone),



E. 1-phenylpropan-1-one (propiophenone).

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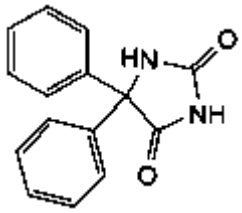
Phenytoin

General Notices

(Ph. Eur. monograph 1253)



$C_{15}H_{12}N_2O_2$ 252.3 *57-41-0*

Action and use

Antiepileptic.

Preparation

Phenytoin Oral Suspension

Ph Eur

DEFINITION

5,5-Diphenylimidazolidine-2,4-dione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *phenytoin CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Dissolve 1.0 g in a mixture of 5 mL of *1 M sodium hydroxide* and 20 mL of *water R*.

Acidity or alkalinity

To 1.0 g add 45 mL of *water R* and boil for 2 min. Allow to cool and filter. Wash the filter with *carbon dioxide-free water R* and dilute the combined filtrate and washings to 50 mL with the same solvent. To 10 mL of the solution add 0.15 mL of *methyl red solution R*. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red. To 10 mL of the solution add 0.15 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *2,2-diphenylglycine R* (impurity C) in 100 mL of the mobile phase.

Reference solution (c) Dissolve 10 mg of *phenytoin for system suitability CRS* (containing impurities D and E) in the mobile phase, add 1 mL of reference solution (b) and dilute to 10 mL with the mobile phase.

Reference solution (d) Dissolve 50.0 mg of *phenytoin CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm).

Mobile phase Mix 20 volumes of *methanol R2*, 35 volumes of *acetonitrile R1* and 45 volumes of a 5.75 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (c).

Run time 4 times the retention time of phenytoin.

Identification of impurities Use the chromatogram supplied with *phenytoin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D and E.

Relative retention With reference to phenytoin (retention time = about 4 min): impurity C = about 0.5; impurity D = about 0.6; impurity E = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 3.5 between the peaks due to impurities D and E.

Limits:

— *correction factors*: for the calculation of content, multiply the peaks areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity E = 1.4;

— *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

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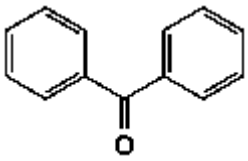
Calculate the percentage content of $C_{15}H_{12}N_2O_2$ taking into account the assigned content of *phenytoin CRS*.

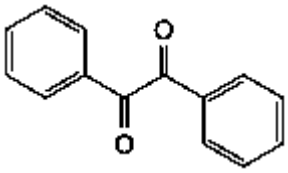
IMPURITIES

Specified impurities *C, D, E.*

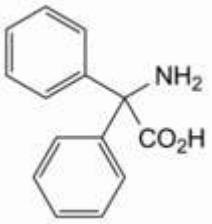
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, F.*



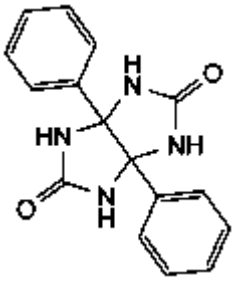
A. diphenylmethanone (benzophenone),



B. diphenylethanedione (benzil),



C. amino(diphenyl)acetic acid (2,2-diphenylglycine),



D. 3a,6a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione,

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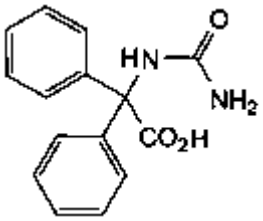
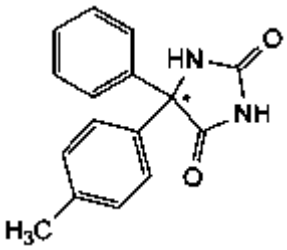


E. (carbamoylamino)diphenylacetic acid,



F. (5Ξ)-5-(4-methylphenyl)-5-phenylimidazolidine-2,4-dione.

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Phenytoin Capsules

General Notices

Phenytoin Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Antiepileptic.

DEFINITION

Phenytoin Capsules contain Phenytoin Sodium.

The capsules comply with the requirements stated under Capsules and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Phenytoin Sodium. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

Content of phenytoin sodium, $C_{15}H_{11}N_2NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.5 g of Phenytoin Sodium with 10 mL of *water*. Filter and add 2M *hydrochloric acid* to the filtrate until a white precipitate is formed. Centrifuge the precipitated mixture, dissolve the residue in *methanol*, evaporate and dry at 105° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of phenytoin *(RS 272)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in the mobile phase.

(1) Mix with the aid of ultrasound a quantity of the contents of the capsules containing 50 mg of Phenytoin Sodium with 30 mL of mobile phase and dilute to 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume to 5 volumes.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack ODS AQ 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 220 nm.

(g) Inject 20 µL of each solution.

(h) Allow the chromatography to proceed for 4 times the retention time of phenytoin.

MOBILE PHASE

200 volumes of *methanol*, 350 volumes of *acetonitrile R1* and 450 volumes of 0.05M *ammonium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed condition the relative retentions with reference to phenytoin (retention time about 4 minutes) are: impurity C, about 0.5; impurity D, about 0.6; impurity E, about 0.8, impurity A, about 3.2 and impurity B, about 3.8.

SYSTEM SUITABILITY

The test is not valid unless: in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (2) is at least 40.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity D and impurity E using the chromatogram obtained with solution (3). Multiply the area of these peaks by the corresponding correction factors: impurity D, 1.7 and impurity E, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in the mobile phase.

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(1) Mix with the aid of ultrasound a quantity of the capsule contents containing 50 mg of Phenytoin Sodium with 30 mL of mobile phase, dilute to 50 mL and filter. Further dilute 1 volume to 10 volumes.

(2) 0.01% w/v of *phenytoin sodium BPCRS*.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}N_2NaO_2$ in the capsules from the chromatograms obtained and using the declared content of $C_{15}H_{11}N_2NaO_2$ in *phenytoin sodium BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenytoin Sodium.

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Phenytoin Injection

General Notices

Action and use

Antiepileptic.

DEFINITION

Phenytoin Injection is a sterile solution containing 5% w/v of Phenytoin Sodium in a mixture of 40% v/v of Propylene Glycol and 10% v/v of Ethanol in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phenytoin sodium, $C_{15}H_{11}N_2NaO_2$

4.75 to 5.25% w/v.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

To 6 g of the injection, add 25 mL of *water* and extract with successive quantities of 50, 30 and 30 mL of *ethyl acetate*, shaking each extract thoroughly for 1 minute, allowing to stand for 5 minutes and again shaking for 1 minute before separating the solvent. Wash each extract by shaking thoroughly for 1 minute with the same 15 mL of water, filter the extracts successively and wash the filter with 10 mL of *ethyl acetate*. Combine the ethyl acetate washing and extracts, evaporate the solvent and dry the residue to constant weight at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of phenytoin *(RS 272)*.

TESTS

Alkalinity

pH, 11.5 to 12.1, Appendix V L.

Weight per mL

1.025 to 1.035 g, Appendix V G.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in the mobile phase.

(1) Dilute 1 mL of the injection to 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume to 5 volumes.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack ODS AQ 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 220 nm.

(g) Inject 20 µL of each solution.

(h) Allow the chromatography to proceed for 4 times the retention time of phenytoin.

MOBILE PHASE

200 volumes of *methanol*, 350 volumes of *acetonitrile R1* and 450 volumes of 0.05M *ammonium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed condition the relative retentions with reference to phenytoin (retention time about 4 minutes) are: impurity C, about 0.5; impurity D, about 0.6; impurity E, about 0.8, impurity A, about 3.2 and impurity B, about 3.8.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (2) is at least 40.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity D and impurity E using the chromatogram obtained with solution (3). Multiply the area of these peaks by the corresponding correction factors: impurity D, 1.7 and impurity E, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Ethanol and propylene glycol

Carry out the method for *gas chromatography*, Appendix III B, using a solution containing 2% v/v of *methanol* and 4% v/v of *ethylene glycol* in *water* as the internal standard.

(1) To 5 mL of the injection, add 50 mL of the internal standard and dilute to 100 mL with *water*.

(2) Dilute 5 mL of the injection to 100 mL with *water*.

(3) Equal volumes of the internal standard and a solution containing 1% v/v of *ethanol* and 4% w/v of *propylene glycol* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a film (1 µm) of *polyethylene glycol* (Stabilwax is suitable).

(b) Use *helium* as the carrier gas at 5 mL per minute.

(c) Use the gradient conditions described below.

(d) Use an inlet temperature of 240°.

(e) Use a flame ionisation detector at a temperature of 250°.

(f) Inject 0.2 µL of each solution.

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature	Comment
0-4	50°	isothermal
4-16	50°→230°	linear gradient
16-21	230°	isothermal

When the chromatograms are recorded under the prescribed conditions the retentions relative to ethylene glycol are: methanol, about 0.27; ethanol, about 0.32 and propylene glycol, about 0.98.

SYSTEM SUITABILITY

Inject solution (3) six times. The test is not valid unless the relative standard deviation of the areas of the peaks due to ethanol and propylene glycol is at most 2.0% for each.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methanol and ethanol is at least 5.0 and the *resolution* between the peaks due to propylene glycol and ethylene glycol is at least 5.0.

LIMITS

Calculate the ratio of the area of the peak due to ethanol to the area of the peak due to methanol and the ratio of the area of the peak due to propylene glycol to the area of the peak due to ethylene glycol from the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1):

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the content of ethanol is not less than 9.0% v/v and not greater than 11.0% v/v;

the content of propylene glycol is not less than 37.0% v/v and not greater than 43.0% v/v.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in the mobile phase.

(1) Dilute 1 weighed volume of the injection to 50 volumes. Further dilute 1 volume to 10 volumes.

(2) 0.01% w/v of *phenytoin sodium BPCRS*.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the injection, Appendix V G, and calculate the content of $C_{15}H_{11}N_2NaO_2$, weight in volume, using the declared content of $C_{15}H_{11}N_2NaO_2$ in *phenytoin sodium BPCRS*.

STORAGE

Phenytoin Injection should be protected from light. Solutions in which a haziness or precipitate develops should not be used.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenytoin Sodium.

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Phenytoin Oral Suspension

General Notices

Phenytoin Oral Suspensions from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Antiepileptic.

DEFINITION

Phenytoin Oral Suspension is a suspension of Phenytoin in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Phenytoin. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

Content of phenytoin, $C_{15}H_{12}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Add 5 mL of *water* to a quantity of the oral suspension containing 30 mg of Phenytoin and extract with five 4-mL quantities of *diethyl ether*. Wash the combined extracts with three 2-mL quantities of *water* and evaporate the washed extract to dryness under a stream of *nitrogen*. The *infrared absorption spectrum*, Appendix II A, of the dried residue is concordant with the reference spectrum of phenytoin (*RS 272*).

TESTS

Acidity

pH, 4.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared immediately before use in the mobile phase.

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(1) Add 5 mL of *water* and 2 mL of *2M hydrochloric acid* to a quantity of the oral suspension containing 30 mg of Phenytoin, mix well and extract with five 20-mL quantities of *diethyl ether*. Combine the ether extracts, wash with three 10-mL quantities of *water*, evaporate to dryness and dissolve the residue in 30 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume to 5 volumes.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack ODS AQ 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 220 nm.

(g) Inject 20 µL of each solution.

(h) Allow the chromatography to proceed for 4 times the retention time of phenytoin.

MOBILE PHASE

200 volumes of *methanol*, 350 volumes of *acetonitrile R1* and 450 volumes of 0.05M *ammonium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed condition the retention times relative to phenytoin (retention time about 4 minutes) are: impurity C, about 0.5; impurity D, about 0.6; impurity E, about 0.8, impurity A, about 3.2 and impurity B, about 3.8.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (2) is at least 40.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity D and impurity E using the chromatogram obtained with solution (3). Multiply the area of these peaks by the corresponding correction factors: impurity D, 1.7 and impurity E, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared immediately before use in the mobile phase.

(1) Add 5 mL of *water* and 2 mL of *2M hydrochloric acid* to a weighed quantity of the oral suspension containing 30 mg of Phenytoin, mix well and extract with five 20-mL quantities of *diethyl ether*. Combine the ether extracts, wash with three 10-mL quantities of *water* and evaporate to dryness. Dissolve the residue in 30 mL of mobile phase and dilute to produce 50 mL. Dilute 1 volume of the resulting solution to 5 volumes with mobile phase.

(2) 0.012% w/v of *phenytoin sodium BPCRS*.

(3) 0.12% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{11}N_2O_2$, weight in volume, using the declared content of $C_{15}H_{11}N_2NaO_2$ in *phenytoin sodium BPCRS*. Each mg of $C_{15}H_{11}N_2NaO_2$ is equivalent to 0.9198 mg of $C_{15}H_{11}N_2O_2$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenytoin.

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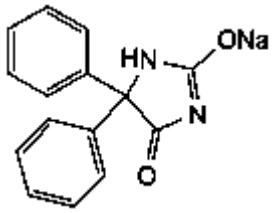
Phenytoin Sodium

General Notices

(Ph. Eur. monograph 0521)



$C_{15}H_{11}N_2NaO_2$ 274.3 *630-93-3*

Action and use

Antiepileptic.

Preparations

Phenytoin Capsules

Phenytoin Injection

Phenytoin Tablets

Ph Eur

DEFINITION

Sodium 4-oxo-5,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-olate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic, crystalline powder.

Solubility

Soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

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IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Suspend 0.1 g in 20 mL of water R. Acidify with dilute hydrochloric acid R and shake with 3 quantities, each of 30 mL, of ethyl acetate R. Wash the combined ethyl acetate layers with water R, evaporate to dryness and dry the residue at 100-105 °C (test residue). Repeat the operations using 0.1 g of phenytoin sodium CRS (reference residue). Examine as discs prepared using potassium bromide R.

Comparison phenytoin sodium CRS.

B. Thin-layer chromatography (2.2.27).

Solvent mixture acetone R, methanol R (50:50 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution Dissolve 20 mg of phenytoin sodium CRS in the solvent mixture and dilute to 10 mL with the solvent mixture.

Plate TLC silica gel F_{254} plate R.

Mobile phase concentrated ammonia R, toluene R, 2-propanol R (10:40:50 *V/V/V*).

Application 10 µL as bands of 8 mm.

Development Over 2/3 of the plate.

Drying At 80 °C for 5 min; allow to cool.

Detection Examine in ultraviolet light at 254 nm.

Results The principal zone in the chromatogram obtained with the test solution is similar in position and size to the principal zone in the chromatogram obtained with the reference solution.

C. Ignite 1 g and cool. Add 2 mL of water R to the residue and neutralise the solution with hydrochloric acid R. Filter and dilute the filtrate to 4 mL with water R. 0.1 mL of the solution gives reaction (b) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Suspend 1.0 g in 5 mL of water R and dilute to 20 mL with 0.1 M sodium hydroxide.

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Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *2,2-diphenylglycine R* (impurity C) in 100 mL of the mobile phase.

Reference solution (c) Dissolve 10 mg of *phenytoin for system suitability CRS* (containing impurities D and E) in the mobile phase, add 1 mL of reference solution (b) and dilute to 10 mL with the mobile phase.

Reference solution (d) Dissolve 50.0 mg of *phenytoin CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm).

Mobile phase Mix 20 volumes of *methanol R2*, 35 volumes of *acetonitrile R1* and 45 volumes of a 5.75 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (c).

Run time 4 times the retention time of phenytoin.

Identification of impurities Use the chromatogram supplied with *phenytoin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D and E.

Relative retention With reference to phenytoin (retention time = about 4 min): impurity C = about 0.5; impurity D = about 0.6; impurity E = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 3.5 between the peaks due to impurities D and E.

Limits:

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— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity E = 1.4;

— *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Free phenytoin

Dissolve 0.30 g in 10 mL of a mixture of equal volumes of *pyridine R* and *water R*. Add 0.5 mL of *phenolphthalein solution R* and 3 mL of *silver nitrate solution in pyridine R*. Not more than 1.0 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.00 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{15}H_{11}N_2NaO_2$ taking into account the assigned content of *phenytoin CRS*, and a conversion factor of 1.09.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *C, D, E.*

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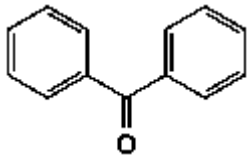
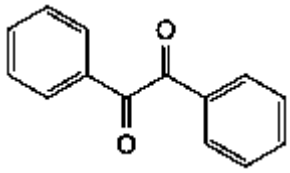
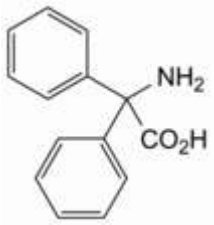
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, F.



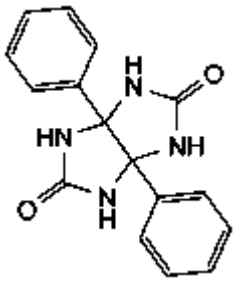
A. diphenylmethanone (benzophenone),



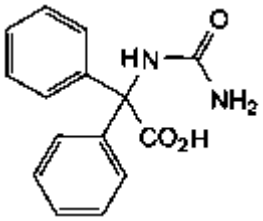
B. diphenylethanedione (benzil),



C. amino(diphenyl)acetic acid (2,2-diphenylglycine),



D. 3a,6a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione,



E. (carbamoylamino)diphenylacetic acid,

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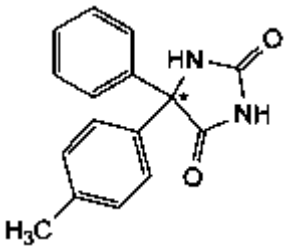

F. (5Ξ)-5-(4-methylphenyl)-5-phenylimidazolidine-2,4-dione.

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Phenytoin Tablets

General Notices

Phenytoin Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Antiepileptic.

DEFINITION

Phenytoin Tablets contain Phenytoin Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Phenytoin Sodium. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

Content of phenytoin sodium, $C_{15}H_{11}N_2NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Phenytoin Sodium with 10 mL of *water*, filter through a 0.45-µm nylon filter and acidify the filtrate with 2M *hydrochloric acid* until a white precipitate is formed. Filter the precipitate through a sintered glass filter, dissolve the residue in *methanol*, evaporate under the solvent under a stream of *nitrogen* and dry the residue at 105° for 30 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of phenytoin (*RS 272*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in the mobile phase.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 50 mg of Phenytoin Sodium with 30 mL and dilute to 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume to 5 volumes.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack ODS AQ 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 220 nm.

(g) Inject 20 µL of each solution.

(h) Allow the chromatography to proceed for 4 times the retention time of phenytoin.

MOBILE PHASE

200 volumes of *methanol*, 350 volumes of *acetonitrile R1* and 450 volumes of 0.05M *ammonium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed condition the relative retentions with reference to phenytoin (retention time about 4 minutes) are: impurity C, about 0.5; impurity D, about 0.6; impurity E, about 0.8, impurity A, about 3.2 and impurity B, about 3.8.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (2) is at least 40.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity D and impurity E using the chromatogram obtained with solution (3). Multiply the area of these peaks by the corresponding correction factors: impurity D, 1.7 and impurity E, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in the mobile phase.

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(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 50 mg of Phenytoin Sodium with 30 mL, dilute to 50 mL and filter. Further dilute 1 volume to 10 volumes.

(2) 0.01% w/v of *phenytoin sodium BPCRS*.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}N_2NaO_2$ in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{11}N_2NaO_2$ in *phenytoin sodium BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenytoin Sodium.

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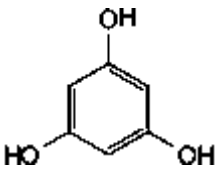
Phloroglucinol

General Notices

Anhydrous Phloroglucinol

(Ph. Eur. monograph 2301)



$C_6H_6O_3$ 126.1 *108-73-6*

Action and use

Antispasmodic.

Ph Eur

DEFINITION

Benzene-1,3,5-triol.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *anhydrous phloroglucinol CRS*.

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B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.20 g of anhydrous phloroglucinol CRS in methanol R and dilute to 10 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase *anhydrous formic acid R*, hexane R, ethyl acetate R (2:37.5:62.5 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 2.50 g in ethanol (96 per cent) R and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

pH (2.2.3)

4.0 to 6.0.

Dilute 10 mL of solution S to 100 mL with carbon dioxide-free water R.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light*.

Solvent mixture Mobile phase B, mobile phase A (10:90 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

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Reference solution (b) Dissolve 6 mg each of *resorcinol R* (impurity B), *phloroglucide R* (impurity D) and *pyrogallol R* (impurity A) in 10 mL of the solvent mixture, add 2 mL of the test solution and dilute to 20 mL with the solvent mixture. Dilute 1 mL of this solution to 50 mL with the solvent mixture.

Reference solution (c) Dissolve 4 mg each of *benzene-1,2,4-triol R* (impurity E), *2,6-dichlorophenol R* (impurity I), *4-chlororesorcinol R* (impurity K) and *3,5-dichloroaniline R* (impurity L) in 10 mL of the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (d) Dissolve 10 mg of the substance to be examined in 10 mL of the solvent mixture, add 1 mL of reference solution (c) and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	100	0
9 - 15	100 → 50	0 → 50
15 - 25	50 → 20	50 → 80
25 - 30	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and D; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities E, I, K and L.

Relative retention With reference to phloroglucinol (retention time = about 12 min): impurity E = about 0.7; impurity A = about 0.9; impurity D = about 1.3; impurity B = about 1.35; impurity K = about 1.5; impurity I = about 1.8; impurity L = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity A and phloroglucinol; minimum 4.0 between the peaks due to impurities D and B.

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Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity D = 0.2; impurity E = 0.7; impurity I = 0.6; impurity K = 0.6; impurity L = 0.4;

— *impurities A, D, E, I, K, L*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 500 ppm.

Dilute 3 mL of solution S to 15 mL with *distilled water R*.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 50 mL of *water R*. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

1 mL of *1 M sodium hydroxide* is equivalent to 63.05 mg of $C_6H_6O_3$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, D, E, I, K, L.*

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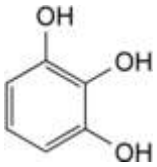
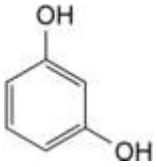
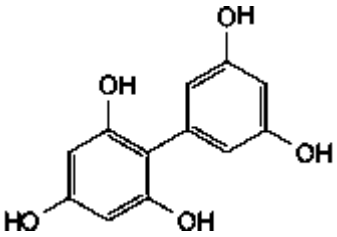
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, O.



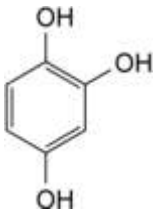
A. benzene-1,2,3-triol (pyrogallol),



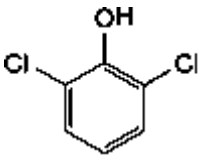
B. benzene-1,3-diol (resorcinol),



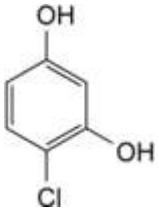
D. 2,3′,4,5′,6-biphenylpentol (phloroglucide),



E. benzene-1,2,4-triol,



I. 2,6-dichlorophenol,



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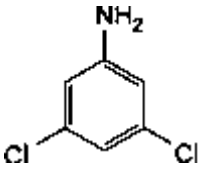
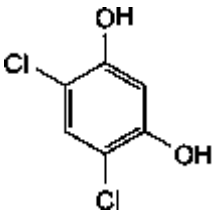
K. 4-chlorobenzene-1,3-diol (4-chlororesorcinol),



L. 3,5-dichloroaniline,



O. 4,6-dichlorobenzene-1,3-diol (4,6-dichlororesorcinol).

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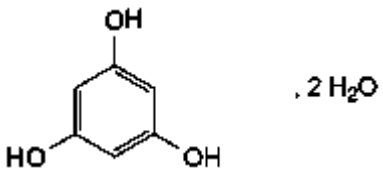
Phloroglucinol Dihydrate

General Notices

(Ph. Eur. monograph 2302)



$C_6H_6O_3,2H_2O$ 162.1 *6099-90-7*

Action and use

Antispasmodic.

Ph Eur

DEFINITION

Benzene-1,3,5-triol dihydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Previously dry the substance to be examined in an oven at 105 °C.

Comparison *anhydrous phloroglucinol CRS*.

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B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.20 g of *anhydrous phloroglucinol CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *hexane R*, *ethyl acetate R* (2:37.5:62.5 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 2.50 g in *ethanol (96 per cent) R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

pH (2.2.3)

4.0 to 6.0.

Dilute 10 mL of solution S to 100 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Solvent mixture Mobile phase B, mobile phase A (10:90 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

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Reference solution (b) Dissolve 6 mg each of *resorcinol R* (impurity B), *phloroglucide R* (impurity D) and *pyrogallol R* (impurity A) in 10 mL of the solvent mixture, add 2 mL of the test solution and dilute to 20 mL with the solvent mixture. Dilute 1 mL of this solution to 50 mL with the solvent mixture.

Reference solution (c) Dissolve 4 mg each of *benzene-1,2,4-triol R* (impurity E), *2,6-dichlorophenol R* (impurity I), *4-chlororesorcinol R* (impurity K) and *3,5-dichloroaniline R* (impurity L) in 10 mL of the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (d) Dissolve 10 mg of the substance to be examined in 10 mL of the solvent mixture, add 1 mL of reference solution (c) and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	100	0
9 - 15	100 → 50	0 → 50
15 - 25	50 → 20	50 → 80
25 - 30	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and D; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities E, I, K and L.

Relative retention With reference to phloroglucinol (retention time = about 12 min): impurity E = about 0.7; impurity A = about 0.9; impurity D = about 1.3; impurity B = about 1.35; impurity K = about 1.5; impurity I = about 1.8; impurity L = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity A and phloroglucinol; minimum 4.0 between the peaks due to impurities D and B.

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Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity D = 0.2; impurity E = 0.7; impurity I = 0.6; impurity K = 0.6; impurity L = 0.4;

— *impurities A, D, E, I, K, L*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 500 ppm.

Dilute 3 mL of solution S to 15 mL with *distilled water R*.

Loss on drying (2.2.32)

20.0 per cent to 23.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.600 g in 50 mL of *water R*. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

1 mL of *1 M sodium hydroxide* is equivalent to 63.05 mg of $C_6H_6O_3$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, D, E, I, K, L.*

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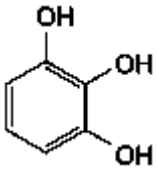
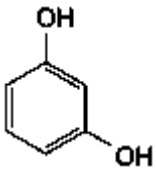
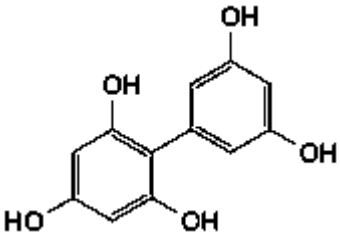
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, O.



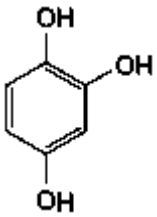
A. benzene-1,2,3-triol (pyrogallol),



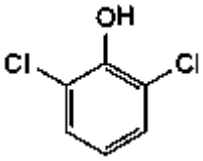
B. benzene-1,3-diol (resorcinol),



D. 2,3′,4,5′,6-biphenylpentol (phloroglucide),



E. benzene-1,2,4-triol,



I. 2,6-dichlorophenol,

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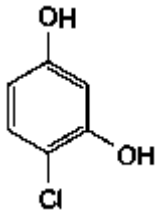
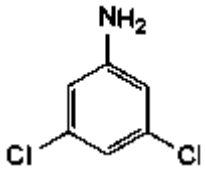
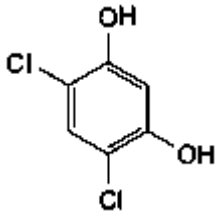


K. 4-chlorobenzene-1,3-diol (4-chlororesorcinol),



L. 3,5-dichloroaniline,



O. 4,6-dichlorobenzene-1,3-diol (4,6-dichlororesorcinol).

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Pholcodine Linctus

General Notices

Pholcodine Oral Solution

Action and use

Opioid receptor agonist; cough suppressant.

DEFINITION

Pholcodine Linctus is an *oral solution* containing 0.1% w/v of Pholcodine and 1% w/v of Citric Acid Monohydrate in a suitable flavoured vehicle.

The linctus complies with the requirements stated under Oral Liquids and with the following requirements.

Content of pholcodine, $C_{23}H_{30}N_2O_4,H_2O$

0.090 to 0.110% w/v.

IDENTIFICATION

To 20 mL add 20 mL of *water*, make alkaline to *litmus paper* with 5M *ammonia*, extract with two 20-mL quantities of *chloroform*, washing each extract with 5 mL of *water*, dry the combined extracts with *anhydrous sodium sulfate*, filter and evaporate to dryness. If necessary add 0.1 mL of *ether* and scratch the side of the vessel with a glass rod to induce crystallisation. The crystals, dried at a pressure not exceeding 2 kPa, comply with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of pholcodine (*RS 273*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.01% w/v solution in 0.01M *sodium hydroxide* exhibits a maximum only at 284 nm.

C. Dissolve the remainder of the crystals in 1 mL of *sulfuric acid* and add 0.05 mL of *ammonium molybdate-sulfuric acid solution*; a pale blue colour is produced. Warm gently; the colour changes to deep blue. Add 0.05 mL of 2M *nitric acid*; the colour changes to brownish red.

ASSAY

To 50 g add sufficient 5M *ammonia* to make the solution alkaline to *litmus paper* and extract with four 25-mL quantities of *chloroform*, washing each extract with the same 5 mL of *water*. Combine the extracts and evaporate until the volume is reduced to 15 mL. Carry out Method I for *non-aqueous titration*, Appendix VIII A, using *0.02M perchloric acid VS* as titrant and *quinaldine red solution* as indicator. Each mL of *0.02M perchloric acid VS* is equivalent to 4.165 mg of $C_{23}H_{30}N_2O_4,H_2O$. Determine the *weight per mL* of the linctus, Appendix V G, and calculate the content of $C_{23}H_{30}N_2O_4,H_2O$, weight in volume.

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STORAGE

Pholcodine Linctus should be protected from light.

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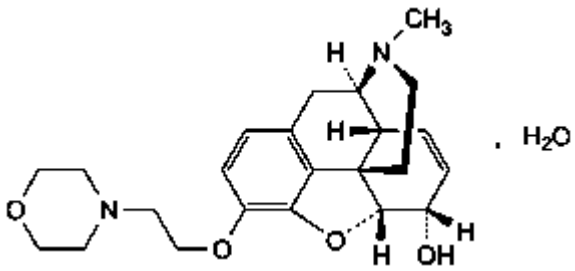
Pholcodine Monohydrate

General Notices

Pholcodine

(Ph. Eur. monograph 0522)



$C_{23}H_{30}N_2O_4,H_2O$ 416.5 *6254-99-5*

Action and use

Opioid receptor agonist; cough suppressant.

Preparations

Pholcodine Linctus

Strong Pholcodine Linctus

Ph Eur

DEFINITION

17-Methyl-3-[2-(morpholin-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan-6α-ol monohydrate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

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Sparingly soluble in water, freely soluble in acetone and in ethanol (96 per cent). It dissolves in dilute mineral acids.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *pholcodine CRS*.

TESTS

Specific optical rotation (2.2.7)

-98 to -94 (dried substance).

Dissolve 1.000 g in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

0.02 M phosphate buffer solution To 80.0 mL of *0.2 M sodium hydroxide* add 100.0 mL of *0.2 M potassium dihydrogen phosphate R* and dilute to 1.0 L with *water R*.

Solvent mixture Dilute 80 mL of *acetonitrile R* to 1 L with the 0.02 M phosphate buffer solution.

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *codeine R* (impurity B) in the solvent mixture and dilute to 10 mL with the solvent mixture. To 0.5 mL of this solution add 0.5 mL of the test solution and dilute to 50 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *pholcodine for peak identification CRS* (containing impurities A, B and D) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *pholcodine for impurity G identification CRS* in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core phenylhexylsilyl silica gel for chromatography R* (2.6 µm);

— *temperature*: 35 °C.

Mobile phase To 50 mL of *tetrahydrofuran for chromatography R* add 75 mL of *acetonitrile R* and dilute to 1000 mL with the 0.02 M phosphate buffer solution; adjust to pH 7.9 ± 0.05 with *0.2 M sodium hydroxide*; the pH must not exceed 8.0.

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Flow rate 1.0 mL/min.

Detection Spectrophotometer at 238 nm.

Injection 20 µL.

Run time 5 times the retention time of pholcodine.

Identification of impurities Use the chromatogram supplied with *pholcodine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and D; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

Relative retention With reference to pholcodine (retention time = about 10 min): impurity A = about 0.4; impurity B = about 0.8; impurity D = about 2.3; impurity G = about 4.2.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity B and pholcodine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 0.5;

— *impurities A, B, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

3.9 per cent to 4.5 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 50 mL of *anhydrous acetic acid R*, warming gently. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

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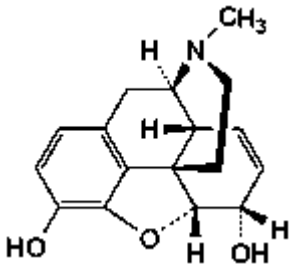
1 mL of *0.1 M perchloric acid* is equivalent to 19.93 mg of $C_{23}H_{30}N_2O_4$.

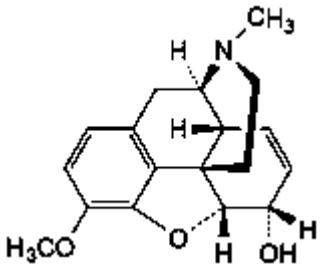
IMPURITIES

Specified impurities A, B, D, G.

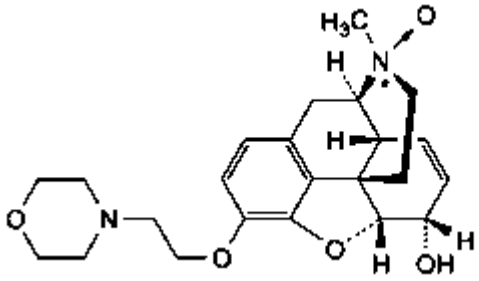
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, E, F.



A. 17-methyl-7,8-didehydro-4,5α-epoxymorphinan-3,6α-diol (morphine),



B. 3-methoxy-17-methyl-7,8-didehydro-4,5α-epoxymorphinan-6α-ol (codeine),



C. (17*RS*)-6α-hydroxy-17-methyl-3-[2-(morpholin-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan 17-oxide (pholcodine *N*-oxide),

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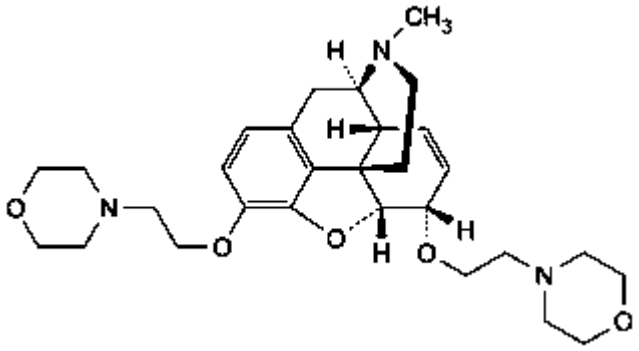
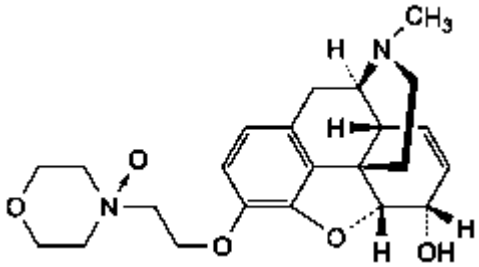
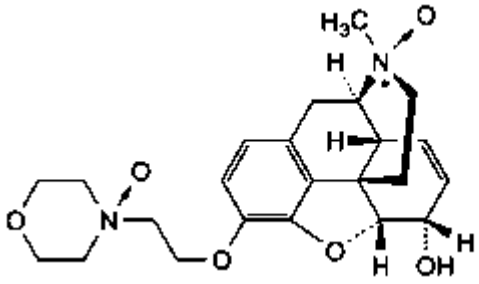


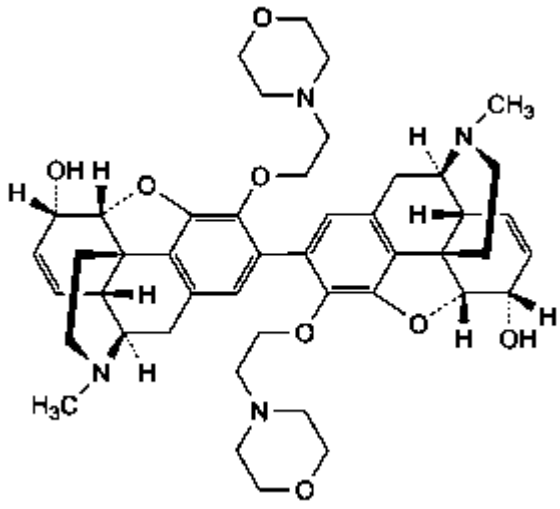
D. 17-methyl-3,6α-bis[2-(morpholin-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan,



E. 4-[2-[(6α-hydroxy-17-methyl-7,8-didehydro-4,5α-epoxymorphinan-3-yl)oxy]ethyl]morpholine 4-oxide (pholcodine *N*′-oxide),



F. (17*RS*)-6α-hydroxy-17-methyl-3-[2-(4-oxidomorpholin-4-ium-4-yl)ethoxy]-7,8-didehydro-4,5α-epoxymorphinan 17-oxide (pholcodine *N*,*N*′-dioxide),



G. 17,17'-dimethyl-3,3'-bis[2-(morpholin-4-yl)ethoxy]-7,7',8,8'-tetradehydro-4,5α:4',5'α-diepoxybimorphinan-6α,6'α-diol (pholcodine dimer).

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Phosphate Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

DEFINITION

Phosphate Oral Solution contains Disodium Hydrogen Phosphate Dihydrate and Phosphoric Acid in Purified Water.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of phosphoric acid, H_3PO_4

95.0 to 105.0% of the stated amount.

Content of total phosphate, calculated as PO_4

95.0 to 105.0% of the stated amount.

Content of sodium, Na

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Yields the reactions characteristic of *sodium salts,* Appendix VI.

B. Yields the reactions characteristic of *phosphates,* Appendix VI.

TESTS

Acidity

pH, 2.6 to 3.0, Appendix V L.

ASSAY

For phosphoric acid

To a volume of the oral solution containing 1.4 g of Phosphoric Acid add 80 mL of *water* and 25 g of *sodium chloride*. Titrate with *0.5M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator.

Each mL of *0.5M sodium hydroxide VS* is equivalent to 24.5 mg of H_3PO_4.

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For total phosphate

Dilute a volume of the oral solution containing 10 mmol of phosphate (PO_4) to 1000 mL with *water*; dilute 25 mL of this solution to 1000 mL with *water*. To 15 mL of the resulting solution add 8 mL of 1M *sulfuric acid*, 2 mL of *ammonium molybdate solution* and 4 mL of *methylaminophenol–sulfite reagent*; mix and allow to stand for 15 minutes. Add sufficient *water* to produce 50 mL, mix, allow to stand for a further 15 minutes and measure the *absorbance* of a 1 cm layer of the resulting solution at 730 nm, Appendix II B.

Calculate the content of total phosphate, PO_4, in the oral solution from a calibration curve obtained from a series of reference solutions prepared in the following manner. Dissolve 1.42 g of *anhydrous disodium hydrogen orthophosphate*, previously dried at 105° for 3 hours, in 1000 mL of *water* and dilute 10 mL of this solution to 250 mL with *water* to produce a solution containing 0.0038% w/v (0.4 mmol per litre) of phosphate (PO_4). To separate 5, 10, 15, 20 and 25 mL volumes of this solution add 8 mL of 1M *sulfuric acid*, 2 mL of *ammonium molybdate solution* and 4 mL of *methylaminophenol–sulfite reagent*; mix and allow to stand for 15 minutes. Add sufficient *water* to produce 50 mL, mix, allow to stand for a further 15 minutes and measure the *absorbance* of a 1 cm layer of the resulting solution at 730 nm, Appendix II B.

For sodium

Prepare a suitable dilution in *water* and determine by *atomic emission spectrophotometry*, Appendix II D, Method I, measuring at 589 nm. Calculate the content of Na by comparing the result with that obtained from a solution prepared by dissolving suitable quantities of *orthophosphoric acid* and *anhydrous disodium hydrogen orthophosphate* in sufficient *water* to produce a solution of the same expected concentration as the diluted preparation being examined.

LABELLING

The label states (1) the strength as a percentage w/v of Phosphoric Acid and of Disodium Hydrogen Phosphate Dihydrate; (2) the approximate concentration of phosphate ions (PO_4^{3-}) in millimoles (mmol) per mL.

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Phosphates Enema

General Notices

Sodium Phosphates Enema

Phosphates Rectal Solution

DEFINITION

Phosphates Enema is a *rectal solution* containing suitable quantities of either Sodium Dihydrogen Phosphate, Sodium Dihydrogen Phosphate Monohydrate, Sodium Dihydrogen Phosphate Dihydrate or Phosphoric Acid and either Disodium Hydrogen Phosphate, Disodium Hydrogen Phosphate Dodecahydrate or Disodium Hydrogen Phosphate Dihydrate in freshly boiled and cooled Purified Water. A suitable antimicrobial preservative may be included.

The composition of two established formulations is described below.

Formula A

Sodium Dihydrogen Phosphate Dihydrate	160 g
Disodium Hydrogen Phosphate Dodecahydrate	60 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

A suitable antimicrobial preservative may be included.

Formula B

Sodium Dihydrogen Phosphate Dihydrate	100 g
Disodium Hydrogen Phosphate Dodecahydrate	80 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

A suitable antimicrobial preservative may be included.

The enema complies with the requirements stated under Rectal Preparations and with the following requirements.

Content of sodium dihydrogen phosphate dihydrate, $NaH_2PO_4,2H_2O$

Formula A: 15.2 to 16.8% w/v; *Formula B*: 9.5 to 10.5% w/v; *any other formulation*: 95.0 to 105.0% of the stated amount.

Content of disodium hydrogen phosphate dodecahydrate, $Na_2HPO_4,12H_2O$

Formula A: 5.6 to 6.4% w/v; *Formula B*: 7.5 to 8.5% w/v; *any other formulation*: 95.0 to 105.0% of the stated amount.

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IDENTIFICATION

A. Yields the reactions characteristic of *sodium salts*, Appendix VI.

B. Yields the reactions characteristic of *phosphates*, Appendix VI.

TESTS

Clarity and colour of solution

The enema being examined is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

Acidity

pH, 5.0 to 6.2, Appendix V L.

ASSAY

For sodium dihydrogen phosphate dihydrate

To 20 mL add 80 mL of *water* and 25 g of *sodium chloride* and titrate with *0.5M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.5M sodium hydroxide VS* is equivalent to 78.00 mg of $NaH_2PO_4,2H_2O$.

For disodium hydrogen phosphate dodecahydrate

Titrate 50 mL with *0.5M hydrochloric acid VS* using 2 mL of a mixture of 4 volumes of *bromocresol green solution* and 1 volume of *methyl red solution* as indicator and titrating to the colour indicative of pH 4.4. Each mL of *0.5M hydrochloric acid VS* is equivalent to 179.0 mg of $Na_2HPO_4,12H_2O$.

LABELLING

The label states (1) where appropriate, that the enema is Formula A or Formula B; (2) for any formulation other than Formula A or B, the content in terms of the amount or equivalent of Sodium Dihydrogen Phosphate Dihydrate and Disodium Hydrogen Phosphate Dodecahydrate.

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Phosphoric Acid

General Notices

(Concentrated Phosphoric Acid, Ph. Eur. monograph 0004)

H_3PO_4 98.0 *7664-38-2*

Preparation

Phosphate Oral Solution

Ph Eur

DEFINITION

Content

84.0 per cent *m/m* to 90.0 per cent *m/m*.

CHARACTERS

Appearance

Clear, colourless, syrupy liquid, corrosive.

Solubility

Miscible with water and with ethanol (96 per cent).

When stored at a low temperature it may solidify into a mass of colourless crystals which do not melt at a temperature below 28 °C.

Relative density

About 1.7.

IDENTIFICATION

A. Dilute with *water R*. The solution is strongly acid (*2.2.4*).

B. Solution S (see Tests) neutralised with *dilute sodium hydroxide solution R* gives the reactions of phosphates (*2.3.1*).

TESTS

Solution S

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Dilute 10.0 g to 150 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Substances precipitated with ammonia

To 10 mL of solution S add 8 mL of *dilute ammonia R1*. Any opalescence in the solution is not more intense than that in a mixture of 10 mL of solution S and 8 mL of *water R*.

Hypophosphorous acid and phosphorous acid

To 5 mL of solution S add 2 mL of *silver nitrate solution R2* and heat on a water-bath for 5 min. The solution shows no change in appearance.

Chlorides (*2.4.4*)

Maximum 50 ppm, determined on solution S.

Sulfates (*2.4.13*)

Maximum 100 ppm.

Dilute 1.5 g to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 50 ppm.

Dilute 3 mL of solution S to 10 mL with *water R*.

ASSAY

Dilute 0.500 g in 30 mL of *water R*. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added at the 2nd inflexion point.

1 mL of *1 M sodium hydroxide* is equivalent to 49.00 mg of H_3PO_4.

STORAGE

In a glass container.

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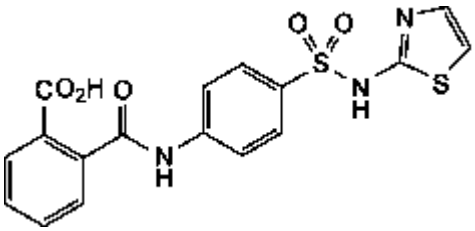
Phthalylsulfathiazole

General Notices

(Ph. Eur. monograph 0352)



$C_{17}H_{13}N_3O_5S_2$ 403.4 *85-73-4*

Action and use

Antibacterial.

Ph Eur

DEFINITION

2-[[4-(Thiazol-2-ylsulfamoyl)phenyl]carbamoyl]benzoic acid.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in dimethylformamide, slightly soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B, E.

Second identification: B, C, D, E.

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *phthalylsulfathiazole CRS*.

B. To 1 g add 8.5 mL of *dilute sodium hydroxide solution R* and boil under a reflux condenser for 30 min. Cool and add 17.5 mL of *dilute hydrochloric acid R*. Shake vigorously and filter. Neutralise the filtrate with *dilute sodium hydroxide solution R*. Filter, wash the precipitate with *water R*, recrystallise from *water R* and dry the crystals at 100-105 °C. The crystals melt (2.2.14) at 200 °C to 203 °C.

C. To 0.1 g in a test-tube add 3 mL of *dilute sulfuric acid R* and 0.5 g of *zinc powder R*. Fumes are evolved which produce a black stain on *lead acetate paper R*.

D. To 0.1 g add 0.5 g of *resorcinol R* and 0.3 mL of *sulfuric acid R* and heat on a water-bath until a homogeneous mixture is obtained. Allow to cool. Add 5 mL of *dilute sodium hydroxide solution R*. Dilute 0.1 mL of this brownish-red mixture to 25 mL with *water R*. An intense green fluorescence appears which disappears on acidification.

E. Dissolve about 10 mg of the crystals obtained in identification test B in 200 mL of *0.1 M hydrochloric acid*. 2 mL of the solution gives the reaction of primary aromatic amines (2.3.1) with formation of an orange precipitate.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

Dissolve 1.0 g in *1 M sodium hydroxide* and dilute to 20 mL with the same solvent.

Acidity

To 2.0 g add 20 mL of *water R*, shake continuously for 30 min and filter. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Sulfathiazole and other primary aromatic amines

Maximum 2.0 per cent.

Dissolve 5 mg in a mixture of 3.5 mL of *water R*, 6 mL of *dilute hydrochloric acid R* and 25 mL of *ethanol (96 per cent) R*, previously cooled to 15 °C. Place immediately in iced water and add 1 mL of a 2.5 g/L solution of *sodium nitrite R*. Allow to stand for 3 min, add 2.5 mL of a 40 g/L solution of *sulfamic acid R* and allow to stand for 5 min. Add 1 mL of a 4 g/L solution of *naphthylethylenediamine dihydrochloride R* and dilute to 50 mL with *water R*. Measured at 550 nm, the absorbance (2.2.25) is not greater than that of a standard prepared at the same time and in the same manner using a mixture of 1 mL of a 100 mL aqueous solution containing 10 mg of *sulfathiazole R* and 0.5 mL of *hydrochloric acid R*; 2.5 mL of *water R*; 6 mL of *dilute hydrochloric acid R*; and 25 mL of *ethanol (96 per cent) R*.

Loss on drying (2.2.32)

Maximum 2 per cent, determined on 1.00 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.300 g in 40 mL of *dimethylformamide R*. Titrate with *0.1 M sodium hydroxide* until the colour becomes blue. using 0.2 mL of *thymolphthalein solution R* as indicator. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 20.17 mg of $C_{17}H_{13}N_3O_5S_2$.

STORAGE

Protected from light.

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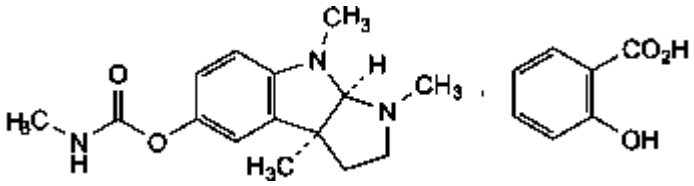
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Physostigmine Salicylate

General Notices

(Ph. Eur. monograph 0286)



$C_{22}H_{27}N_3O_5$ 413.5 *57-64-7*

Action and use

Cholinesterase inhibitor.

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DEFINITION

Physostigmine salicylate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (3a*S*,8a*R*)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-yl methylcarbamate salicylate, calculated with reference to the dried substance.

CHARACTERS

Colourless or almost colourless crystals, sparingly soluble in water, soluble in ethanol (96 per cent). The crystals gradually become red when exposed to air and light; the colour develops more quickly when the crystals are also exposed to moisture. Aqueous solutions are unstable.

It melts at about 182 °C, with decomposition.

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *physostigmine salicylate CRS*.

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B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Heat about 10 mg in a porcelain dish with a few drops of *dilute ammonia R1*. An orange colour develops. Evaporate the solution to dryness. The residue dissolves in *alcohol R* giving a blue solution. Add 0.1 mL of *glacial acetic acid R*. The colour becomes violet. Dilute with *water R*. An intense red fluorescence appears.

D. Solution S (see Tests) gives reaction (a) of salicylates (*2.3.1*).

TESTS

Solution S

Dissolve 0.900 g, without heating, in 95 mL of *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent. Prepare immediately before use.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 5.1 to 5.9.

Specific optical rotation (*2.2.7*)

-90 to -94, determined on solution S and calculated with reference to the dried substance.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a) Dissolve 0.2 g of the substance to be examined in *alcohol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 2.5 mL of test solution (a) to 50 mL with *alcohol R*.

Reference solution (a) Dissolve 10 mg of *physostigmine salicylate CRS* in *alcohol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 2 mL of reference solution (a) to 20 mL with *alcohol R*.

Apply to the plate 20 µL of each solution. Develop over a path of 15 cm using a mixture of 2 volumes of *concentrated ammonia R*, 23 volumes of *2-propanol R* and 100 volumes of *cyclohexane R*. Dry the plate in a current of cold air and carry out a second development in the same direction. Allow the plate to dry in air and spray with freshly prepared *potassium iodobismuthate solution R* and then with *dilute hydrogen peroxide solution R*. Examine the plate within 2 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

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To 5 mL of solution S add a few crystals of *potassium iodate R*, 0.05 mL of *dilute hydrochloric acid R* and 2 mL of *chloroform R*. Shake. No violet colour develops in the chloroform layer within 1 min.

Sulfates (*2.4.13*)

15 mL of solution S complies with the limit test for sulfates (0.1 per cent).

Loss on drying (*2.2.32*)

Not more than 1.0 per cent, determined on 1.00 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Dissolve 0.350 g in 50 mL of a mixture of equal volumes of *anhydrous acetic acid R* and *chloroform R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 41.35 mg of $C_{22}H_{27}N_3O_5$.

STORAGE

Store in an airtight container, protected from light.

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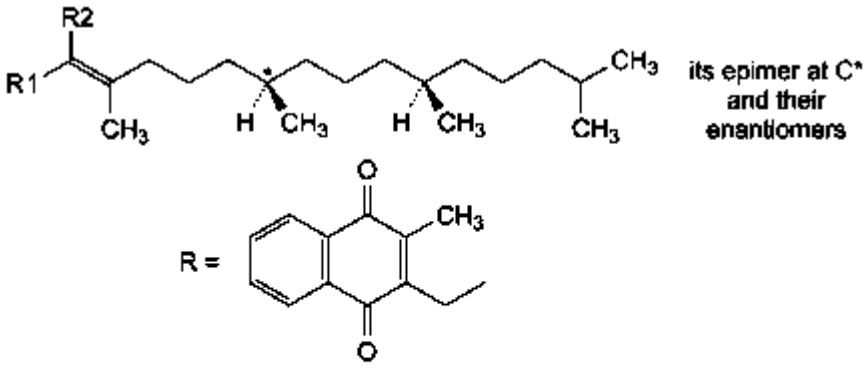
Phytomenadione

General Notices

(all-rac-Phytomenadione, Ph. Eur. monograph 3011)



Phytomenadione	R1	R2	Molecular formula	M_r
trans isomers	R	H	$C_{31}H_{46}O_2$	450.7
cis isomers	H	R	$C_{31}H_{46}O_2$	450.7

$C_{31}H_{46}O_2$ 450.7 *81818-54-4*

Action and use

Vitamin K analogue.

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DEFINITION

Mixture of the 4 stereoisomers of 2-methyl-3-[(2*E*,7Ξ,11Ξ)-3,7,11,15-tetramethylhexadec-2-en-1-yl]naphthalene-1,4-dione (*trans*-phytomenadione isomers) and the 4 stereoisomers of 2-methyl-3-[(2*Z*,7Ξ,11Ξ)-3,7,11,15-tetramethylhexadec-2-en-1-yl]naphthalene-1,4-dione (*cis*-phytomenadione isomers).

Content

— *trans*-phytomenadione isomers: minimum 85.0 per cent;

— sum of *trans*-phytomenadione and *cis*-phytomenadione isomers: 97.0 per cent to 103.0 per cent.

CHARACTERS

Appearance

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Clear, intense yellow, viscous, oily liquid.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent), miscible with fatty oils.

It decomposes on exposure to actinic light.

Refractive index

About 1.526.

IDENTIFICATION

Prepare the solutions immediately before use and protect from light.

A. Optical rotation (see Tests).

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution (a) Dissolve 10.0 mg of the substance to be examined in *trimethylpentane R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 10.0 mL of test solution (a) to 50.0 mL with *trimethylpentane R*.

Spectral range 275-340 nm for test solution (a); 230-280 nm for test solution (b).

Absorption maxima 327 nm for test solution (a); 243 nm, 249 nm, 261 nm and 270 nm for test solution (b).

Absorption minimum 285 nm for test solution (a).

Specific absorbance at the absorption maximum at 327 nm 67 to 73 for test solution (a).

C. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 2.5 g in *trimethylpentane R* and dilute to 25 mL with the same solvent.

Optical rotation (2.2.7)

-0.05° to + 0.05°, measured at 25 °C.

Dissolve 0.25 g in *trimethylpentane R* and dilute to 25.0 mL with the same solvent.

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Acid value (*2.5.1*)

Maximum 2.0, determined on 2.00 g.

Impurity A

Thin-layer chromatography (*2.2.27*). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 0.40 g of the substance to be examined in *cyclohexane R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 4.0 mg of *menadione R* (impurity A) in *cyclohexane R* and dilute to 50.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *cyclohexane R*, *toluene R* (20:80 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air for 5 min.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Impurity A = about 0.2; *trans*-phytomenadione isomers = about 0.5.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with the reference solution (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of *phytomenadione CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *trans-epoxyphytomenadione CRS* (impurity B) in 1 mL of the mobile phase. Add 0.4 mL of the solution to 5 mL of reference solution (a) and dilute to 100 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 25.0 mL with the mobile phase.

Column:

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— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *silica gel for chromatography R* (5 µm).

Mobile phase *octanol R*, *di-isopropyl ether R*, *heptane R* (1:3.3:1000 *V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration With the mobile phase for at least 24 h.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Run time 1.6 times the retention time of *trans*-phytomenadione isomers.

Relative retention With reference to *trans*-phytomenadione isomers (retention time = about 27 min): impurity B = about 0.6; *cis*-phytomenadione isomers = about 0.65.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity B and *cis*-phytomenadione isomers; minimum 4.0 between the peaks due to *cis*-phytomenadione isomers and *trans*-phytomenadione isomers.

Calculation of percentage contents:

— for each impurity, use the concentration of *trans*-phytomenadione isomers in reference solution (c), taking into account their content as determined in the assay.

Limits:

— *impurity B*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

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Injection Test solution and reference solution (d).

System suitability Reference solution (d):

— *repeatability*: maximum relative standard deviation of 1.0 per cent for the peak due to *trans*-phytomenadione isomers, determined on 6 injections.

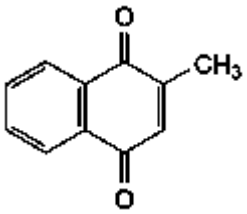
Calculate the percentage contents of *trans*-phytomenadione isomers and *cis*-phytomenadione isomers taking into account the assigned content of *phytomenadione CRS*.

STORAGE

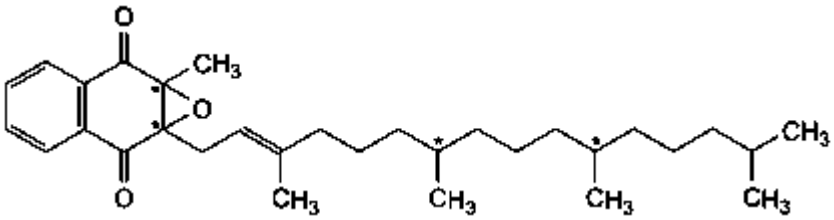
Protected from light.

IMPURITIES

Specified impurities *A, B.*



A. 2-methylnaphthalene-1,4-dione (menadione),



B. (1a*Ξ*,7a*Ξ*)-1a-methyl-7a-[(2*E*,7*Ξ*,11*Ξ*)-3,7,11,15-tetramethylhexadec-2-en-1-yl]-1a,7a-dihydronaphtho[2,3-*b*]oxirene-2,7-dione (*trans*-epoxyphytomenadione isomers).

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Phytomenadione Injection

General Notices

Action and use

Vitamin K analogue.

DEFINITION

Phytomenadione Injection is a sterile preparation of Phytomenadione in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phytomenadione, $C_{31}H_{46}O_2$

90.0 to 115.0% of the stated amount.

CHARACTERISTICS

A clear to slightly opalescent liquid when maintained at a temperature below 25°.

IDENTIFICATION

A. Dilute with *absolute ethanol* to produce a solution containing 0.01% w/v of Phytomenadione. The *light absorption* of the solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum at 328 nm and a minimum at 292 nm.

B. Dilute a quantity of the solution used in test A with *absolute ethanol* to produce a solution containing 0.001% w/v of Phytomenadione. The *light absorption* of the solution, Appendix II B, in the range 230 to 350 nm exhibits maxima at 245, 249, 263 and 271 nm and minima at 256 nm and 266 nm.

TESTS

Acidity or alkalinity

pH, 5.0 to 7.5, Appendix V L.

ASSAY

Carry out the following procedure in subdued light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection containing 10 mg of Phytomenadione with sufficient of the mobile phase to produce 100 mL.

(2) 0.01% w/v of *phytomenadione BPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *water* and 95 volumes of *ethanol* (*96%*).

DETERMINATION OF CONTENT

Calculate the content of $C_{31}H_{46}O_2$ in the injection using the declared content of $C_{31}H_{46}O_2$ in *phytomenadione BPCRS*.

STORAGE

Phytomenadione Injection deteriorates on exposure to light and should be stored in the dark. It should not be allowed to freeze.

LABELLING

The label states that the injection should not be used if separation has occurred or if oil droplets have appeared.

When vitamin K_1 injection is prescribed or demanded, Phytomenadione Injection shall be dispensed or supplied.

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Phytomenadione Tablets

General Notices

Action and use

Vitamin K analogue.

DEFINITION

Phytomenadione Tablets contain Phytomenadione.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of phytomenadione, $C_{31}H_{46}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Phytomenadione with 50 mL of *absolute ethanol* for 1 hour, allow to stand and dilute 5 mL of the clear supernatant liquid to 50 mL with *absolute ethanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum at 328 nm and a minimum at 292 nm. Dilute a suitable volume of the solution with sufficient *absolute ethanol* to produce a solution containing 0.001% w/v of Phytomenadione. The *light absorption* of this solution, in the range 230 to 350 nm, exhibits maxima at 245, 249, 263 and 271 nm and minima at 256 nm and 266 nm.

TESTS

Disintegration

The requirement for Disintegration does not apply to Phytomenadione Tablets.

Menadione

Carry out the following procedure in subdued light. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 50 mg of Phytomenadione in 5 mL of *absolute ethanol* with the aid of ultrasound for 5 minutes, add 15 mL of *2,2,4-trimethylpentane*, shake for 1 minute, centrifuge and use the supernatant liquid.
(2) 0.0025% w/v of *menadione* in *2,4,4-trimethylpentane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

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(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *methanol*, 20 volumes of *ether* and 80 volumes of *cyclohexane*.

LIMITS

Any *secondary spot* corresponding to menadione in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. Carry out the following procedure in subdued light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of 0.5M *ammonia* to a quantity of the powdered tablets containing 10 mg of Phytomenadione and mix with the aid of ultrasound for 5 minutes. Add 90 mL of *ethanol* (*96%*) and mix with the aid of ultrasound for 10 minutes. Shake for 10 minutes, add sufficient *ethanol* (*96%*) to produce 100 mL, centrifuge and use the clear supernatant layer.

(2) 0.01% w/v of *phytomenadione BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *water* and 95 volumes of *ethanol* (*96%*).

DETERMINATION OF CONTENT

Calculate the content of $C_{31}H_{46}O_2$ in the tablets using the declared content of $C_{31}H_{46}O_2$ in *phytomenadione BPCRS*.

LABELLING

The label states that the tablets should be chewed before swallowing or allowed to dissolve slowly in the mouth.

When vitamin K_1 tablets are prescribed or demanded, Phytomenadione Tablets shall be dispensed or supplied.

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Phytosterol

General Notices

(Ph. Eur. monograph 1911)

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DEFINITION

Natural mixture of sterols obtained from plants of the genera *Hypoxis*, *Pinus* and *Picea*.

Content

Minimum 70.0 per cent of β-sitosterol (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in tetrahydrofuran, sparingly soluble in ethyl acetate.

IDENTIFICATION

A. Mix 1 mL of *acetic anhydride R* with 0.5 mL of solution S (see Tests). After the addition of 0.1 mL of *sulfuric acid R* a red colour is produced, which changes rapidly to violet, then to blue and finally to green.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the peak in the chromatogram obtained with reference solution (b).

TESTS

Solution S

Dissolve 1.0 g in *tetrahydrofuran R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

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Acidity or alkalinity

Shake 0.20 g with a mixture of 4.0 mL of *ethyl acetate R* and 10.0 mL of *carbon dioxide-free water R* for 3 min. Allow the layers to separate. To the aqueous layer add 0.1 mL of *bromothymol blue solution R1*. If the solution is yellow, not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour to blue. If the solution is blue, not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour to yellow.

Specific optical rotation (*2.2.7*)

-28.0 to -15.0 (dried substance).

Dissolve 0.500 g in *ethyl acetate R* and dilute to 10.0 mL with the same solvent.

Acid value (*2.5.1*)

Maximum 1.0, determined on 2.0 g.

Peroxide value (*2.5.5*)

Maximum 10.0.

Saponification value (*2.5.6*)

Maximum 1.0.

Carry out the test using 2.50 g of the substance to be examined, *0.1 M alcoholic potassium hydroxide*, *0.1 M hydrochloric acid*, and a factor of 5.61 (instead of 28.05).

Other sterols

Examine the chromatogram obtained with the test solution in the assay (Figure 1911.-1).

Composition of the other sterols:

— *cholesterol*: maximum 0.5 per cent;

— *brassicasterol*: maximum 0.5 per cent;

— *campesterol*: maximum 15.0 per cent;

— *campestanol*: maximum 5.0 per cent;

— *stigmasterol*: maximum 5.0 per cent;

— *sitostanol*: maximum 15.0 per cent;

— *Δ7-stigmastenol*: maximum 5.0 per cent.

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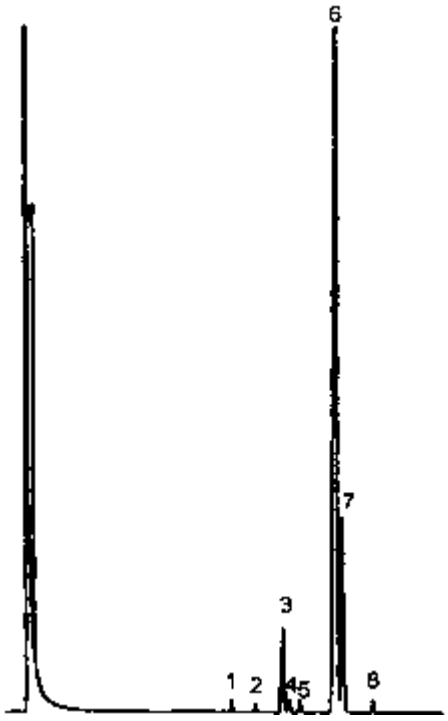

1. cholesterol
2. brassicasterol
3. campesterol
4. campestanol
5. stigmasterol
6. β-sitosterol
7. sitostanol
8. Δ7-stigmastenol

Figure 1911.-1. – *Chromatogram for the assay of phytosterol (trimethylsilyl derivatives)*

Loss on drying (2.2.32)

Maximum 4.0 per cent, determined on 0.250 g by drying in an oven at 105 °C for 2 h.

Total ash (2.4.16)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Dissolve 0.100 g in tetrahydrofuran R and dilute to 10.0 mL with the same solvent. Introduce 100 µL of this solution into a 3 mL flask and evaporate to dryness under nitrogen R. Add 100 µL of a freshly prepared mixture of 50 µL of 1-methylimidazole R and 1.0 mL of heptafluoro-N-methyl-N-(trimethylsilyl)butanamide R, close the flask tightly and heat to 100 °C for 15 min. Allow to cool.

Reference solution (a) Dissolve 25 mg of β-sitosterol R and 25 mg of sitostanol R in tetrahydrofuran R and dilute to 10.0 mL with the same solvent. Introduce 100 µL of this solution into a 3 mL flask and evaporate to dryness under nitrogen R. Add 100 µL of a freshly

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prepared mixture of 50 µL of *1-methylimidazole R* and 1.0 mL of *heptafluoro-N-methyl-N-(trimethylsilyl)butanamide R*. Close the flask tightly and heat to 100 °C for 15 min. Allow to cool.

Reference solution (b) Dissolve 0.100 g of *β-sitosterol R* in *tetrahydrofuran R* and dilute to 10.0 mL with the same solvent. Introduce 100 µL of this solution into a 3 mL flask and evaporate to dryness under *nitrogen R*. Add 100 µL of a freshly prepared mixture of 50 µL of *1-methylimidazole R* and 1.0 mL of *heptafluoro-N-methyl-N-(trimethylsilyl)butanamide R*. Close the flask tightly and heat to 100 °C for 15 min. Allow to cool.

Column:

— *material*: quartz;

— *size*: *l* = 25 m, Ø = 0.3 mm;

— *stationary phase*: *vinyl(1)phenyl(5)methyl(94)polysiloxane R* (1 µm).

Carrier gas *hydrogen for chromatography R*.

Flow rate 2 mL/min.

Split ratio 1:20.

Temperature:

— *column*: 280 °C;

— *injection port and detector*: 300 °C.

Detection Flame ionisation.

Injection 1 µL.

Relative retentions With reference to β-sitosterol (retention time = about 16 min): cholesterol = about 0.7; brassicasterol = about 0.77; campesterol = about 0.84; campestanol = about 0.86; stigmasterol = about 0.9; sitostanol = about 1.02; Δ7-stigmastenol = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 1.0 between the peaks due to β-sitosterol and sitostanol.

STORAGE

In an airtight container, protected from light.

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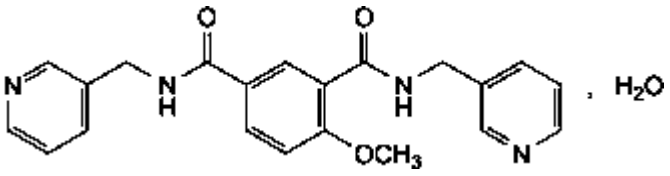
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Picotamide Monohydrate

General Notices

(Ph. Eur. monograph 1358)



$C_{21}H_{20}N_4O_3,H_2O$ 394.4

Action and use

Thromboxane Synthetase inhibitor; thromboxane receptor antagonist; antiplatelet agent.

Ph Eur

DEFINITION

Picotamide monohydrate contains not less than 98.0 per cent and not more than 101.0 per cent of 4-methoxy-*N*,*N*′-bis(pyridin-3-ylmethyl)benzene-1,3-dicarboxamide, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, slightly soluble in water, soluble in anhydrous ethanol and in methylene chloride. It dissolves in dilute mineral acids.

It shows polymorphism (5.9).

IDENTIFICATION

Examine by infrared spectrophotometry (2.2.24), comparing with the spectrum obtained with *picotamide monohydrate CRS*. If the spectra obtained in the solid state shows differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

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Dissolve 2.5 g in *methanol R* and dilute to 50 mL with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel F_{254} plate R*.

Test solution Dissolve 0.5 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 10 mL with *methanol R*. Dilute 1 mL of the solution to 20 mL with *methanol R*.

Reference solution (b) Dilute 5 mL of reference solution (a) to 10 mL with *methanol R*.

Reference solution (c) Dissolve 0.5 g of the substance to be examined and 5 mg of *picotamide impurity A CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Apply to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture 0.8 volumes of *glacial acetic acid R*, 1 volume of *water R*, 2.5 volumes of *methanol R* and 8 volumes of *butanol R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the principal spot in the chromatogram obtained with reference solution (a) (0.5 per cent) and not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated principal spots.

Chlorides (*2.4.4*)

Dissolve 0.25 g in a mixture of 2.5 mL of *dilute nitric acid R* and 12.5 mL of *water R*. The solution complies with the limit test for chlorides (200 ppm).

Water (*2.5.12*)

4.5 per cent to 5.0 per cent, determined on 0.300 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in a mixture of 20 mL of *anhydrous acetic acid R* and 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 18.82 mg of $C_{21}H_{20}N_4O_3$.

IMPURITIES

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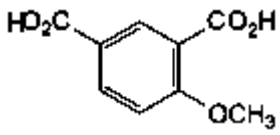
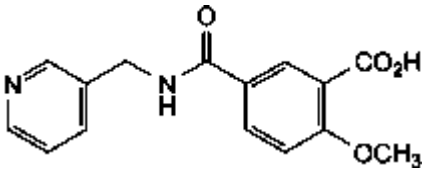
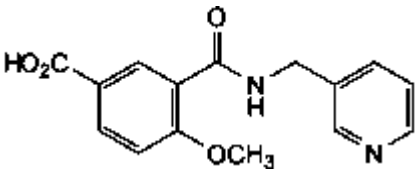


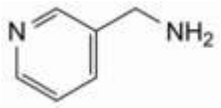
A. 4-methoxybenzene-1,3-dicarboxylic acid,



B. 2-methoxy-5-[[(pyridin-3-ylmethyl)amino]carbonyl]benzoic acid,



C. 4-methoxy-3-[[(pyridin-3-ylmethyl)amino]carbonyl]benzoic acid,



D. (pyridin-3-yl)methanamine.

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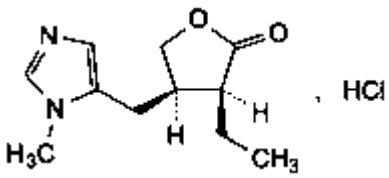
Pilocarpine Hydrochloride

General Notices

(Ph. Eur. monograph 0633)



$C_{11}H_{17}ClN_2O_2$ 244.7 *54-71-7*

Action and use

Cholinoceptor agonist; treatment of glaucoma.

Preparation

Pilocarpine Hydrochloride Eye Drops

Ph Eur

DEFINITION

(3*S*,4*R*)-3-Ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Very soluble in water and freely soluble in ethanol (96 per cent).

mp

About 203 °C.

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IDENTIFICATION

First identification: A, B, D.

Second identification: C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *pilocarpine hydrochloride CRS*.

If the substances are examined as discs, prepare them using *potassium chloride R*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 2 mL with the same solvent.

Reference solution Dissolve 10 mg of *pilocarpine hydrochloride CRS* in *methanol R* and dilute to 2 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (1:14:85 *V/V/V*).

Application 2 µL.

Development Over a path of 15 cm.

Drying At 100-105 °C for 10 min, then allow to cool.

Detection Spray with *dilute potassium iodobismuthate solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

pH (2.2.3)

3.5 to 4.5 for solution S.

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Specific optical rotation (2.2.7)

+ 89 to + 93 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with *water R*. Dilute 2.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (b) Dissolve 5.0 mg of *pilocarpine nitrate for system suitability CRS* (containing impurity A) in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (c) To 5 mL of the test solution, add 0.1 mL of *ammonia R* and heat the solution on a water-bath for 30 min, cool and dilute to 25 mL with *water R*. Dilute 3 mL of this solution to 25 mL with *water R*. Mainly pilocarpic acid (impurity B) is formed.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase Mix 55 volumes of *methanol R*, 60 volumes of *acetonitrile R* and 885 volumes of a 0.679 g/L solution of *tetrabutylammonium dihydrogen phosphate R* previously adjusted to pH 7.7 with *dilute ammonia R2*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time Twice the retention time of pilocarpine.

Elution order Impurity B, impurity C, impurity A, pilocarpine.

Retention time Pilocarpine = about 20 min.

System suitability Reference solution (b):

— *resolution*: minimum 1.6 between the peaks due to impurity A and pilocarpine.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

— *sum of impurities A and B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

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— *sum of impurities other than A and B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S. Prepare the standard using 5 mL of *iron standard solution (1 ppm Fe) R* and 5 mL of *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *ethanol (96 per cent) R* and add 5 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 24.47 mg of $C_{11}H_{17}ClN_2O_2$.

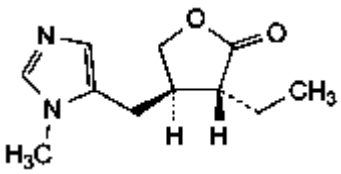
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



A. (3*R*,4*R*)-3-ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)-one (isopilocarpine),

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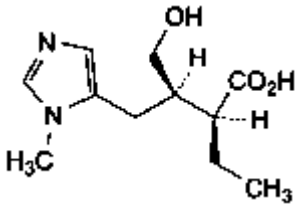
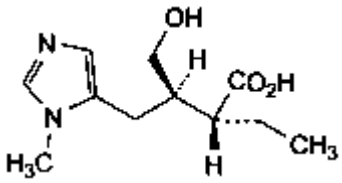


B. (2*S*,3*R*)-2-ethyl-3-(hydroxymethyl)-4-(1-methyl-1*H*-imidazol-5-yl)butanoic acid (pilocarpic acid),



C. (2*R*,3*R*)-2-ethyl-3-(hydroxymethyl)-4-(1-methyl-1*H*-imidazol-5-yl)butanoic acid (isopilocarpic acid).

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Pilocarpine Hydrochloride Eye Drops

General Notices

Action and use

Cholinoceptor agonist; treatment of glaucoma.

DEFINITION

Pilocarpine Hydrochloride Eye Drops are a sterile solution of Pilocarpine Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of pilocarpine hydrochloride, $C_{11}H_{16}N_2O_2$,HCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

To a volume containing 10 mg of Pilocarpine Hydrochloride add 0.1 mL of 1M *sulfuric acid*, 1 mL of *hydrogen peroxide solution* (*20 vol*), 1 mL of *toluene* and 0.05 mL of *potassium chromate solution*, shake well and allow to separate. The toluene layer is bluish violet and the aqueous layer remains yellow.

Pilocarpic acid

Carry out the method for *liquid chromatography*, Appendix III D, using 20 µL of each of the following solutions. For solution (1) dilute a suitable volume with *water* to produce a solution containing 0.080% w/v of Pilocarpine Hydrochloride. For solution (2) dilute 2 volumes of solution (1) to 25 volumes with *water*. For solution (3) dissolve 8.0 mg of *pilocarpine nitrate BPCRS* in 10 mL of 0.0025M *sodium hydroxide*, heat in a boiling water bath for 30 minutes and cool.

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable), (b) as the mobile phase a mixture of 55 volumes of *methanol*, 60 volumes of *acetonitrile* and 885 volumes of 0.002M *tetrabutylammonium dihydrogen orthophosphate*, the pH of the mixture being adjusted to 7.75 using 6M *ammonia*, with a flow rate of 1.2 mL per minute and (c) a detection wavelength of 220 nm. Record the chromatogram of solution (1) for twice the retention time of the main peak.

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *pilocarpine nitrate BPCRS*.

In the chromatogram obtained with solution (1) the area of any peak corresponding to pilocarpic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (8%).

ASSAY

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ASSAY

Use Method A for eye drops that contain less than 1% w/v of Pilocarpine Hydrochloride and in which benzalkonium chloride is used as an antimicrobial preservative. For other eye drops use Method B.

A. To 2 mL in a stoppered flask add 5 mL of *mixed phosphate buffer pH 10*, 5 mL of *chloroform* and 0.1 mL of *bromophenol blue solution*. Titrate slowly with 0.01M *sodium tetraphenylborate VS*, shaking well between successive small additions, until the chloroform layer becomes colourless. Using a further 2 mL of the eye drops, carry out the procedure described under Method B beginning at the words 'add 5 mL of *acetate buffer pH 3.7* ...'. The difference between the titrations at pH 3.7 and pH 10 represents the amount of sodium tetraphenylborate required.

B. Dilute if necessary with *water* to produce a solution containing 1% w/v of Pilocarpine Hydrochloride. To 2 mL add 5 mL of *acetate buffer pH 3.7* and 15 mL of 0.01M *sodium tetraphenylborate VS*, mix and allow to stand for 10 minutes. Filter, wash the container and filter with 5 mL of *water*, combine the filtrate and washings and titrate with 0.005M *cetylpyridinium chloride VS* using 0.5 mL of *bromophenol blue solution* as indicator. Repeat the operation without the preparation being examined. The difference between the titrations represents the amount of sodium tetraphenylborate required.

Each mL of 0.01M *sodium tetraphenylborate VS* is equivalent to 2.447 mg of $C_{11}H_{16}N_2O_2$,HCl.

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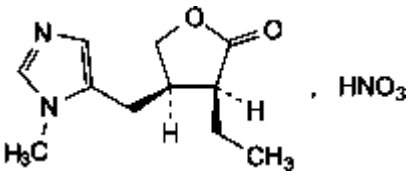
Pilocarpine Nitrate

General Notices

(Ph. Eur. monograph 0104)



$C_{11}H_{17}N_3O_5$ 271.3 *148-72-1*

Action and use

Cholinoceptor agonist; treatment of glaucoma.

Preparation

Pilocarpine Nitrate Eye Drops

Ph Eur

DEFINITION

(3*S*,4*R*)-3-Ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)-one nitrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent).

It is sensitive to light.

mp

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About 174 °C, with decomposition.

IDENTIFICATION

First identification: A, B, D.

Second identification: C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *pilocarpine nitrate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *pilocarpine nitrate CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (1:14:85 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying At 100-105 °C for 10 min and allow to cool.

Detection Spray with *potassium iodobismuthate solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives the reaction of nitrates (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent. Prepare immediately before use.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (2.2.3)

3.5 to 4.5 for solution S.

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Specific optical rotation (2.2.7)

+ 80 to + 83 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with *water R*. Dilute 2.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (b) Dissolve 5.0 mg of *pilocarpine nitrate for system suitability CRS* (containing impurity A) in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (c) To 5 mL of the test solution, add 0.1 mL of *ammonia R* and heat the solution on a water-bath for 30 min, cool and dilute to 25 mL with *water R*. Dilute 3 mL of this solution to 25 mL with *water R*. Mainly pilocarpic acid (impurity B) is formed.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase Mix 55 volumes of *methanol R*, 60 volumes of *acetonitrile R* and 885 volumes of a 0.679 g/L solution of *tetrabutylammonium dihydrogen phosphate R* previously adjusted to pH 7.7 with *dilute ammonia R2*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time Twice the retention time of pilocarpine.

Elution order Impurity B, impurity C, impurity A, pilocarpine.

Retention time Pilocarpine = about 20 min.

System suitability Reference solution (b):

— *resolution*: minimum 1.6 between the peaks due to impurity A and pilocarpine.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

— *sum of impurities A and B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

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— *sum of impurities other than A and B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent); disregard any peak due to the nitrate ion with a relative retention with reference to pilocarpine of about 0.3.

Chlorides (2.4.4)

Maximum 70 ppm, determined on solution S.

Iron (2.4.9)

Maximum 10 ppm, determined on solution S. Prepare the standard using 5 mL of *iron standard solution (1 ppm Fe) R* and 5 mL of *water R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 27.13 mg of $C_{11}H_{17}N_3O_5$.

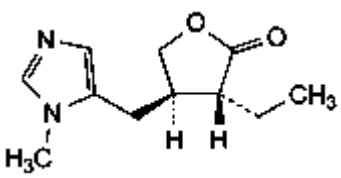
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



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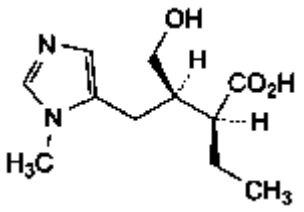
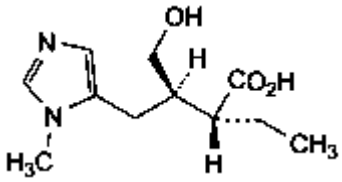
A. (3*R*,4*R*)-3-ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)-one (isopilocarpine),



B. (2*S*,3*R*)-2-ethyl-3-(hydroxymethyl)-4-(1-methyl-1*H*-imidazol-5-yl)butanoic acid (pilocarpic acid),



C. (2*R*,3*R*)-2-ethyl-3-(hydroxymethyl)-4-(1-methyl-1*H*-imidazol-5-yl)butanoic acid (isopilocarpic acid).

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Pilocarpine Nitrate Eye Drops

General Notices

Action and use

Cholinoceptor agonist; treatment of glaucoma.

DEFINITION

Pilocarpine Nitrate Eye Drops are a sterile solution of Pilocarpine Nitrate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of pilocarpine nitrate, $C_{11}H_{16}N_2O_2,HNO_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Evaporate to dryness a volume containing 20 mg of Pilocarpine Nitrate on a water bath and heat for 1 hour at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pilocarpine nitrate (*RS 274*).

TESTS

Acidity

pH 3.0 to 5.5, Appendix V L.

Pilocarpic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume with *water* to produce a solution containing 0.080% w/v of Pilocarpine Nitrate.

(2) Dilute 1 volume of solution (1) to 25 volumes with *water*.

(3) Dissolve 8.0 mg of *pilocarpine nitrate BPCRS* in 10 mL of 0.0025M *sodium hydroxide*, heat in a boiling water bath for 30 minutes and cool (pilocarpic acid is produced).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

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(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography of solution (1) to proceed for twice the retention time of the main peak.

MOBILE PHASE

55 volumes of *methanol*, 60 volumes of *acetonitrile* and 885 volumes of 0.002M *tetrabutylammonium dihydrogen orthophosphate*, the pH of the mixture being adjusted to pH 7.75 using 6M *ammonia*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *pilocarpine nitrate BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to pilocarpic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the eye drops with *water* to produce a solution containing 0.08% w/v of Pilocarpine Nitrate.

(2) 0.08% w/v of *pilocarpine nitrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Two major peaks are obtained with both solutions. Disregard the principal peak with the shorter retention time (nitric acid).

(h) Allow the chromatography of solution (1) to proceed for twice the retention time of the main peak.

MOBILE PHASE

55 volumes of *methanol*, 60 volumes of *acetonitrile* and 885 volumes of 0.002M *tetrabutylammonium dihydrogen orthophosphate*, the pH of the mixture being adjusted to pH 7.75 using 6M *ammonia*.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{16}N_2O_2,HNO_3$ using the declared content of $C_{11}H_{16}N_2O_2,HNO_3$ in *pilocarpine nitrate BPCRS*.

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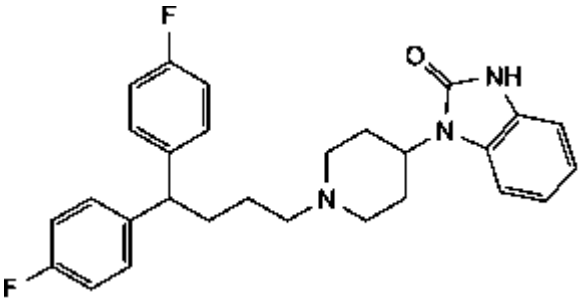
Pimozide

General Notices

(Ph. Eur. monograph 1254)



$C_{28}H_{29}F_2N_3O$ 461.6 *2062-78-4*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Pimozide Tablets

Ph Eur

DEFINITION

1-[1-[4,4-Bis(4-fluorophenyl)butyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

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First identification: B.

Second identification: A, C, D.

A. Melting point (2.2.14): 216 °C to 220 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *pimozide CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (a) Dissolve 30 mg of *pimozide CRS* in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (b) Dissolve 30 mg of *pimozide CRS* and 30 mg of *benperidol CRS* in the mobile phase and dilute to 10 mL with the mobile phase.

Plate *TLC silica gel plate R*.

Mobile phase *acetone R*, *methanol R* (10:90 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In a current of warm air for 15 min.

Detection Expose to iodine vapour until the spots appear.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, then add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*, add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

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Dissolve 0.2 g in *methanol R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *pimozide CRS* and 2.0 mg of *mebendazole CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: solution containing 2.5 g/L of *ammonium acetate R* and 8.5 g/L of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	80 → 70	20 → 30
10 - 15	70	30
15 - 20	80	20

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Relative retention With reference to pimozide (retention time = about 8 min): impurity A = about 0.1; mebendazole = about 0.88; impurity B = about 0.9; impurity C = about 0.95; impurity D = about 1.1; impurity E = about 1.3.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to mebendazole and pimozide.

Limits:

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— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.75 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

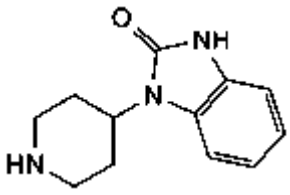
1 mL of *0.1 M perchloric acid* is equivalent to 46.16 mg of $C_{28}H_{29}F_2N_3O$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*



A. 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one,

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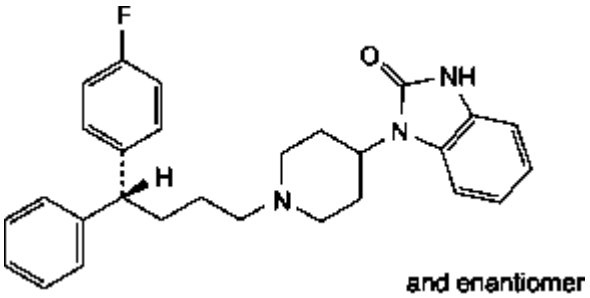
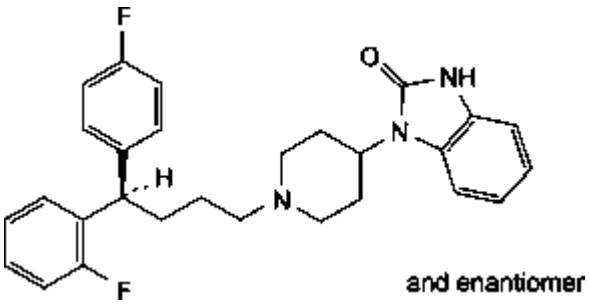
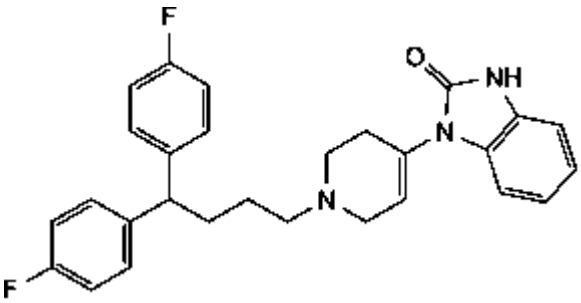


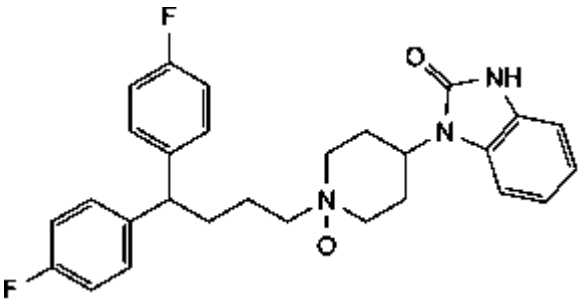
B. 1-[1-[(4*RS*)-4-(4-fluorophenyl)-4-phenylbutyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,



C. 1-[1-[(4*RS*)-4-(2-fluorophenyl)-4-(4-fluorophenyl)butyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,



D. 1-[1-[4,4-bis(4-fluorophenyl)butyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,



E. 1-[1-[4,4-bis(4-fluorophenyl)butyl]piperidin-4-yl 1-oxide]-1,3-dihydro-2*H*-benzimidazol-2-one.

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Pimozide Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Pimozide Tablets contain Pimozide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pimozide, $C_{28}H_{29}F_2N_3O$

95.0% to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Pimozide with 20 mL of *dichloromethane* for 5 minutes, filter through a glass microfibre filter (Whatman GF/C is suitable) and evaporate the filtrate to dryness under reduced pressure. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pimozide (*RS 389*).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 20 mL sample of the medium and filter through a 0.45-µm polytetrafluoroethylene filter. Use the filtered medium, diluted with the dissolution medium if necessary, expected to contain 0.0002% w/v of Pimozide.

(2) 0.0002% w/v of *pimozide BPCRS* in *water*.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of pimozide, $C_{28}H_{29}F_2N_3O$, in the medium from the chromatograms obtained and using the declared content of $C_{28}H_{29}F_2N_3O$ in *pimozide BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of *methanol* to a quantity of the powdered tablets containing 40 mg of Pimozide, shake for 30 minutes, mix with the aid of ultrasound for 10 minutes, centrifuge and filter the supernatant liquid through a 0.45-µm polytetrafluoro-ethylene filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

(3) 0.005% w/v of *pimozide BPCRS* and 0.002% w/v of *mebendazole* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil ODS is suitable).

(b) Use linear gradient elution and the mobile phases described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.25% w/v of *ammonium acetate* and 0.85% w/v of *tetrabutylammonium hydrogen sulfate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	80→70	20→30	linear gradient
10-15	70	30	isocratic
15-16	70→80	30→20	linear gradient
16-30	80	20	isocratic

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SYSTEM SUITABILITY

Equilibrate the column for at least 10 minutes with the initial mobile phase. The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the principal peak in the chromatogram obtained with solution (2) (0.75%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Pimozide comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake one tablet with 7 mL of *methanol* for 30 minutes, dilute with sufficient *methanol* to produce a solution containing 0.01% w/v of Pimozide, mix with the aid of ultrasound for 10 minutes, centrifuge and filter the supernatant liquid through a 0.45-µm polytetrafluoroethylene filter.

(2) 0.010% w/v of *pimozide BPCRS* in *methanol*.

(3) 0.005% w/v of *pimozide BPCRS* and 0.002% w/v of *mebendazole* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{29}F_2N_3O$ in each tablet using the declared content of $C_{28}H_{29}F_2N_3O$ in *pimozide BPCRS*.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Pimozide with 35 mL of *methanol* for 30 minutes, dilute to 50 mL with *methanol*, mix with the aid of ultrasound for 10 minutes, centrifuge and filter the supernatant liquid through a 0.45-µm polytetrafluoroethylene filter.

(2) 0.04% w/v of *pimozide BPCRS* in *methanol*.

(3) 0.004% w/v of *pimozide BPCRS* and 0.002% w/v of *mebendazole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{29}F_2N_3O$ in the tablets using the declared content of $C_{28}H_{29}F_2N_3O$ in *pimozide BPCRS*.

STORAGE

Pimozide Tablets should be kept protected from light.

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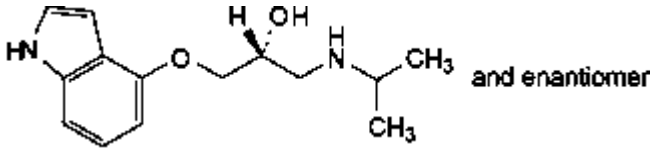
Pindolol

General Notices

(Ph. Eur. monograph 0634)



$C_{14}H_{20}N_2O_2$ 248.3 *13523-86-9*

Action and use

Beta-adrenoceptor antagonist.

Preparation

Pindolol Tablets

Ph Eur

DEFINITION

Pindolol contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (2*RS*)-1-(1*H*-indol-4-yloxy)-3-[(1-methylethyl)amino]propan-2-ol, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, slightly soluble in methanol. It dissolves in dilute mineral acids.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (2.2.14): 169 °C to 174 °C.

B. Dissolve 20.0 mg in a 0.085 per cent *V/V* solution of *hydrochloric acid R* in *methanol R* and dilute to 100.0 mL with the same solution. Dilute 10.0 mL of the solution to 100.0 mL with a 0.085 per cent *V/V* solution of *hydrochloric acid R* in *methanol R*. Examined between 230 nm and 320 nm (2.2.25), the solution shows two absorption maxima, at 264 nm and at 287 nm, and a shoulder at 275 nm. The specific absorbance at the maxima are 330 to 350 and 170 to 190, respectively.

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C. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *pindolol CRS*.

D. Examine in daylight the chromatograms on plate A obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

Dissolve 0.5 g in *dilute acetic acid R* and dilute to 10 mL with the same acid. The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_5 or B_5 (2.2.2, *Method II*).

Related substances

Examine by thin-layer chromatography (2.2.27), using *silica gel GF_{254} R* as the coating substance. *Carry out all operations as rapidly as possible, protected from light*.

Test solution (a) Dissolve 0.10 g of the substance to be examined in a mixture of 1 volume of *anhydrous acetic acid R* and 99 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents. Prepare immediately before use and apply this solution to the plate last.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a mixture of 1 volume of *anhydrous acetic acid R* and 99 volumes of *methanol R*.

Reference solution (a) Dissolve 20 mg of *pindolol CRS* in a mixture of 1 volume of *anhydrous acetic acid R* and 99 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.5 mL of reference solution (a) to 50 mL with a mixture of 1 volume of *anhydrous acetic acid R* and 99 volumes of *methanol R*.

A. Apply separately 5 µL of each solution. Develop the plate without delay over a path of 10 cm using a freshly prepared mixture of 4 volumes of *concentrated ammonia R*, 50 volumes of *ethyl acetate R* and 50 volumes of *methanol R*. Dry the plate briefly in a current of cold air. Spray the plate without delay with *dimethylaminobenzaldehyde solution R7* and heat to 50 °C for 20 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.3 per cent).

B. Apply separately 10 µL of each solution. Develop the plate without delay over a path of 10 cm using a freshly prepared mixture of 4 volumes of *concentrated ammonia R*, 50 volumes of *ethyl acetate R* and 50 volumes of *methanol R*. Dry the plate briefly in a current of cold air. Examine the plate without delay in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot and the spots detected on plate A, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.3 per cent).

Loss on drying (2.2.32)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

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Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

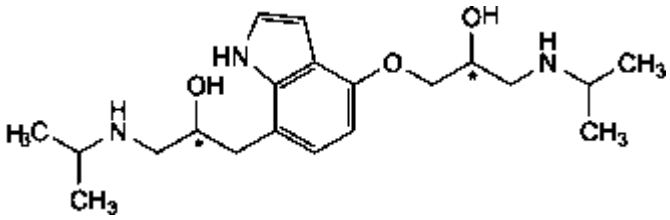
Dissolve 0.200 g in 80 mL of *methanol R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 24.83 mg of $C_{14}H_{20}N_2O_2$.

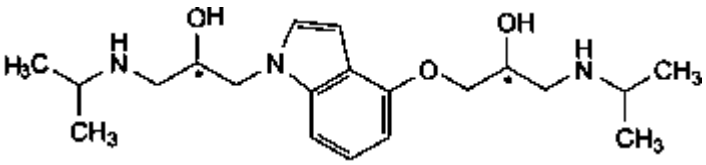
STORAGE

Store protected from light.

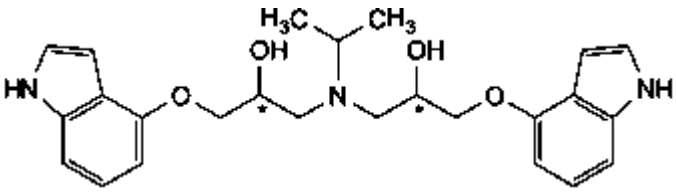
IMPURITIES



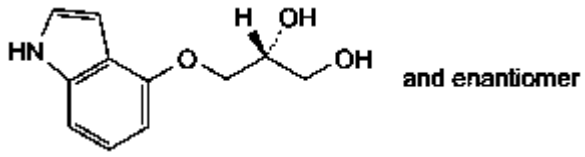
A. 1-[[7-[2-hydroxy-3-[(1-methylethyl)amino]propyl]-1*H*-indol-4-yl]oxy]-3-[(1-methylethyl)amino]propan-2-ol,



B. 1-[4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-1*H*-indol-1-yl]-3-[(1-methylethyl)amino]propan-2-ol,



C. 1,1′-[(1-methylethyl)imino]bis[3-(1*H*-indol-4-yloxy)propan-2-ol],



D. (2*RS*)-3-(1*H*-indol-4-yloxy)propane-1,2-diol,

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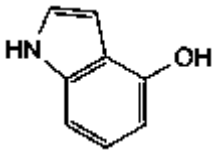
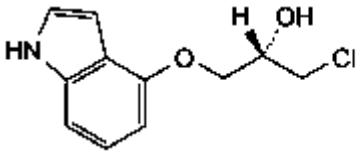


E. 1*H*-indol-4-ol,



F. (2*RS*)-1-chloro-3-(1*H*-indol-4-yloxy)propan-2-ol.

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Pindolol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Pindolol Tablets contain Pindolol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pindolol, $C_{14}H_{20}N_2O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Pindolol with 80 mL of *ether* for 30 minutes, filter and dry the extract with *anhydrous sodium sulfate*. Filter the dried extract, remove the ether using a rotary evaporator and dry the residue over *phosphorus pentoxide* at 110° at a pressure not exceeding 2 kPa for 1 hour. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of pindolol (*RS 275*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits two maxima, at 264 nm and 287 nm.

C. Shake a quantity of the powdered tablets containing 20 mg of Pindolol with 5 mL of a mixture of 1 volume of *glacial acetic acid* and 99 volumes of *methanol* for 45 minutes. Centrifuge and dilute 1 mL of the supernatant liquid to 50 mL with the acetic acid-methanol mixture. To 2 mL of this solution add 1 mL of *dimethylaminobenzaldehyde solution R7*. A violet-blue colour is produced.

TESTS

Related substances

Carry out the following procedure as rapidly as possible protected from light. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Pindolol with 5 mL of a mixture of 1 volume of *glacial acetic acid* and 99 volumes of *methanol* for 15 minutes, centrifuge and use the supernatant liquid; apply to the plate as the last solution.

(2) Dilute 1 volume of solution (1) to 10 volumes with the acetic acid-methanol mixture and further dilute 7 volumes of this solution to 100 volumes with the same solvent mixture.

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(3) Dilute 1 volume of solution (1) to 10 volumes with the acetic acid-methanol mixture and further dilute 3 volumes of this solution to 100 volumes with the same solvent mixture.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the chromatograms without delay. Develop the plate to 10 cm.

(e) After removal of the plate, spray immediately with *dimethylaminobenzaldehyde solution R7* and warm at 50° for 20 minutes.

MOBILE PHASE

4 volumes of 13.5M *ammonia*, 50 volumes of *ethyl acetate* and 50 volumes of *methanol*.

LIMITS

Any spot with an Rf value of about 0.1 in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.7%).

Any other *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.3%).

Disregard any spot remaining on the line of application.

ASSAY

Shake a quantity of whole tablets containing 90 mg of Pindolol with 90 mL of *methanol* for 45 minutes. Centrifuge and dilute 15 mL of the supernatant liquid to 100 mL with *methanol*. Dilute 5 mL of this solution to 50 mL with *methanol* and measure the *absorbance* of the resulting solution at the maximum at 264 nm, Appendix II B. Calculate the content of $C_{14}H_{20}N_2O_2$ taking 338 as the value of A (1%, 1 cm) at the maximum at 264 nm. Make no allowance for the fact that fewer than 20 tablets may have been taken.

STORAGE

Pindolol Tablets should be protected from light.

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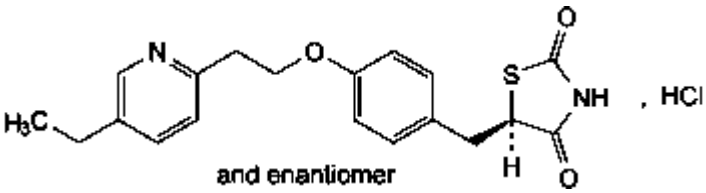
Pioglitazone Hydrochloride

General Notices

(Ph. Eur. monograph 2601)



$C_{19}H_{21}ClN_2O_3S$ 392.9 *112529-15-4*

Action and use

Peroxisome proliferator-activated receptor (PPAR)-gamma agonist; treatment of diabetes mellitus.

Ph Eur

DEFINITION

(5*RS*)-5-[[4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl]methyl]thiazolidine-2,4-dione hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white crystals or crystalline powder.

Solubility

Practically insoluble in water, slightly soluble to soluble in methanol, very slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pioglitazone hydrochloride CRS*.

B. Dissolve 25 mg in 0.5 mL of *nitric acid R* and add 2 mL of *dilute nitric acid R*. The solution gives reaction (a) of chlorides (*2.3.1*).

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TESTS

Specific optical rotation (2.2.7)

-0.2 to + 0.2.

Dissolve 2.5 g in *dimethylformamide R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 20 mg of the substance to be examined in 20 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Suspend 5 mg of *pioglitazone for system suitability CRS* (containing impurities B and C) in 5 mL of *methanol R*. Heat at 60 °C for about 30 s, cool to room temperature and dilute to 25.0 mL with the mobile phase. Filter through a membrane filter (nominal pore size 0.45 µm).

Reference solution (c) Dissolve 50.0 mg of *pioglitazone hydrochloride CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R*, *acetonitrile R*, 7.71 g/L solution of *ammonium acetate R* (1:25:25 *V/V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 269 nm.

Injection 40 µL of test solution (a) and reference solutions (a) and (b).

Run time 4 times the retention time of pioglitazone.

Identification of impurities Use the chromatogram supplied with *pioglitazone for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to pioglitazone (retention time = about 7 min): impurity B = about 1.4; impurity C = about 3.0.

System suitability Reference solution (b):

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— *resolution*: minimum 5.0 between the peaks due to pioglitazone and impurity B.

Limits:

— *impurities B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.32)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

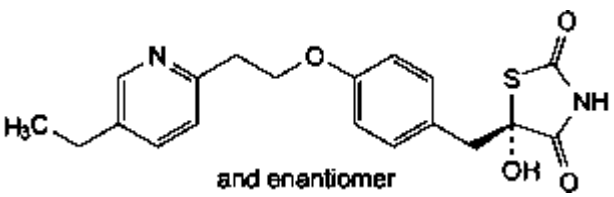
Injection 20 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{19}H_{21}ClN_2O_3S$ taking into account the assigned content of *pioglitazone hydrochloride CRS*.

IMPURITIES

Specified impurities *B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E.*



A. (5*RS*)-5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-5-hydroxythiazolidine-2,4-dione,

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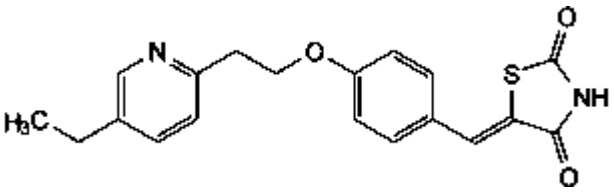
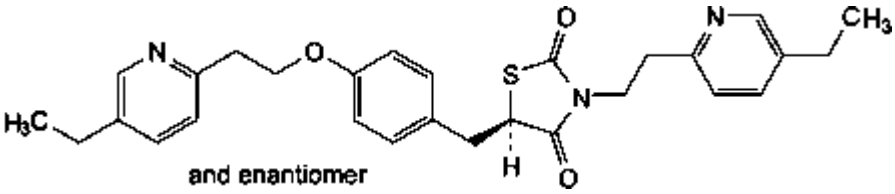
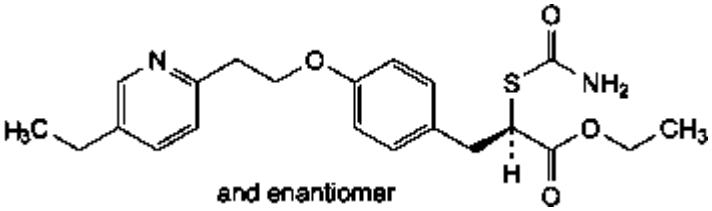


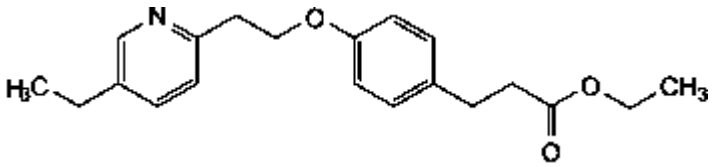
B. (5*Z*)-5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methylene]thiazolidine-2,4-dione,



C. (5*RS*)-5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-3-[2-(5-ethylpyridin-2-yl)ethyl]thiazolidine-2,4-dione,



D. ethyl (2*RS*)-2-(carbamoylsulfanyl)-3-[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]propanoate,



E. ethyl 3-[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]propanoate.

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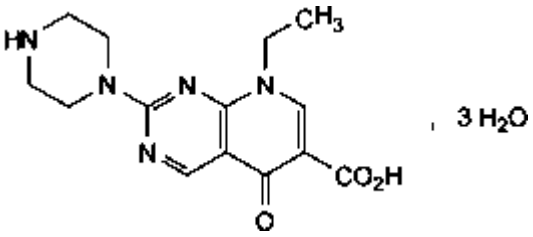
Pipemidic Acid Trihydrate

General Notices

(Ph. Eur. monograph 1743)



$C_{14}H_{17}N_5O_3,3H_2O$ 357.4 *72571-82-5*

Action and use

Antibacterial.

Ph Eur

DEFINITION

8-Ethyl-5-oxo-2-(piperazin-1-yl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid trihydrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow or yellow, crystalline powder.

Solubility

Very slightly soluble in water and in methylene chloride, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of acids and of alkali hydroxides.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pipemidic acid trihydrate CRS*.

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TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in 10 mL of the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 1.0 mg of *ethyl parahydroxybenzoate R* in 2.0 mL of the test solution and dilute to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (5 µm).

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a solution containing 5.7 g/L of *citric acid monohydrate R* and 1.7 g/L of *sodium decanesulfonate R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 20 µL.

Run time 2.5 times the retention time of pipemidic acid.

Relative retention With reference to pipemidic acid (retention time = about 15 min): ethyl parahydroxybenzoate = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to ethyl parahydroxybenzoate and pipemidic acid.

Limits:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

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14.0 per cent to 16.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.240 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

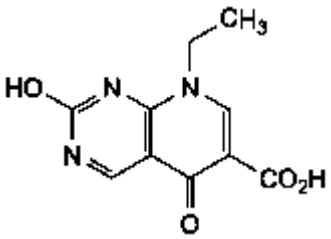
1 mL of *0.1 M perchloric acid* is equivalent to 30.33 mg of $C_{14}H_{17}N_5O_3$.

STORAGE

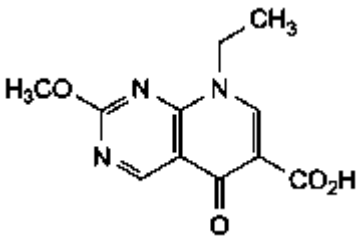
Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F.*



A. 8-ethyl-2-hydroxy-5-oxo-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid,



B. 8-ethyl-2-methoxy-5-oxo-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid,

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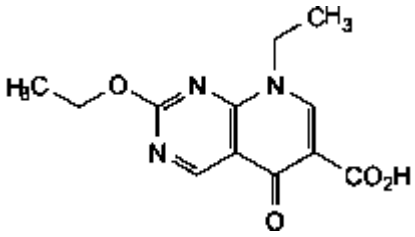
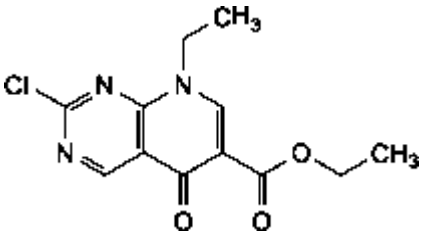
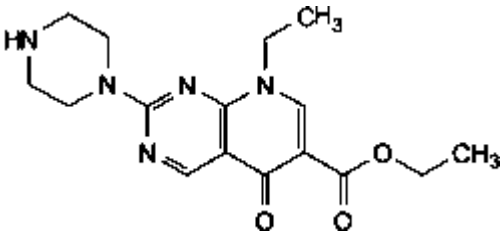


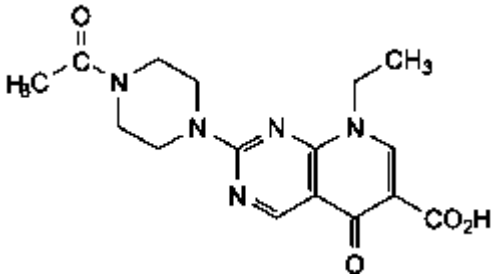
C. 2-ethoxy-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid,



D. ethyl 2-chloro-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate,



E. ethyl 8-ethyl-5-oxo-2-(piperazin-1-yl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylate,



F. 2-(4-acetylpiperazin-1-yl)-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid (acetylpipemidic acid).

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Piperacillin Infusion

General Notices

Piperacillin Intravenous Infusion

Piperacillin for Intravenous Infusion

Action and use

Penicillin antibacterial.

DEFINITION

Piperacillin Infusion is a sterile solution containing Piperacillin Sodium. It is prepared by diluting Piperacillin for Infusion with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations.

STORAGE

Piperacillin Infusion should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

PIPERACILLIN FOR INFUSION

DEFINITION

Piperacillin for Infusion is a sterile material consisting of either Piperacillin Sodium or piperacillin sodium prepared by the interaction of Piperacillin with Sodium Bicarbonate, with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of anhydrous piperacillin, $C_{23}H_{27}N_5O_7S$

94.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powder containing the equivalent of 0.25 g of anhydrous piperacillin in 20 mL of *water*, add 0.5 mL of *dilute hydrochloric acid*, mix well, allow to stand until a precipitate appears and filter through a membrane filter (Millipore GS or HA is suitable). The *infrared absorption spectrum* of the dried precipitate, Appendix II A, is concordant with the spectrum of *piperacillin BPCRS*.

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

Piperacillin Infusion prepared from Piperacillin Sodium complies with the following additional test.

C. Yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity

pH of a solution containing the equivalent of 20% w/v of anhydrous piperacillin, 4.8 to 6.8, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of the container in sufficient of the mobile phase to produce a solution containing the equivalent of 0.039% w/v of anhydrous piperacillin.

(2) 0.0008% w/v of *piperacillin BPCRS* in the mobile phase.

(3) 0.0004% w/v of *piperacillin BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak with a retention time relative to piperacillin of about 0.6 is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (3) (3.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Water

Not more than 2% w/w, Appendix IX C. Use 0.5 g.

If the contents of the sealed container have been freeze-dried *in situ*, not more than 0.9% w/w, Appendix IX C. Use 0.5 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of a sealed container in *water BET* to give a solution containing the equivalent of 50 mg of anhydrous piperacillin per mL (solution A). The endotoxin limit concentration of solution A is 2.5 IU of endotoxin per mL.

ASSAY

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Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions.

(1) Dissolve a quantity of the mixed contents of the 10 containers in sufficient of the mobile phase to produce a solution containing the equivalent of 0.039% w/v of anhydrous piperacillin.
(2) Dissolve 40 mg of *piperacillin BPCRS* in *methanol* and dilute to 100 mL with the mobile phase.
(3) 0.01% w/v of *anhydrous ampicillin BPCRS* and 0.02% w/v of *piperacillin BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 to 10 µm) (Beckman Ultrasphere ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

3 volumes of 0.4M *tetrabutylammonium hydroxide*, 100 volumes of 0.2M *sodium dihydrogen orthophosphate monohydrate*, 447 volumes of *water* and 450 volumes of *methanol* which has been allowed to cool and the pH adjusted initially to 5.6 with 20% w/v *orthophosphoric acid* and finally to 5.5 with 2% w/v *orthophosphoric acid*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 16.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{27}N_5O_7S$ in a container of average content weight from the declared content of $C_{23}H_{27}N_5O_7S$ in *piperacillin BPCRS*.

STORAGE

The sealed container should be protected from moisture.

LABELLING

The label of the sealed container states the quantity of active ingredient contained in it in terms of the equivalent amount of anhydrous piperacillin.

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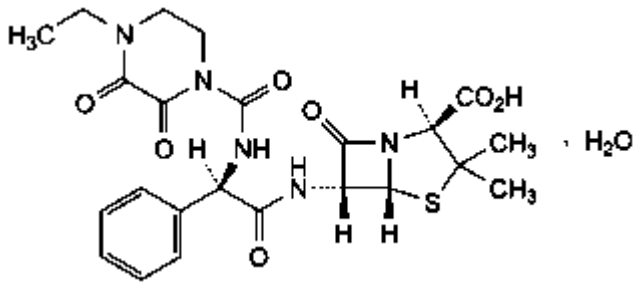
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Piperacillin Monohydrate

General Notices

Piperacillin

(Ph. Eur. monograph 1169)



$C_{23}H_{27}N_5O_7S,H_2O$ 535.6 *66258-76-2*

Action and use

Penicillin antibacterial.

Preparation

Piperacillin Infusion

Ph Eur

DEFINITION

(2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

The manufacturing process is evaluated to determine the potential presence of *N*,*N*-dimethylaniline. Where necessary, the manufacturing process is validated to demonstrate that the piperacillin monohydrate complies with the following test:

***N*,*N*-Dimethylaniline** (*2.4.26, Method A*)

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Maximum 20 ppm.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in methanol, slightly soluble in ethyl acetate.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *piperacillin CRS*.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and its absorbance (2.2.25) at 430 nm is not greater than 0.10.

Dissolve 2.50 g in *sodium carbonate solution R* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.120 g of the substance to be examined in mobile phase B and dilute to 20.0 mL with mobile phase B.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B.

Reference solution (b) Dissolve 6 mg of *piperacillin impurity I CRS* in mobile phase B and dilute to 20 mL with mobile phase B.

Reference solution (c) Dissolve 6 mg of *anhydrous ampicillin CRS* (impurity A) in mobile phase B and dilute to 20 mL with mobile phase B.

Reference solution (d) To 2 mL of reference solution (b), add 1 mL of reference solution (c) and dilute to 10 mL with mobile phase B.

Reference solution (e) Dissolve 6 mg of *piperacillin for peak identification CRS* (containing impurities A, B, C, D, E, F, G, I, J, K, L, M, O, P, Q, R, S and T) in mobile phase B and dilute to 1 mL with mobile phase B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (5 µm);

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— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 3 mL of a 320 g/L solution of *tetrabutylammonium hydroxide R*, 100 mL of a 27.6 g/L solution of *sodium dihydrogen phosphate R*, 275 mL of *methanol R1* and 622 mL of *water for chromatography R*; adjust the apparent pH to 5.5 with *phosphoric acid R*;

— *mobile phase B*: mix 3 mL of a 320 g/L solution of *tetrabutylammonium hydroxide R*, 100 mL of a 27.6 g/L solution of *sodium dihydrogen phosphate R*, 282 mL of *water for chromatography R* and 615 mL of *methanol R1*; adjust the apparent pH to 5.5 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	100	0
6 - 55	100 → 71	0 → 29
55 - 73	71 → 10	29 → 90
73 - 85	10	90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Autosampler Set at 4 °C.

Injection 10 µL of the test solution and reference solutions (a), (d) and (e).

Identification of impurities Use the chromatogram supplied with *piperacillin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, B, C, D, E, F, G, I, J, K, L, M, O, P, Q, R, S and T.

Relative retention With reference to piperacillin (retention time = about 54 min): impurity E = about 0.05; impurity I = about 0.12; impurity A = about 0.14; impurity G = about 0.30; impurity J = about 0.36; impurity F = about 0.57; impurity K = about 0.60; impurity L = about 0.65; impurity B (isomer 1) = about 0.71; impurity M = about 0.75; impurity B (isomer 2) = about 0.83; impurity C (isomer 1) = about 0.87; impurity C (isomer 2) = about 0.92; impurity O = about 1.23; impurity P = about 1.26; impurity Q = about 1.31; impurity R = about 1.36; impurity S = about 1.38; impurity T = about 1.41; impurity D = about 1.54.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurities I and A.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.3; impurity E = 0.4; impurity I = 3.2;

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— for each impurity, use the concentration of piperacillin monohydrate in reference solution (a).

Limits:

— *impurity G*: maximum 1.5 per cent;

— *impurities B (sum of isomers), D*: for each impurity, maximum 1.0 per cent;

— *impurity F*: maximum 0.8 per cent;

— *impurity C (sum of isomers)*: maximum 0.7 per cent;

— *impurity S*: maximum 0.5 per cent;

— *impurity T*: maximum 0.3 per cent;

— *impurities A, E, I, J, K, L, M, O, P, Q, R*: for each impurity, maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 2.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

2.0 per cent to 4.0 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, 31.2 g/L solution of *sodium dihydrogen phosphate R* (25:75 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of *piperacillin CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dissolve 0.1 g of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *piperacillin impurity N CRS* in the solvent mixture and dilute to 25 mL with the solvent mixture.

Reference solution (d) To 5 mL of reference solution (b), add 0.1 mL of reference solution (c) and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 24 mL of an 80 g/L solution of *tetrabutylammonium hydroxide R*, 200 mL of *acetonitrile for chromatography R*, 200 mL of a 31.2 g/L solution of *sodium dihydrogen phosphate R* and 576 mL of *water for chromatography R*; adjust the apparent pH to 5.5 with *dilute phosphoric acid R* or *dilute sodium hydroxide solution R*;

— *mobile phase B*: mix 24 mL of an 80 g/L solution of *tetrabutylammonium hydroxide R*, 126 mL of *water for chromatography R*, 200 mL of a 31.2 g/L solution of *sodium dihydrogen phosphate R* and 650 mL of *acetonitrile for chromatography R*; adjust the apparent pH to 5.5 with *dilute phosphoric acid R* or *dilute sodium hydroxide solution R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3.5	100	0
3.5 - 4	100 → 92	0 → 8
4 - 14	92 → 86	8 → 14
14 - 15	86 → 0	14 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (a) and (d).

Relative retention With reference to piperacillin (retention time = about 13 min): impurity N = about 0.96.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity N and piperacillin.

Calculate the percentage content of $C_{23}H_{27}N_5O_7S$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *piperacillin CRS*.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, I, J, K, L, M, O, P, Q, R, S, T.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, N.*

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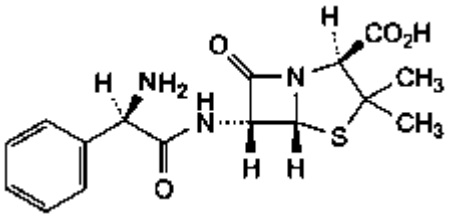
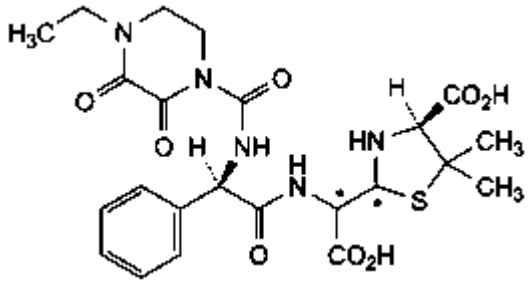
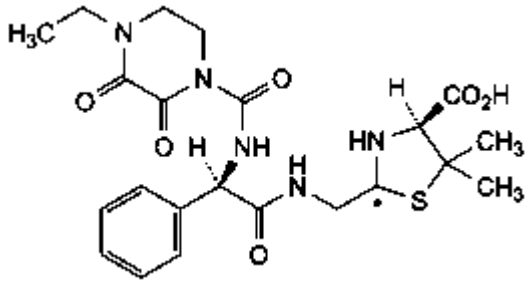


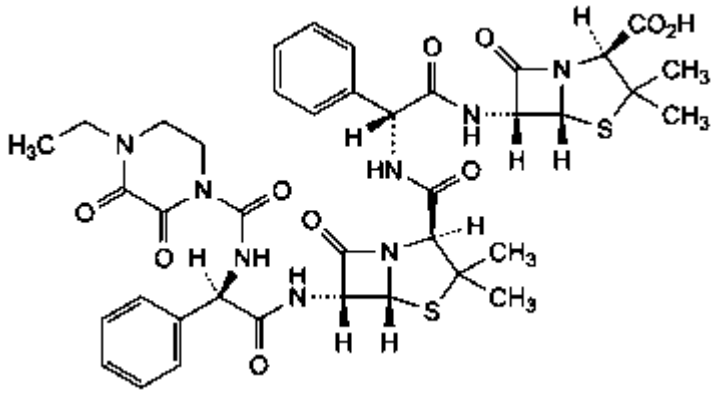
A. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (ampicillin),



B. (2*Ξ*,4*S*)-2-[(*Ξ*)-carboxy[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of piperacillin),



C. (2*Ξ*,4*S*)-2-[[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penilloic acids of piperacillin),



D. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[(2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (piperacillinylampicillin),

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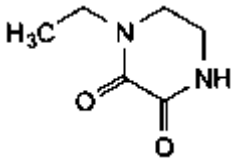
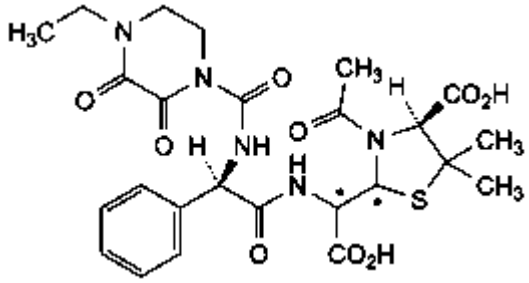
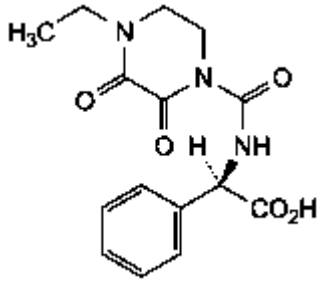


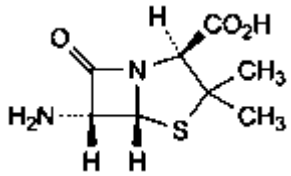
E. 1-ethylpiperazine-2,3-dione,



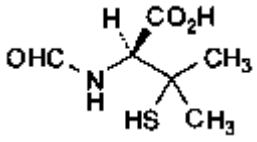
F. (2Ξ,4*S*)-3-acetyl-2-[(Ξ)-carboxy[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (acetylated penicilloic acids of piperacillin),



G. (*R*)-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)phenylacetic acid,



H. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillamic acid),



I. (2*S*)-2-formamido-3-methyl-3-sulfanylbutanoic acid (*N*-formylpenicillamine),

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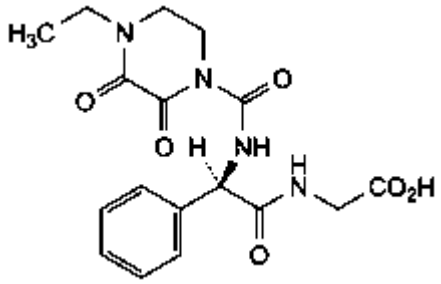
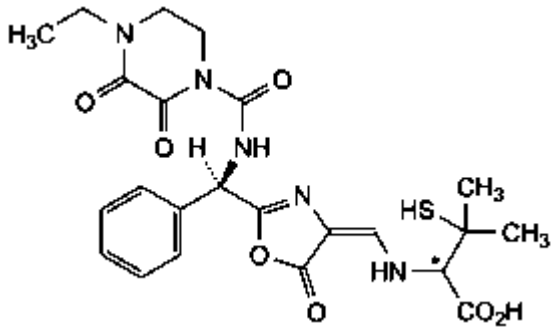
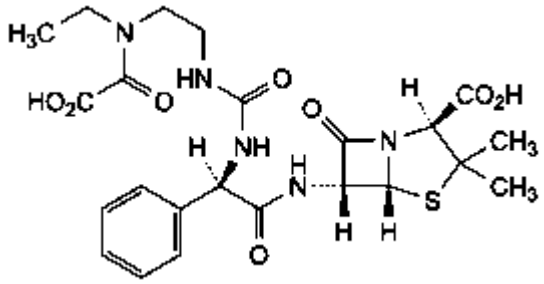


J. [(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]acetic acid,

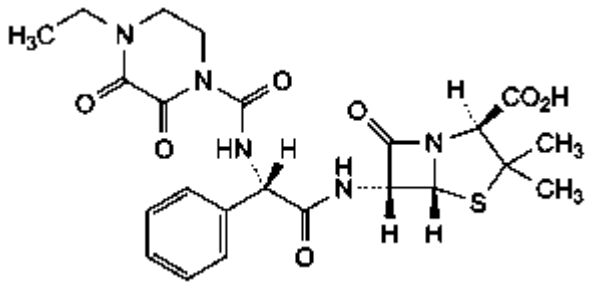


K. (2Ξ)-2-[[(*E*)-[2-[(*R*)-[(4-ethyl-2,3-dioxopiperazine-1-carboxamido)phenylmethyl]-5-oxo-1,3-oxazol-4(5*H*)-ylidene]methyl]amino]-3-methyl-3-sulfanylbutanoic acid (penicillenic acid),

L. unknown structure,



M. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[[[2-[ethyl(oxalo)amino]ethyl]carbamoyl]amino]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



N. (2*S*,5*R*,6*R*)-6-[(2*S*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-piperacillin),

O. unknown structure,

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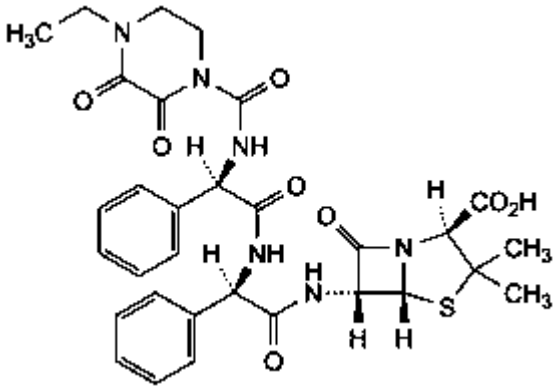
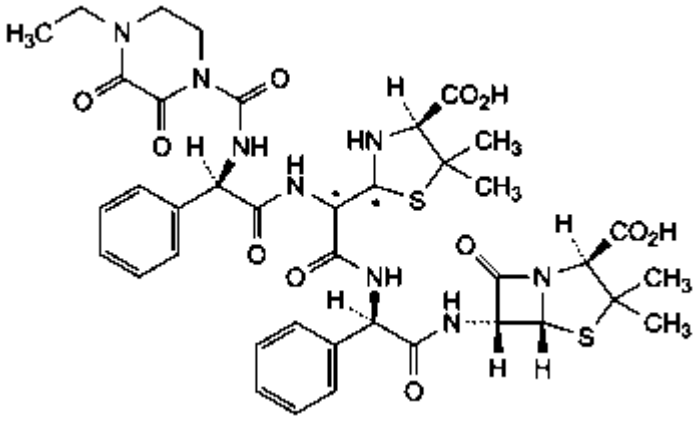
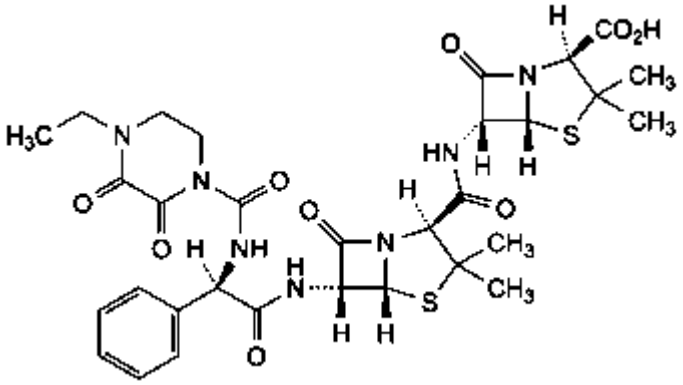


P. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

Q. unknown structure,



R. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[(2*Ξ*)-2-[(2*Ξ*,4*S*)-4-carboxy-5,5-dimethyl-1,3-thiazolidin-2-yl]-2-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



S. (2*S*,5*R*,6*R*)-6-[(2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

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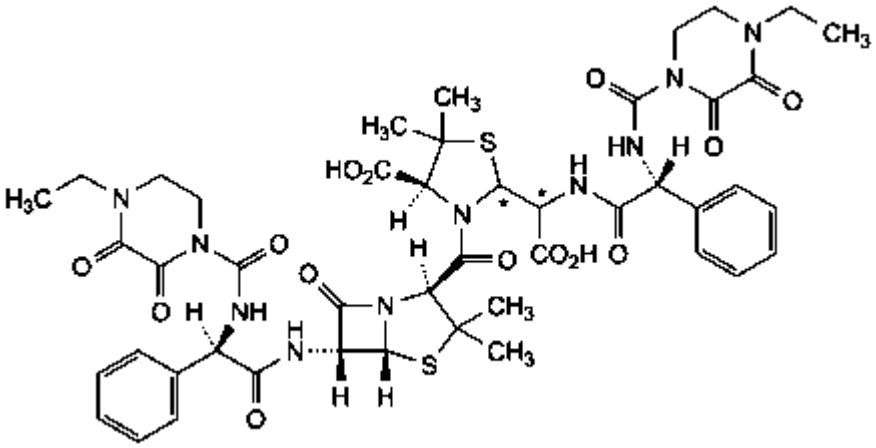

T. (2Ξ,4*S*)-2-[(Ξ)-carboxy[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-3-[(2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carbonyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid.

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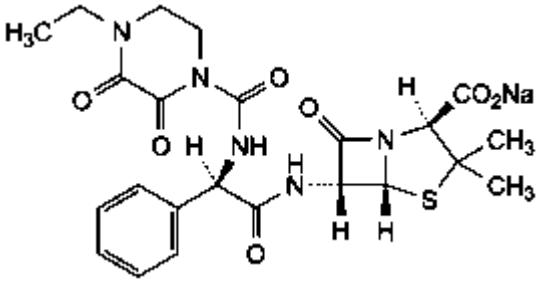
Piperacillin Sodium

General Notices

(Ph. Eur. monograph 1168)



$C_{23}H_{26}N_5NaO_7S$ 539.5 *59703-84-3*

Action and use

Penicillin antibacterial.

Ph Eur

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

95.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

The manufacturing process is evaluated to determine the potential presence of *N*,*N*-dimethylaniline. Where necessary, the manufacturing process is validated to demonstrate that the piperacillin sodium complies with the following test:

***N*,*N*-Dimethylaniline** (*2.4.26, Method A*)

Maximum 20 ppm.

CHARACTERS

Appearance

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Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in ethyl acetate.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dissolve 0.250 g in *water R*, add 0.5 mL of *dilute hydrochloric acid R* and 5 mL of *ethyl acetate R*; stir and allow to stand for 10 min in iced water. Filter the crystals through a small sintered-glass filter (40), applying suction. Wash with 5 mL of *water R* and 5 mL of *ethyl acetate R*, then dry in an oven at 60 °C for 60 min.

Comparison *piperacillin CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 430 nm is not greater than 0.10.

pH (*2.2.3*)

5.0 to 7.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.120 g of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B.

Reference solution (b) Dissolve 6 mg of *piperacillin impurity I CRS* in mobile phase B and dilute to 20 mL with mobile phase B.

Reference solution (c) Dissolve 6 mg of *anhydrous ampicillin CRS* (impurity A) in mobile phase B and dilute to 20 mL with mobile phase B.

Reference solution (d) To 2 mL of reference solution (b), add 1 mL of reference solution (c) and dilute to 10 mL with mobile phase B.

Reference solution (e) Dissolve 6 mg of *piperacillin for peak identification CRS* (containing impurities A, B, C, D, E, F, G, I, J, K, L, M, O, P, Q, R, S and T) in mobile phase B and dilute to 1 mL with mobile phase B.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 3 mL of a 320 g/L solution of *tetrabutylammonium hydroxide R*, 100 mL of a 27.6 g/L solution of *sodium dihydrogen phosphate R*, 275 mL of *methanol R1* and 622 mL of *water for chromatography R*; adjust the apparent pH to 5.5 with *phosphoric acid R*;

— *mobile phase B*: mix 3 mL of a 320 g/L solution of *tetrabutylammonium hydroxide R*, 100 mL of a 27.6 g/L solution of *sodium dihydrogen phosphate R*, 282 mL of *water for chromatography R* and 615 mL of *methanol R1*; adjust the apparent pH to 5.5 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	100	0
6 - 55	100 → 71	0 → 29
55 - 73	71 → 10	29 → 90
73 - 85	10	90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Autosampler Set at 4 °C.

Injection 10 µL of the test solution and reference solutions (a), (d) and (e).

Identification of impurities Use the chromatogram supplied with *piperacillin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, B, C, D, E, F, G, I, J, K, L, M, O, P, Q, R, S and T.

Relative retention With reference to piperacillin (retention time = about 54 min): impurity E = about 0.05; impurity I = about 0.12; impurity A = about 0.14; impurity G = about 0.30; impurity J = about 0.36; impurity F = about 0.57; impurity K = about 0.60; impurity L = about 0.65; impurity B (isomer 1) = about 0.71; impurity M = about 0.75; impurity B (isomer 2) = about 0.83; impurity C (isomer 1) = about 0.87; impurity C (isomer 2) = about 0.92; impurity O = about 1.23; impurity P = about 1.26; impurity Q = about 1.31; impurity R = about 1.36; impurity S = about 1.38; impurity T = about 1.41; impurity D = about 1.54.

System suitability Reference solution (d):

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— *resolution*: minimum 1.5 between the peaks due to impurities I and A.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.3; impurity E = 0.4; impurity I = 3.2;

— for each impurity, use the concentration of piperacillin sodium in reference solution (a).

Limits:

— *impurity G*: maximum 1.5 per cent;

— *impurities B (sum of isomers), D*: for each impurity, maximum 1.0 per cent;

— *impurity F*: maximum 0.8 per cent;

— *impurity C (sum of isomers)*: maximum 0.7 per cent;

— *impurity S*: maximum 0.5 per cent;

— *impurities L, T*: for each impurity, maximum 0.3 per cent;

— *impurities A, E, I, J, K, M, O, P, Q, R*: for each impurity, maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 2.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 2.0 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, 31.2 g/L solution of sodium dihydrogen phosphate R (25:75 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of piperacillin CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dissolve 0.1 g of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of piperacillin impurity N CRS in the solvent mixture and dilute to 25 mL with the solvent mixture.

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Reference solution (d) To 5 mL of reference solution (b), add 0.1 mL of reference solution (c) and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 24 mL of an 80 g/L solution of *tetrabutylammonium hydroxide R*, 200 mL of *acetonitrile for chromatography R*, 200 mL of a 31.2 g/L solution of *sodium dihydrogen phosphate R* and 576 mL of *water for chromatography R*; adjust the apparent pH to 5.5 with *dilute phosphoric acid R* or *dilute sodium hydroxide solution R*;

— *mobile phase B*: mix 24 mL of an 80 g/L solution of *tetrabutylammonium hydroxide R*, 126 mL of *water for chromatography R*, 200 mL of a 31.2 g/L solution of *sodium dihydrogen phosphate R* and 650 mL of *acetonitrile for chromatography R*; adjust the apparent pH to 5.5 with *dilute phosphoric acid R* or *dilute sodium hydroxide solution R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3.5	100	0
3.5 - 4	100 → 92	0 → 8
4 - 14	92 → 86	8 → 14
14 - 15	86 → 0	14 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (a) and (d).

Relative retention With reference to piperacillin (retention time = about 13 min): impurity N = about 0.96.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity N and piperacillin.

Calculate the percentage content of $C_{23}H_{26}N_5NaO_7S$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *piperacillin CRS* and a conversion factor of 1.042.

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

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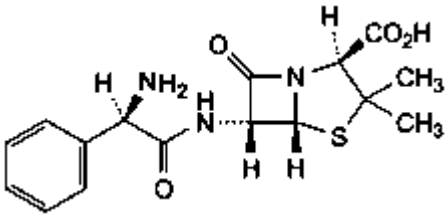
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

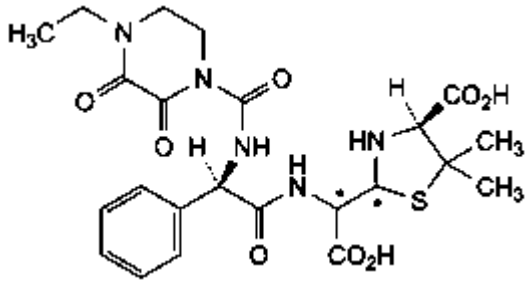
IMPURITIES

Specified impurities *A, B, C, D, E, F, G, I, J, K, L, M, O, P, Q, R, S, T.*

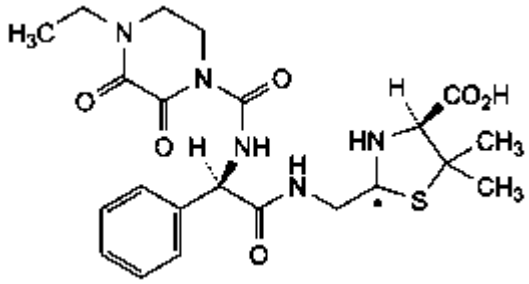
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, N.*



A. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (ampicillin),



B. (2Ξ,4*S*)-2-[(Ξ)-carboxy[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of piperacillin),



C. (2Ξ,4*S*)-2-[[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penilloic acids of piperacillin),

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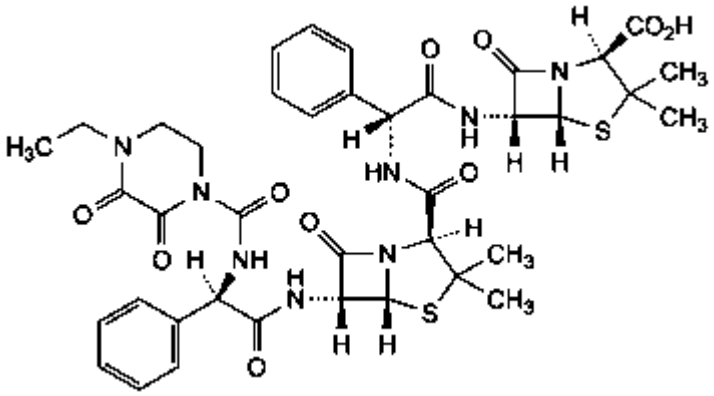
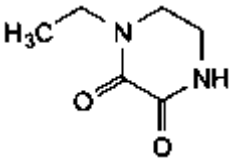
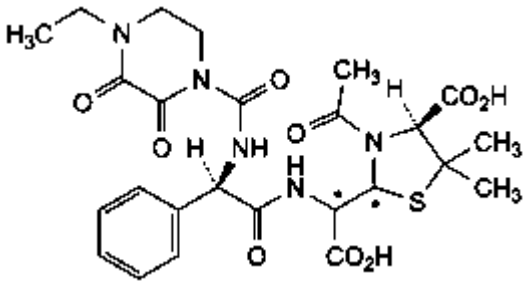


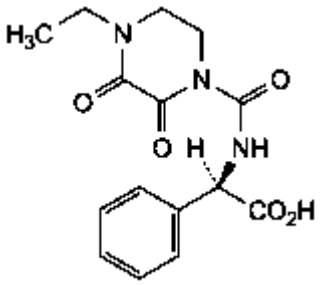
D. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[(2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (piperacillinylampicillin),



E. 1-ethylpiperazine-2,3-dione,



F. (2Ξ,4*S*)-3-acetyl-2-[(Ξ)-carboxy[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (acetylated penicilloic acids of piperacillin),



G. (*R*)-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)phenylacetic acid,

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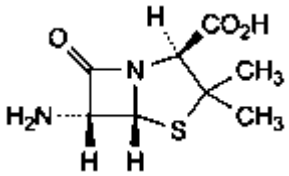
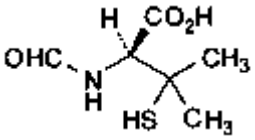
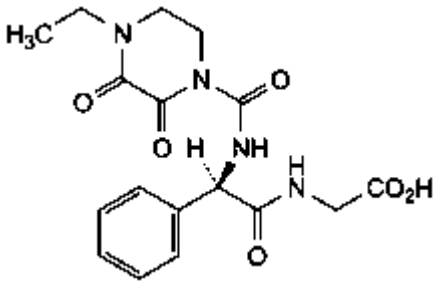


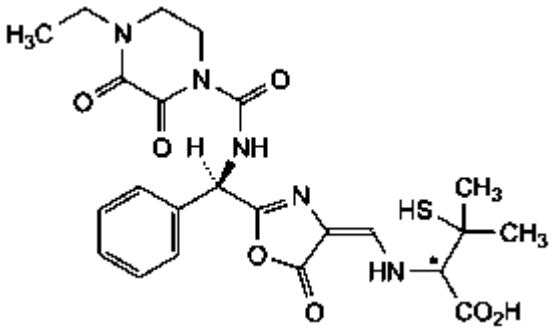
H. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



I. (2*S*)-2-formamido-3-methyl-3-sulfanylbutanoic acid (*N*-formylpenicillamine),

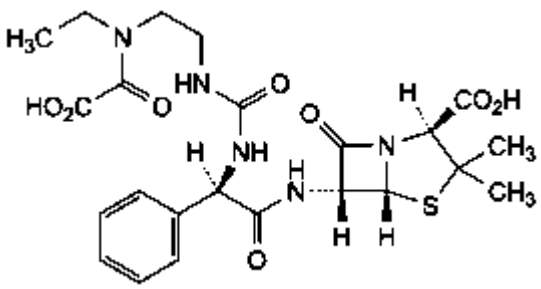


J. [(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]acetic acid,



K. (2Ξ)-2-[[(*E*)-[2-[(*R*)-[(4-ethyl-2,3-dioxopiperazine-1-carboxamido)phenylmethyl]-5-oxo-1,3-oxazol-4(5*H*)-ylidene]methyl]amino]-3-methyl-3-sulfanylbutanoic acid (penicillenic acid),

L. unknown structure,



M. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[[[2-[ethyl(oxalo)amino]ethyl]carbamoyl]amino]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

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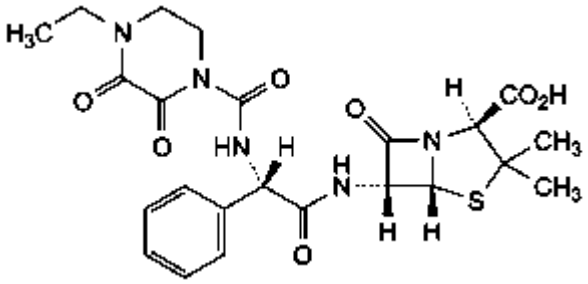
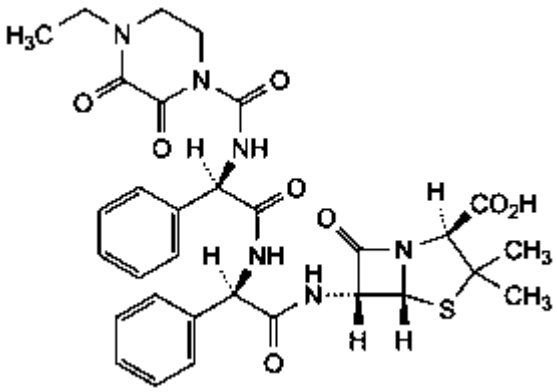


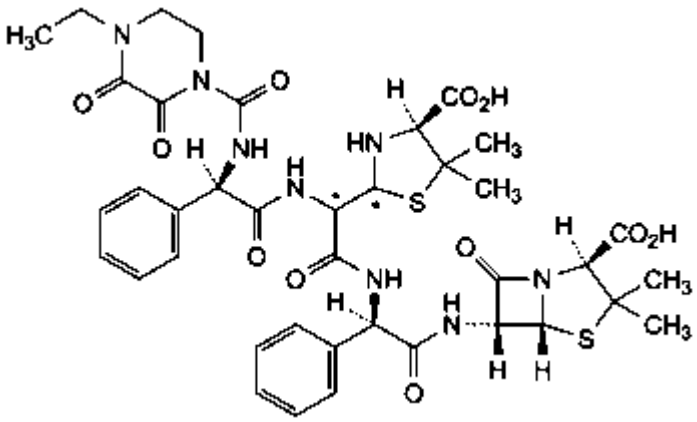
N. (2*S*,5*R*,6*R*)-6-[(2*S*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-piperacillin),

O. unknown structure,



P. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

Q. unknown structure,



R. (2*S*,5*R*,6*R*)-6-[(2*R*)-2-[(2Ξ)-2-[(2Ξ,4*S*)-4-carboxy-5,5-dimethyl-1,3-thiazolidin-2-yl]-2-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

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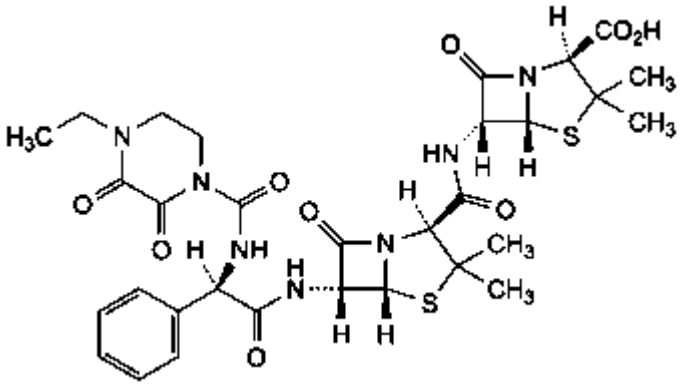
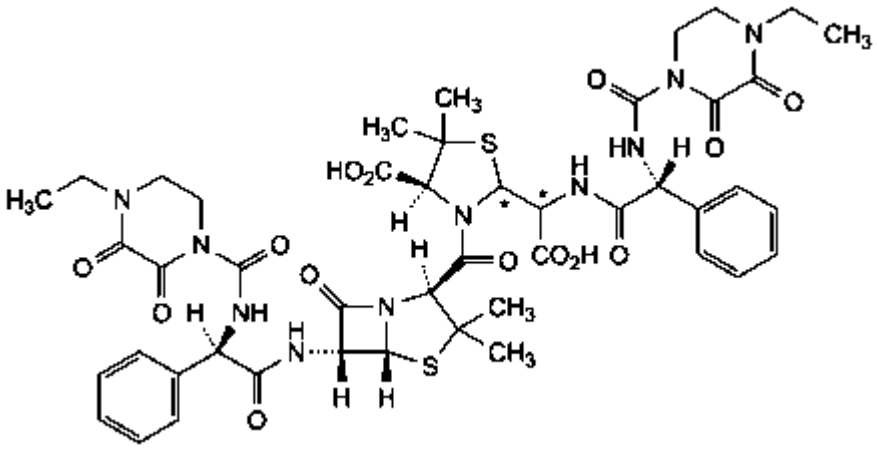


S. (2*S*,5*R*,6*R*)-6-[(2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



T. (2Ξ,4*S*)-2-[(Ξ)-carboxy[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-3-[(2*S*,5*R*,6*R*)-6-[(2*R*)-2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carbonyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid.

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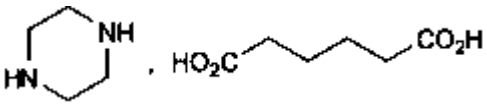
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Piperazine Adipate

General Notices

(Ph. Eur. monograph 0423)



$C_{10}H_{20}N_2O_4$ 232.3 *142-88-1*

Action and use

Anthelminthic.

Ph Eur

DEFINITION

Piperazine adipate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of piperazine hexanedioate, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white crystalline powder, soluble in water, practically insoluble in ethanol (96 per cent). It melts at about 250 °C, with decomposition.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *piperazine adipate CRS*. Examine the substances prepared as discs.

B. Examine the chromatograms obtained in the test for related substances after spraying with the ninhydrin solutions. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

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C. To 10 mL of solution S (see Tests) add 5 mL of *hydrochloric acid R* and shake with three quantities, each of 10 mL, of *ether R*. Evaporate the combined ether layers to dryness. The residue, washed with 5 mL of *water R* and dried at 100 °C to 105 °C, melts (*2.2.14*) at 150 °C to 154 °C.

TESTS

Solution S

Dissolve 2.5 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a suitable silica gel as the coating substance.

Test solution (a) Dissolve 1.0 g of the substance to be examined in 6 mL of *concentrated ammonia R* and dilute to 10 mL with *ethanol R*.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R*.

Reference solution (a) Dissolve 0.1 g of *piperazine adipate CRS* in a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b) Dissolve 25 mg of *ethylenediamine R* in a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (c) Dissolve 25 mg of *triethylenediamine R* in a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (d) Dissolve 12.5 mg of *triethylenediamine R* in 5.0 mL of test solution (a) and dilute to 50 mL with a mixture of 2 volumes of *ethanol R* and 3 volumes of *concentrated ammonia R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 15 cm using a freshly prepared mixture of 20 volumes of *concentrated ammonia R* and 80 volumes of *acetone R*. Dry the plate at 105 °C and spray successively with a 3 g/L solution of *ninhydrin R* in a mixture of 3 volumes of *anhydrous acetic acid R* and 100 volumes of *butanol R* and a 1.5 g/L solution of *ninhydrin R* in *ethanol R*. Dry the plate at 105 °C for 10 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent). Spray the plate with *0.05 M iodine* and allow to stand for about 10 min. Any spot corresponding to triethylenediamine in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.25 per cent). The test is not valid unless the chromatogram obtained with reference solution (d) shows two clearly separated spots. Disregard any spots remaining on the line of application.

Water (*2.5.12*)

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Not more than 0.5 per cent, determined on 1.00 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 10 mL of *anhydrous acetic acid R* with gentle heating and dilute to 70 mL with the same acid. Titrate with *0.1 M perchloric acid* using 0.25 mL of *naphtholbenzein solution R* as indicator until the colour changes from brownish-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 11.61 mg of $C_{10}H_{20}N_2O_4$.

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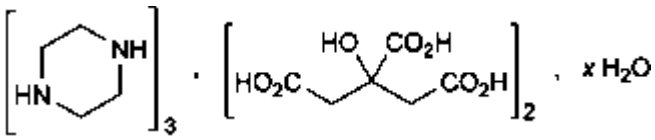
Piperazine Citrate

General Notices

(Ph. Eur. monograph 0424)



$C_{24}H_{46}N_6O_{14},xH_2O$ 643 (anhydrous substance)

Action and use

Anthelminthic.

Preparation

Piperazine Citrate Elixir

Ph Eur

DEFINITION

Piperazine citrate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of tripiperazine bis(2-hydroxy-propane-1,2,3-tricarboxylate), calculated with reference to the anhydrous substance. It contains a variable quantity of water.

CHARACTERS

A white or almost white granular powder, freely soluble in water, practically insoluble in ethanol (96 per cent).

After drying at 100 °C to 105 °C, it melts at about 190 °C.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *piperazine citrate CRS*. Dry the substance to be examined and the reference substance at 120 °C for 5 h, powder the substances avoiding uptake of water, prepare discs and record the spectra without delay.

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B. Examine the chromatograms obtained in the test for related substances after spraying with the ninhydrin solutions. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.5 g in *water R* and dilute to 5 mL with the same solvent. The solution gives the reaction of citrates (*2.3.1*).

TESTS

Solution S

Dissolve 1.25 g in *water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a suitable silica gel as the coating substance.

Test solution (a) Dissolve 1.0 g of the substance to be examined in 6 mL of *concentrated ammonia R* and dilute to 10 mL with *anhydrous ethanol R*.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a mixture of 2 volumes of *anhydrous ethanol R* and 3 volumes of *concentrated ammonia R*.

Reference solution (a) Dissolve 0.1 g of *piperazine citrate CRS* in a mixture of 2 volumes of *anhydrous ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b) Dissolve 25 mg of *ethylenediamine R* in a mixture of 2 volumes of *anhydrous ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (c) Dissolve 25 mg of *triethylenediamine R* in a mixture of 2 volumes of *anhydrous ethanol R* and 3 volumes of *concentrated ammonia R* and dilute to 100 mL with the same mixture of solvents.

Reference solution (d) Dissolve 12.5 mg of *triethylenediamine R* in 5.0 mL of test solution (a) and dilute to 50 mL with a mixture of 2 volumes of *anhydrous ethanol R* and 3 volumes of *concentrated ammonia R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 15 cm using a freshly prepared mixture of 20 volumes of *concentrated ammonia R* and 80 volumes of *acetone R*. Dry the plate at 105 °C and spray successively with a 3 g/L solution of *ninhydrin R* in a mixture of 3 volumes of *anhydrous acetic acid R* and 100 volumes of *butanol R* and a 1.5 g/L solution of *ninhydrin R* in *anhydrous ethanol R*. Dry the plate at 105 °C for 10 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent). Spray the plate with *0.05 M iodine* and allow to stand for about 10 min. Any spot corresponding to triethylenediamine in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.25 per cent). The test is not valid unless the

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chromatogram obtained with reference solution (d) shows 2 clearly separated spots. Disregard any spots remaining on the line of application.

Water (2.5.12)

10.0 per cent to 14.0 per cent, determined on 0.300 g by the semi-micro determination of water.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 10 mL of *anhydrous acetic acid R* with gentle heating and dilute to 70 mL with the same acid. Titrate with *0.1 M perchloric acid* using 0.25 mL of *naphtholbenzein solution R* as indicator until the colour changes from brownish-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 10.71 mg of $C_{24}H_{46}N_6O_{14}$.

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Piperazine Citrate Elixir

General Notices

Piperazine Citrate Oral Solution

Action and use

Antihelminthic.

DEFINITION

Piperazine Citrate Elixir is an *oral solution* containing 18.75% w/v of Piperazine Citrate in a suitable flavoured vehicle.

The elixir complies with the requirements stated under Oral Liquids and with the following requirements.

Content of piperazine citrate, $(C_4H_{10}N_2)_3,2C_6H_8O_7$

15.3 to 17.7% w/v.

IDENTIFICATION

A. To 1 mL add 5 mL of *2M hydrochloric acid* and, with stirring, 1 mL of a freshly prepared 50% w/v solution of *sodium nitrite*, cool in ice for 15 minutes, induce crystallisation, wash the crystalline precipitate with *water* and dry at 105°. The *melting point* is about 159°, Appendix V A.

B. Warm 10 mL with *activated charcoal* and filter. Boil a portion of the filtrate with an excess of *mercury(II) sulfate solution*, filter, boil the filtrate and add 0.25 mL of *dilute potassium permanganate solution*. The potassium permanganate solution is decolourised and a white precipitate is produced.

C. Acidify a portion of the filtrate obtained in test B with 1M *sulfuric acid*, add 0.25 mL of *dilute potassium permanganate solution*, warm until the colour is discharged and add an excess of *bromine water*. A white precipitate is produced either immediately or on cooling.

TESTS

Weight per mL

1.20 to 1.30 g, Appendix V G.

ASSAY

To 1.5 g add 3.5 mL of 0.5M *sulfuric acid* and 10 mL of *water*, add 100 mL of *picric acid solution R1*, heat on a water bath for 15 minutes, allow to stand for 1 hour and filter through a sintered-glass filter (ISO 4793, porosity grade 4, is suitable). Wash the residue with successive 10 mL quantities of a mixture of equal volumes of a saturated solution of *picric acid* and *water* until the washings are free from sulfate, then

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wash the residue with five 10 mL quantities of *absolute ethanol* and dry to constant weight at 105°. Each g of residue is equivalent to 0.3935 g of $(C_4H_{10}N_2)_3,2C_6H_8O_7$. Use the weight per mL of the elixir to calculate the percentage weight in volume of $(C_4H_{10}N_2)_3,2C_6H_8O_7$.

STORAGE

Piperazine Citrate Elixir should be protected from light.

Piperazine Citrate Elixir contains, in 5mL, the equivalent of about 750 mg of piperazine hydrate.

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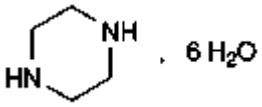
Piperazine Hydrate

General Notices

(Ph. Eur. monograph 0425)



$C_4H_{10}N_2,6H_2O$ 194.2 *142-63-2*

Action and use

Anthelminthic.

Ph Eur

DEFINITION

Piperazine hexahydrate.

Content

98.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

Colourless, deliquescent crystals.

Solubility

Freely soluble in water and in ethanol (96 per cent).

mp

About 43 °C.

IDENTIFICATION

First identification: A.

Second identification: B, C.

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A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dry the substance to be examined and the reference substance *in vacuo* (2.2.32) for 48 h, powder the substances avoiding uptake of water, prepare discs and record the spectra without delay.

Comparison *piperazine hydrate CRS*.

B. Examine the chromatograms obtained in the test for related substances after spraying with the ninhydrin solutions.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.5 g in 5 mL of *dilute sodium hydroxide solution R*. Add 0.2 mL of *benzoyl chloride R* and mix. Continue to add *benzoyl chloride R* in portions of 0.2 mL until no further precipitate is formed. Filter and wash the precipitate with a total of 10 mL of *water R* added in small portions. Dissolve the precipitate in 2 mL of hot *ethanol (96 per cent) R* and pour the solution into 5 mL of *water R*. Allow to stand for 4 h, filter, wash the crystals with *water R* and dry at 100-105 °C. The crystals melt (2.2.14) at 191 °C to 196 °C.

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_8 (2.2.2, *Method II*).

pH (2.2.3)

10.5 to 12.0 for solution S.

Related substances

Thin-layer chromatography (2.2.27).

Solvent mixture *anhydrous ethanol R*, *concentrated ammonia R* (40:60 *V/V*).

Test solution (a) Dissolve 1.0 g of the substance to be examined in 6 mL of *concentrated ammonia R* and dilute to 10 mL with *anhydrous ethanol R*.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 0.1 g of *piperazine hydrate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 25 mg of *ethylenediamine R* in the solvent mixture and dilute to 100 mL with the solvent mixture.

Reference solution (c) Dissolve 25 mg of *triethylenediamine R* in the solvent mixture and dilute to 100 mL with the solvent mixture.

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Reference solution (d) Dissolve 12.5 mg of *triethylenediamine R* in 5.0 mL of test solution (a) and dilute to 50 mL with the solvent mixture.

Plate Suitable silica gel as the coating substance.

Mobile phase *concentrated ammonia R*, *acetone R* (20:80 *V/V*); use a freshly prepared mixture.

Application 5 µL.

Development Over a path of 15 cm.

Drying At 105 °C.

Detection A Spray successively with a 3 g/L solution of *ninhydrin R* in a mixture of 3 volumes of *anhydrous acetic acid R* and 100 volumes of *butanol R* and a 1.5 g/L solution of *ninhydrin R* in *anhydrous ethanol R* and dry the plate at 105 °C for 10 min.

Limits A Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent).

Detection B Spray with *0.05 M iodine* and allow to stand for about 10 min.

Limits B Any spot corresponding to triethylenediamine in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.25 per cent).

System suitability Reference solution (d):

— the chromatogram shows 2 clearly separated spots.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 80.0 mg in 10 mL of *anhydrous acetic acid R* with gentle heating and dilute to 70 mL with the same acid. Titrate with *0.1 M perchloric acid* using 0.25 mL of *naphtholbenzein solution R* as indicator until the colour changes from brownish-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 9.705 mg of $C_4H_{10}N_2,6H_20$.

STORAGE

In an airtight container, protected from light.

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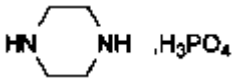
Piperazine Phosphate

General Notices



$C_4H_{10}N_2,H_3PO_4,H_2O$ 202.1 *18534-18-4*

Action and use

Anthelminthic.

Preparations

Piperazine Phosphate Chewable Tablets

Piperazine Phosphate Tablets

DEFINITION

Piperazine Phosphate contains not less than 98.5% and not more than 100.5% of $C_4H_{10}N_2,H_3PO_4$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white, crystalline powder; odourless or almost odourless.

Sparingly soluble in *water*; practically insoluble in *ethanol (96%)*.

IDENTIFICATION

A. Dissolve 0.1 g in 5 mL of *water*, add 0.5 g of *sodium hydrogen carbonate*, 0.5 mL of a 5% w/v solution of *potassium hexacyanoferrate(III)* and 0.1 mL of *mercury*. Shake vigorously for 1 minute and allow to stand for 20 minutes. A reddish colour is produced slowly.

B. Dissolve 0.2 g in 5 mL of *2M hydrochloric acid*, add with stirring 1 mL of a 50% w/v solution of *sodium nitrite* and cool in ice for 15 minutes, stirring if necessary to induce crystallisation. The *melting point* of the crystals, after washing with 10 mL of iced *water* and drying at 105°, is about 159°, Appendix V A.

C. A solution yields the reactions characteristic of *phosphates*, Appendix VI.

TESTS

Acidity

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pH of a 1% w/v solution, 6.0 to 6.5, Appendix V L.

Water

8.0 to 9.5% w/w, Appendix IX C. Use 0.25 g.

ASSAY

Dissolve 0.2 g in a mixture of 3.5 mL of 0.5M *sulfuric acid* and 10 mL of *water*. Add 100 mL of *picric acid solution R1*, heat on a water bath for 15 minutes and allow to stand for 1 hour. Filter through a sintered-glass filter (ISO 4793, porosity grade 4, is suitable) and wash the residue with successive 10 mL quantities of a mixture of equal volumes of a saturated solution of *picric acid* and *water* until the washings are free from sulfate. Wash the residue with five 10 mL quantities of *absolute ethanol* and dry to constant weight at 100° to 105°. Each g of residue is equivalent to 0.3382 g of $C_4H_{10}N_2,H_3PO_4$.

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Piperazine Phosphate Chewable Tablets

General Notices

Chewable Piperazine Phosphate Tablets

Action and use

Antihelminthic.

DEFINITION

Piperazine Phosphate Chewable Tablets contain Piperazine Phosphate. They may contain suitable flavouring agents.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of piperazine phosphate, $C_4H_{10}N_2,H_3PO_4,H_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 1 g of Piperazine Phosphate with 20 mL of *water* and filter. The filtrate complies with the following tests.

A. Dilute 1 mL to 5 mL with *water*, add 0.5 g of *sodium hydrogen carbonate*, 0.5 mL of a freshly prepared 5% w/v solution of *potassium hexacyanoferrate*(III) and 0.1 mL of *mercury*, shake vigorously for 1 minute and allow to stand for 20 minutes. A reddish colour is produced slowly.

B. To 4 mL add 1 mL of *hydrochloric acid* and, with stirring, 1 mL of a 50% w/v solution of *sodium nitrite* and cool in ice for 15 minutes, stirring if necessary to induce crystallisation. The *melting point* of the crystals, after washing with 10 mL of cold *water* and drying at 105°, is about 159°, Appendix V A.

C. Yields the reactions characteristic of *phosphates*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Piperazine Phosphate Chewable Tablets.

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.15 g of Piperazine Phosphate with 10 mL of *water* for 1 hour, filter and wash the residue with two 10 mL quantities of *water*. To the combined extract and washings add 5 mL of 1M *sulfuric acid* and

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50 mL of *picric acid solution R1*, bring to the boil, allow to stand for several hours, filter through a sintered-glass crucible (ISO 4793, porosity grade 4, is suitable) and wash the residue with successive 10 mL quantities of a mixture of equal volumes of a saturated solution of *picric acid* and *water* until the washings are free from sulfate. Wash the residue with five 10 mL quantities of *absolute ethanol* and dry to constant weight at 100° to 105°. Each g of residue is equivalent to 0.3714 g of $C_4H_{10}N_2,H_3PO_4,H_2O$.

520 mg of Piperazine Phosphate is approximately equivalent to 500 mg of piperazine hydrate.

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Piperazine Phosphate Tablets

General Notices

Action and use

Antihelminthic.

DEFINITION

Piperazine Phosphate Tablets contain Piperazine Phosphate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of piperazine phosphate, $C_4H_{10}N_2,H_3PO_4,H_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 1 g of Piperazine Phosphate with 20 mL of *water* and filter. The filtrate complies with the following tests.

A. Dilute 1 mL to 5 mL with *water*, add 0.5 g of *sodium hydrogen carbonate*, 0.5 mL of a freshly prepared 5% w/v solution of *potassium hexacyanoferrate*(III) and 0.1 mL of *mercury*, shake vigorously for 1 minute and allow to stand for 20 minutes. A reddish colour is produced slowly.

B. To 4 mL add 1 mL of *hydrochloric acid* and, with stirring, 1 mL of a 50% w/v solution of *sodium nitrite* and cool in ice for 15 minutes, stirring if necessary to induce crystallisation. The *melting point* of the crystals, after washing with 10 mL of cold *water* and drying at 105°, is about 159°, Appendix V A.

C. Yields the reactions characteristic of *phosphates*, Appendix VI.

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.15 g of Piperazine Phosphate with 10 mL of *water* for 1 hour, filter and wash the residue with two 10 mL quantities of *water*. To the combined extract and washings add 5 mL of 1M *sulfuric acid* and 50 mL of *picric acid solution R1*, bring to the boil, allow to stand for several hours, filter through a sintered-glass crucible (ISO 4793, porosity grade 4, is suitable) and wash the residue with successive 10 mL quantities of a mixture of equal volumes of a saturated solution of *picric acid* and *water* until the washings are free from sulfate. Wash the residue with five 10 mL quantities of *absolute ethanol* and dry to constant weight at 100° to 105°. Each g of residue is equivalent to 0.3714 g of $C_4H_{10}N_2,H_3PO_4,H_2O$.

520 mg of Piperazine Phosphate is approximately equivalent to 500 mg of piperazine hydrate.

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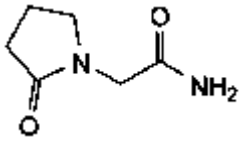
Piracetam

General Notices

(Ph. Eur. monograph 1733)



$C_6H_{10}N_2O_2$ 142.2 *7491-74-9*

Action and use

Nootropic; cortical myoclonus.

Ph Eur

DEFINITION

2-(2-Oxopyrrolidin-1-yl)acetamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *piracetam CRS*.

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If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *ethanol (96 per cent) R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (10:90 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Test solution (b) Dilute 10.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of the substance to be examined and 10 µL of *2-pyrrolidone R* (impurity A) in the solvent mixture and dilute to 100 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *piracetam CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm).

Mobile phase Mix 10 volumes of *acetonitrile R1* and 90 volumes of a 1.0 g/L solution of *dipotassium hydrogen phosphate R*; adjust to pH 6.0 with *dilute phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 8 times the retention time of piracetam.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

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Relative retention With reference to piracetam (retention time = about 4 min): impurity A = about 1.15;.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to piracetam and impurity A;

— *symmetry factor*: maximum 2.0 for the peak due to piracetam.

Calculation of percentage contents:

— for each impurity, use the concentration of piracetam in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.03 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (c).

Run time 1.5 times the retention time of piracetam.

Calculate the percentage content of $C_6H_{10}N_2O_2$ taking into account the assigned content of *piracetam CRS*.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.

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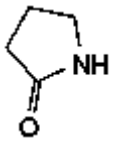
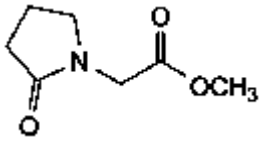
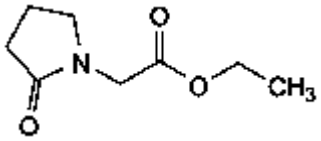


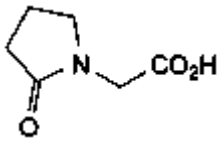
A. pyrrolidin-2-one (2-pyrrolidone),



B. methyl (2-oxopyrrolidin-1-yl)acetate,



C. ethyl (2-oxopyrrolidin-1-yl)acetate,



D. (2-oxopyrrolidin-1-yl)acetic acid.

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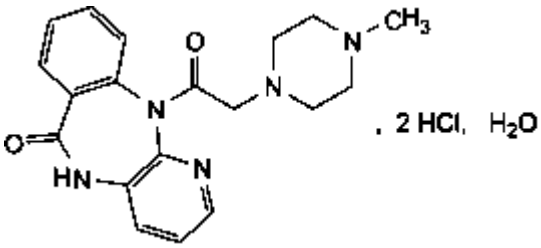
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Pirenzepine Hydrochloride

General Notices

(Pirenzepine Dihydrochloride Monohydrate, Ph. Eur. monograph 2001)



$C_{19}H_{23}Cl_2N_5O_2,H_2O$ 442.3

Action and use

Muscarinic M_3 receptor antagonist.

Ph Eur

DEFINITION

11-[(4-Methylpiperazin-1-yl)acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one dihydrochloride monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in methanol, very slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

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First identification: B, D.

Second identification: A, C, D.

A. Dissolve 30.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *methanol R*. Examined between 240 nm and 360 nm (*2.2.25*), the solution shows an absorption maximum at 283 nm. The specific absorbance at the maximum is 190 to 205 (anhydrous substance).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pirenzepine dihydrochloride monohydrate CRS*.

C. Examine the chromatograms obtained in the test for impurity D.

Results The principal zone obtained in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal zone in the chromatogram obtained with reference solution (d).

D. To 0.2 mL of solution S (see Tests) add 1.8 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution GY_5 (*2.2.2, Method II*).

pH (*2.2.3*)

1.0 to 2.0 for solution S.

Impurity D

Thin-layer chromatography (*2.2.27*).

Test solution (a) To 0.10 g add 0.1 mL of *concentrated ammonia R* and dilute to 10 mL with *methanol R*.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) To 0.1 g of *pirenzepine dihydrochloride monohydrate CRS* add 0.1 mL of *concentrated ammonia R* and dilute to 10 mL with *methanol R*.

Reference solution (b) Dissolve 25 mg of *methylpiperazine R* in *methanol R* and dilute to 25 mL with the same solvent. Dilute 2.0 mL of the solution to 100 mL with *methanol R*.

Reference solution (c) Dilute 5 mL of test solution (a) to 100 mL with *methanol R*. Dilute 4 mL of this solution to 100 mL with *methanol R*. Mix 1 mL with 1 mL of reference solution (b).

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Reference solution (d) Dilute 1 mL of reference solution (a) to 10 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *ethyl acetate R*, *toluene R* (7:25:28:40 *V/V/V/V*).

Application 20 µL as zones of 20 mm by 2 mm.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose the plate to iodine vapour until the zone in the chromatogram obtained with reference solution (b) is clearly visible (at most 60 min).

System suitability The test is not valid unless the chromatogram obtained with reference solution (c) shows 2 clearly separated zones.

Limit:

— *impurity D*: any zone corresponding to impurity D in the chromatogram obtained with test solution (a) is not more intense than the zone in the chromatogram obtained with reference solution (b) (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.30 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent. To 1.0 mL of the solution add 5 mL of *methanol R* and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 0.1 g of *1-phenylpiperazine R* in *methanol R* and dilute to 10 mL with the same solvent. Mix 1 mL of the solution with 1 mL of the test solution, add 5 mL of *methanol R* and dilute to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 2.0 g of *sodium dodecyl sulfate R* in *water R*, adjust to pH 3.2 with *acetic acid R* and dilute to 1000 mL with *water R*,

— *mobile phase B*: *methanol R*,

— *mobile phase C*: *acetonitrile R*,

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 15	55 → 25	30	15 → 45
15 - 18	25 → 20	30 → 0	45 → 80

Flow rate 1 mL/min.

Detection Spectrophotometer at 283 nm.

Injection 10 µL.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to pirenzepine and 1-phenylpiperazine.

Limits:

— *any impurity*: not more than the peak area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.04 per cent).

Water (*2.5.12*)

3.5 per cent to 5.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *water R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume at the first point of inflection.

1 mL of *0.1 M sodium hydroxide* is equivalent to 42.43 mg of $C_{19}H_{23}Cl_2N_5O_2$.

STORAGE

Protected from light.

IMPURITIES

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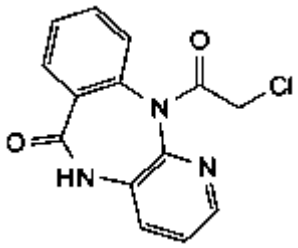
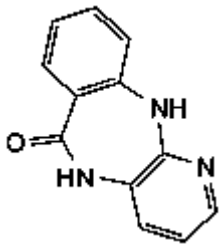
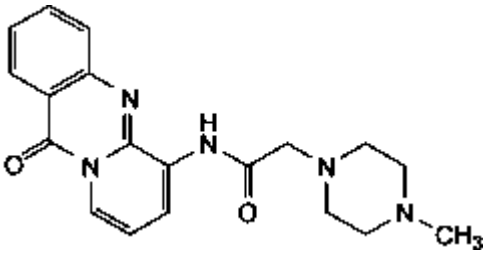


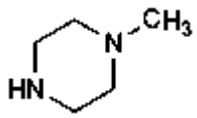
A. 11-(chloroacetyl)-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one,



B. 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one,



C. 6-[[(4-methylpiperazin-1-yl)acetyl]amino]-11*H*-pyrido[2,1-*b*]quinazolin-11-one,



D. 1-methylpiperazine.

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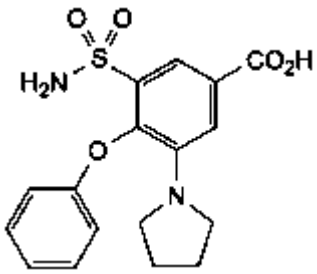
Piretanide

General Notices

(Ph. Eur. monograph 1556)



$C_{17}H_{18}N_2O_5S$ 362.4 *55837-27-9*

Action and use

Thiazide diuretic.

Ph Eur

DEFINITION

4-Phenoxy-3-(pyrrolidin-1-yl)-5-sulfamoylbenzoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellowish-white or yellowish powder.

Solubility

Very slightly soluble in water, sparingly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *piretanide CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution GY_4 (*2.2.2, Method II*).

Dissolve 0.1 g in *methanol R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *anhydrous ethanol R*, *acetonitrile R*, *water R* (10:45:45 *V/V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *piretanide for system suitability CRS* (containing impurities A, B and C) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 0.3 mL of the test solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase A mixture of 35 volumes of *acetonitrile R1* and 65 volumes of a solution prepared as follows: add 1 mL of *trifluoroacetic acid R* to 500 mL of *water for chromatography R*, add 1 mL of *triethylamine R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 10 µL.

Run time 5 times the retention time of piretanide.

Identification of impurities Use the chromatogram supplied with *piretanide for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to piretanide (retention time = about 10 min): impurity A = about 0.8; impurity B = about 3.1; impurity C = about 4.1.

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System suitability Reference solution (a):

— *resolution*: minimum 2 between the peaks due to impurity A and piretanide.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.33 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3.33 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.17 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

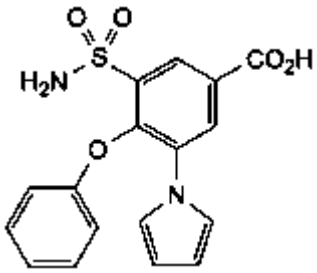
1 mL of *0.1 M perchloric acid* is equivalent to 36.24 mg of $C_{17}H_{18}N_2O_5S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. 4-phenoxy-3-(1*H*-pyrrol-1-yl)-5-sulfamoylbenzoic acid,

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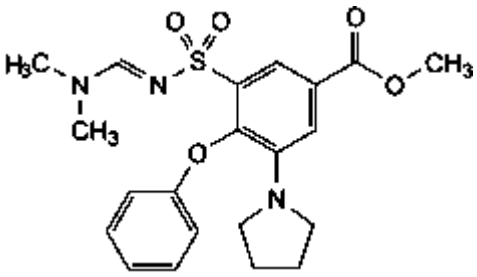
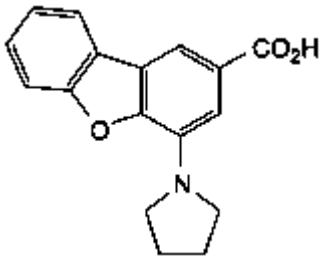


B. methyl-3-[[(dimethylamino)methylidene]sulfamoyl]-4-phenoxy-5-(pyrrolidin-1-yl)benzoate,



C. 4-(pyrrolidin-1-yl)dibenzo[*b*,*d*]furan-2-carboxylic acid.

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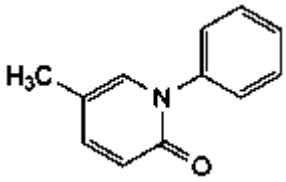
Pirfenidone

General Notices

(Ph. Eur. monograph 2856)



$C_{12}H_{11}NO$ 185.2 *53179-13-8*

Action and use

Treatment of idiopathic pulmonary fibrosis.

Ph Eur

DEFINITION

5-Methyl-1-phenylpyridin-2(1*H*)-one.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or pale yellow, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent), slightly soluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pirfenidone CRS*.

TESTS

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Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (b) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *5-methylpyridin-2-amine R* (impurity A) and 5 mg of *5-methylpyridin-2(1H)-one R* (impurity B) in *methanol R* and dilute to 100 mL with the same solvent. Dilute 1 mL of the solution to 100 mL with the mobile phase.

Reference solution (c) Dissolve 50.0 mg of *pirfenidone CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Add 0.9 mL of *triethylamine R2* to 650 mL of *water for chromatography R* and adjust to pH 3.0 with *phosphoric acid R*. Mix 650 mL of this solution, 130 mL of *methanol R2* and 220 mL of *acetonitrile R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 15 µL of test solution (a) and reference solutions (a) and (b).

Run time 4 times the retention time of pirfenidone.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to pirfenidone (retention time = about 10 min): impurity A = about 0.35; impurity B = about 0.4.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for each impurity, use the concentration of pirfenidone in reference solution (a).

Limits:

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— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying at 80 °C at a pressure not exceeding 75 kPa for 4 h.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

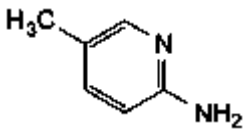
Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

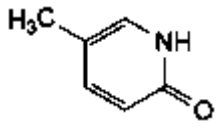
Calculate the percentage content of $C_{12}H_{11}NO$ taking into account the assigned content of *pirfenidone CRS*.

IMPURITIES

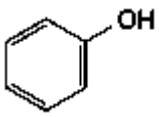
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



A. 5-methylpyridin-2-amine,



B. 5-methylpyridin-2(1*H*)-one,



C. phenol,

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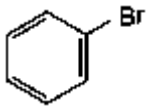

D. bromobenzene.

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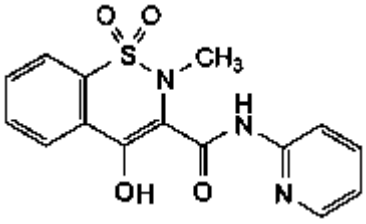
Piroxicam

General Notices

(Ph. Eur. monograph 0944)



$C_{15}H_{13}N_3O_4S$ 331.4 *36322-90-4*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Piroxicam Capsules

Piroxicam Gel

Ph Eur

DEFINITION

4-Hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *piroxicam CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 75 mg of the substance to be examined in *acetonitrile R1*, warming slightly if necessary, and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 7 mg of *piroxicam for system suitability CRS* (containing impurities A, B, D, G and J) in *acetonitrile R1* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with *acetonitrile R1*. Dilute 1.0 mL of this solution to 50.0 mL with *acetonitrile R1*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase Mix 30 volumes of *acetonitrile R1* and 70 volumes of a 6.81 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 5 times the retention time of piroxicam.

Identification of impurities Use the chromatogram supplied with *piroxicam for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, D, G and J.

Relative retention With reference to piroxicam (retention time = about 16 min): impurity A = about 0.1; impurity D = about 0.6; impurity G = about 0.7; impurity B = about 0.8; impurity J = about 1.8.

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System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities G and B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.6;

— *impurities A, B, D, G, J*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 60 mL of a mixture of equal volumes of *acetic anhydride R* and *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 33.14 mg of $C_{15}H_{13}N_3O_4S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, D, G, J.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F, H, I, K, L.*

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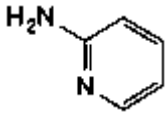
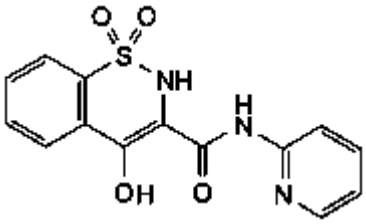
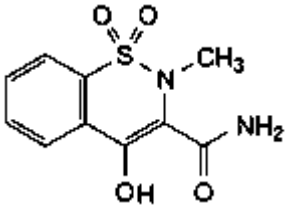


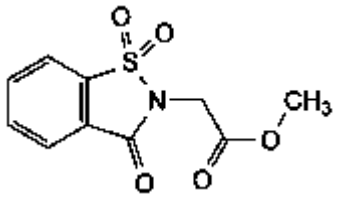
A. pyridin-2-amine,



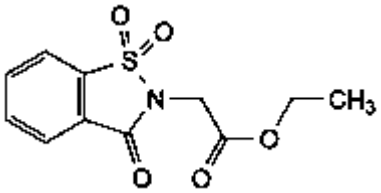
B. 4-hydroxy-*N*-(pyridin-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide,



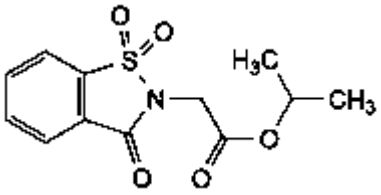
C. 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide,



D. methyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate,



E. ethyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate,



F. 1-methylethyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate,

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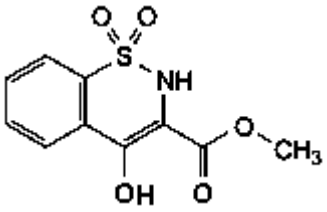
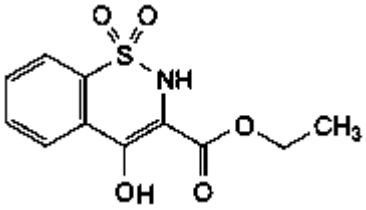
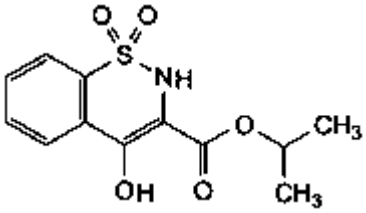


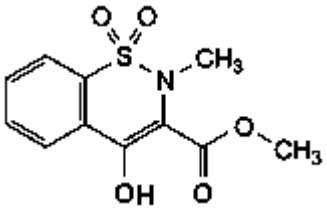
G. methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,



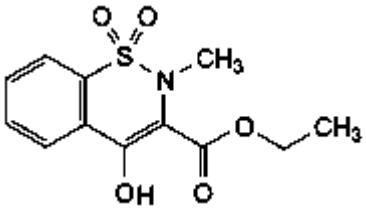
H. ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,



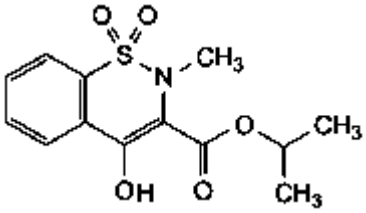
I. 1-methylethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,



J. methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,



K. ethyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide,



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L. 1-methylethyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide.

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Piroxicam Capsules

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Piroxicam Capsules contain Piroxicam.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of piroxicam, $C_{15}H_{13}N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances, the spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (3).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

2-Pyridylamine

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 1 volume of *diethylamine* and 8 volumes of *dichloromethane* as the mobile phase. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) shake a quantity of the contents of the capsules containing 80 mg of Piroxicam with 25 mL of *dichloromethane*, filter, evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 2 mL of *dichloromethane*. Solution (2) contains 0.010% w/v of *2-pyridylamine* in *dichloromethane*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any spot corresponding to 2-pyridylamine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *glacial acetic acid* and 90 volumes of *toluene* as the mobile phase. Apply separately to the plate 7.5 µL of each of the following solutions. For solution (1) shake a quantity of the contents of the capsules containing 80 mg of Piroxicam with 25 mL of *dichloromethane*,

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filter, evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 2 mL of *dichloromethane*. For solution (2) dilute 1 mL of solution (1) to 20 mL with *dichloromethane*. Solution (3) contains 0.20% w/v of *piroxicam BPCRS* in *dichloromethane*. For solution (4) dilute 2 mL of solution (2) to 50 mL with *dichloromethane*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4) (0.2%). Disregard any spot remaining on the line of application.

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *0.1M hydrochloric acid* and rotating the basket at 100 revolutions per minute. Withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted if necessary, at the maximum at 242 nm, Appendix II B. Calculate the total content of piroxicam, $C_{15}H_{13}N_3O_4S$, in the medium taking 352 as the value of A (1%, 1 cm) at the maximum at 242 nm.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add a quantity of the mixed contents of 20 capsules containing 10 mg of Piroxicam to 150 mL of 0.01M *methanolic hydrochloric acid*, mix with the aid of ultrasound for 30 minutes, cool and dilute to 200 mL with the same solvent, filter through glass-fibre paper (Whatman GF/C is suitable) and use the filtrate. Solution (2) contains 0.005% w/v of *piroxicam BPCRS* in 0.01M *methanolic hydrochloric acid*.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) as the mobile phase with a flow rate of 2 mL per minute a mixture of 60 volumes of *methanol* and 40 volumes of a buffer solution prepared by adding a solution containing 5.35 g of *disodium hydrogen orthophosphate* in 100 mL of *water* to a solution containing 7.72 g of *citric acid* in 400 mL of *water* and diluting to 1000 mL and (c) a detection wavelength of 242 nm.

Calculate the content $C_{15}H_{13}N_3O_4S$ using the declared content of $C_{15}H_{13}N_3O_4S$ in *piroxicam BPCRS*.

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Piroxicam Gel

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Piroxicam Gel contains Piroxicam.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of piroxicam, $C_{15}H_{13}N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix a quantity of the gel containing 10 mg of Piroxicam with 0.1 mL of a saturated solution of sodium chloride until the mixture becomes turbid. Dilute to 5 mL with 0.01m methanolic hydrochloric acid, shake well, centrifuge and use the clear supernatant solution. Filter the supernatant solution if necessary

(2) 0.2% w/v of *piroxicam BPCRS* in 0.01M *methanolic hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 10 volumes of *methanol* and 80 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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TESTS

Alkalinity

pH of a 10% w/v solution of the gel, 7.2 to 8.2, Appendix V L.

2-Pyridylamine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions

(1) Add 5 mL of 0.01M *methanolic hydrochloric acid* to a quantity of the gel containing 5 mg of Piroxicam, shake gently for 30 minutes, add 50 mL of the mobile phase and shake vigorously for 30 minutes. Dilute to 100 mL with the mobile phase, mix and filter through a 1-µm glass fibre membrane filter.

(2) Dilute 5 volumes of a 0.00050% w/v solution of 2-*pyridylamine* in 0.01M *methanolic hydrochloric acid* to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Zorbax stablebond C8 is suitable) and a stainless steel guard column (1 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a fluorimetric detector with an excitation wavelength of 313 nm and an emission wavelength of 380 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *methanol*, 30 volumes of *acetonitrile* and 55 volumes of 0.05M *sodium dihydrogen orthophosphate* previously adjusted to pH 3.5 with 5M *orthophosphoric acid*.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to 2-pyridylamine is not greater than that of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of 0.01M *methanolic hydrochloric acid* to a quantity of the gel containing 5 mg of Piroxicam, shake gently for 30 minutes, add 50 mL of the mobile phase and shake vigorously for 30 minutes. Dilute to 100 mL with the mobile phase, mix and filter through a 1-µm glass fibre membrane filter.

(2) 0.10% w/v solution of *piroxicam BPCRS* in 0.01M *methanolic hydrochloric acid*, mix with the aid of ultrasound if necessary, and dilute 5 volumes of this solution to 100 volumes with the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under 2-Pyridylamine may be used with an ultraviolet/visible spectrophotometric detector at a wavelength of 248 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{13}N_3O_4S$ in the gel using the declared content of $C_{15}H_{13}N_3O_4S$ in *piroxicam BPCRS*.

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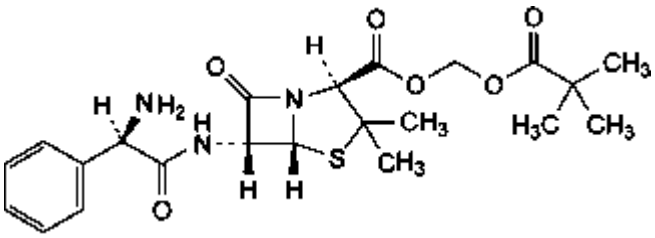
Pivampicillin

General Notices

(Ph. Eur. monograph 0852)



$C_{22}H_{29}N_3O_6S$ 463.6 *33817-20-8*

Action and use

Antibacterial.

Ph Eur

DEFINITION

Methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 2,2-dimethylpropanoate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methanol, soluble in anhydrous ethanol. It dissolves in dilute acids.

IDENTIFICATION

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First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *pivampicillin CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 2 mL of *methanol R*.

Reference solution (a) Dissolve 10 mg of *pivampicillin CRS* in 2 mL of *methanol R*.

Reference solution (b) Dissolve 10 mg of *bacampicillin hydrochloride CRS*, 10 mg of *pivampicillin CRS* and 10 mg of *talampicillin hydrochloride CRS* in 2 mL of *methanol R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 10 volumes of a 272 g/L solution of *sodium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*, 40 volumes of *water R* and 50 volumes of *ethanol (96 per cent) R*.

Application 1 µL.

Development Over a path of 15 cm.

Drying In a current of warm air.

Detection Spray with *ninhydrin solution R1* and heat at 60 °C for 10 min.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is almost colourless. Place the test-tube in a water-bath for 1 min; a dark yellow colour develops.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, *Method I*).

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Dissolve 50 mg in 12 mL of *0.1 M hydrochloric acid*.

Specific optical rotation (*2.2.7*)

+ 208 to + 222 (anhydrous substance).

Dissolve 0.100 g in 5.0 mL of *ethanol (96 per cent) R* and dilute to 10.0 mL with *0.1 M hydrochloric acid*.

Triethanolamine

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.100 g of the substance to be examined in 1.0 mL of a mixture of 1 volume of *water R* and 9 volumes of *acetonitrile R*.

Reference solution Dissolve 5.0 mg of *triethanolamine R* in a mixture of 1 volume of *water R* and 9 volumes of *acetonitrile R* and dilute to 100 mL with the same mixture of solvents.

Plate *TLC silica gel plate R*.

Mobile phase *methanol R*, *butanol R*, *phosphate buffer solution pH 5.8 R*, *glacial acetic acid R*, *butyl acetate R* (5:15:24:40:80 *V/V/V/V/V*).

Application 10 µL.

Development Over a path of 12 cm.

Drying At 110 °C for 10 min and allow to cool.

Chlorine treatment Place at the bottom of a chromatographic tank an evaporating dish containing a mixture of 1 volume of *hydrochloric acid R1*, 1 volume of *water R* and 2 volumes of a 15 g/L solution of *potassium permanganate R*; close the tank and allow to stand for 15 min; place the dried plate in the tank and close the tank; leave the plate in contact with the chlorine vapour in the tank for 15-20 min; withdraw the plate and allow it to stand in air for 2-3 min.

Detection Spray with *tetramethyldiaminodiphenylmethane reagent R*.

Limit:

— *triethanolamine*: any spot due to triethanolamine is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.05 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 50.0 mg of the substance to be examined in 10.0 mL of *acetonitrile R* and dilute to 20 mL with a 1 g/L solution of *phosphoric acid R*.

Reference solution Mix 2.0 mL of the test solution with 9.0 mL of *acetonitrile R* and 9.0 mL of a 1 g/L solution of *phosphoric acid R*.

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Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R*.

Mobile phase:

— *mobile phase A*: mix 50 volumes of a 1.32 g/L solution of *ammonium phosphate R*, adjusted to pH 2.5 with a 100 g/L solution of *phosphoric acid R*, and 50 volumes of *acetonitrile R*;

— *mobile phase B*: mix 15 volumes of a 1.32 g/L solution of *ammonium phosphate R*, adjusted to pH 2.5 with a 100 g/L solution of *phosphoric acid R*, and 85 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 12	0	100
12 - 17	100	0

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL.

Retention time Pivampicillin dimer = about 5 min.

System suitability Reference solution:

— *ratio of the mass distribution ratio*: minimum 12 for the peak due to pivampicillin dimer to that of the peak due to pivampicillin (principal peak).

Limits:

— *total*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with the reference solution (3 per cent);

— *disregard limit*: 0.01 times the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

Test solution To 1.00 g of the substance to be examined in a ground-glass-stoppered tube add 10 mL of *0.5 M sulfuric acid*. Heat the tube for 10 min in a water-bath, cool and add 15 mL of *1 M sodium hydroxide* and 1.0 mL of the internal standard solution. Stopper the tube and shake vigorously for 1 min. Centrifuge if necessary and use the upper layer.

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Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.30 g.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*). *Use the solutions within 2 h of preparation.*

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *pivampicillin CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 25.0 mg of *propyl parahydroxybenzoate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 50.0 mL with the mobile phase. Mix 5.0 mL of this solution with 5.0 mL of reference solution (a).

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 40 volumes of *acetonitrile R* and 60 volumes of a 2.22 g/L solution of *phosphoric acid R* adjusted to pH 2.5 with *triethylamine R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to pivampicillin (1st peak) and propyl parahydroxybenzoate (2nd peak) in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 2.0 for the peak due to pivampicillin in the chromatogram obtained with reference solution (b);

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections of reference solution (a).

Calculate the percentage content of $C_{22}H_{29}N_3O_6S$ from the declared content of *pivampicillin CRS*.

STORAGE

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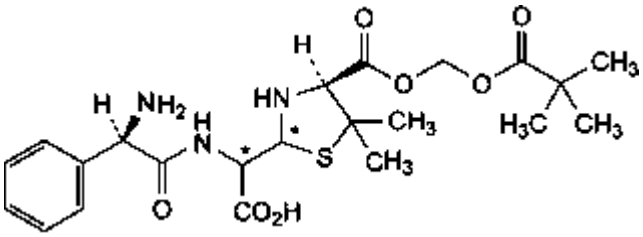
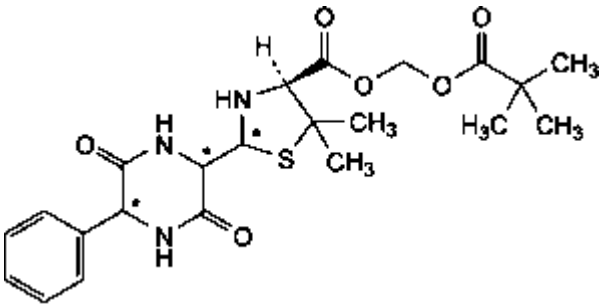
In an airtight container.

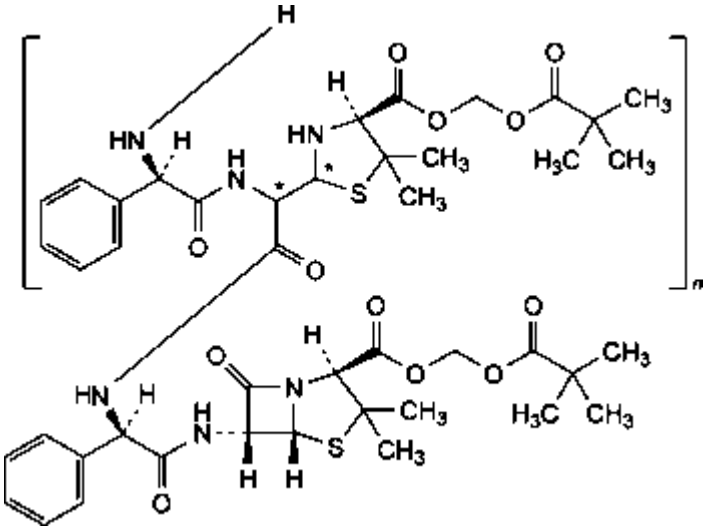
IMPURITIES



A. 2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-[(4*S*)-4-[[[(2,2-dimethylpropanoyl)oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetic acid (penicilloic acids of pivampicillin),



B. methylene (4*S*)-5,5-dimethyl-2-(3,6-dioxo-5-phenylpiperazin-2-yl)thiazolidine-4-carboxylate 2,2-dimethylpropanoate (diketopiperazines of pivampicillin),



C. co-oligomers of pivampicillin and of penicilloic acids of pivampicillin.

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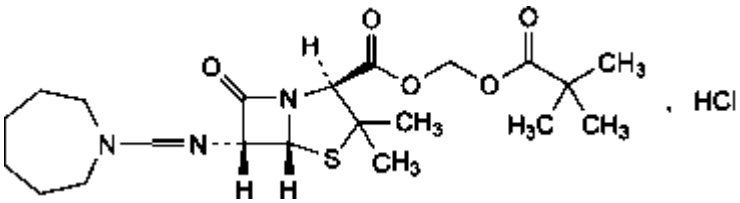
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Pivmecillinam Hydrochloride

General Notices

(Ph. Eur. monograph 1359)



$C_{21}H_{34}ClN_3O_5S$ 476.0 *32887-03-9*

Action and use

Antibacterial.

Preparation

Pivmecillinam Tablets

Ph Eur

DEFINITION

Methylene 2,2-dimethylpropanoate (2*S*,5*R*,6*R*)-6-[[(hexahydro-1*H*-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate hydrochloride.

Semi-synthetic product derived from a fermentation product.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Freely soluble in water, in anhydrous ethanol and in methanol, slightly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *pivmecillinam hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution B_8 (2.2.2, *Method I*).

Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent.

pH (2.2.3)

2.8 to 3.8.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Solvent mixture To 45 volumes of *acetonitrile for chromatography R* add 55 volumes of a 13.5 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of *pivmecillinam hydrochloride CRS* in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *pivmecillinam impurity C CRS* in 2 mL of solvent mixture, using sonication if necessary. To 0.5 mL of this solution, add 5 mg of *pivmecillinam hydrochloride CRS* and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 0.55 g of *tetraethylammonium hydrogen sulfate R* and 1.0 g of *tetramethylammonium hydrogen sulfate R* in the solvent mixture and dilute to 1000 mL with the solvent mixture.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (b) and reference solutions (b) and (c).

Run time 3 times the retention time of pivmecillinam.

System suitability Reference solution (c):

— *resolution*: minimum 3.5 between the peaks due to pivmecillinam (1st peak) and impurity C (2nd peak).

Limits:

— *any impurity*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method A*)

Maximum 20 ppm.

Test solution Prepare as described in the general method but heat at about 27 °C after the addition of *strong sodium hydroxide solution R*, to dissolve the precipitate formed, then add the *trimethylpentane R*.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

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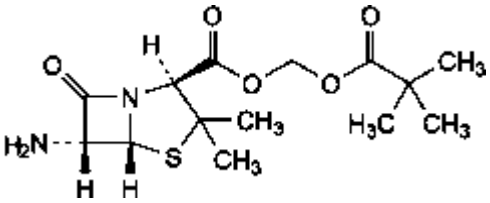
Calculate the percentage content of $C_{21}H_{34}ClN_3O_5S$ from the declared content of *pivmecillinam hydrochloride CRS*.

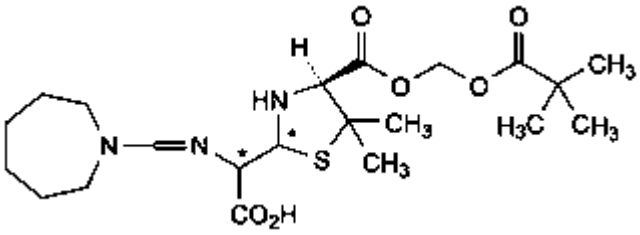
STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

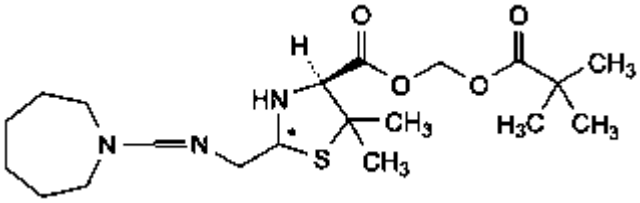
IMPURITIES



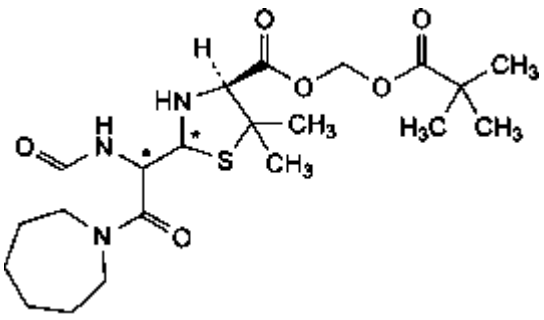
A. methylene (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 2,2-dimethylpropanoate (pivaloyloxymethyl 6-aminopenicillanate),



B. 2-[[(hexahydro-1*H*-azepin-1-yl)methylene]amino]-2-[(4*S*)-4-[[[(2,2-dimethylpropanoyl)oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetic acid (penicilloic acids of pivmecillinam),



C. methylene 2,2-dimethylpropanoate (2*RS*,4*S*)-2-[[[(hexahydro-1*H*-azepin-1-yl)methylene]amino]methyl]-5,5-dimethylthiazolidin-4-carboxylate,



D. methylene 2,2-dimethylpropanoate (4*S*)-2-[1-(formylamino)-2-(hexahydro-1*H*-azepin-1-yl)-2-oxoethyl]-5,5-dimethylthiazolidin-4-carboxylate.

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Pivmecillinam Tablets

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Pivmecillinam Tablets contain Pivmecillinam Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pivmecillinam hydrochloride, $C_{21}H_{34}ClN_3O_5S,HCl$

93.5 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.2 g of Pivmecillinam Hydrochloride with 20 mL of *dichloromethane*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum*, Appendix II A, is concordant with the reference spectrum of pivmecillinam hydrochloride *(RS 506)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. Prepare the solutions immediately before use and protected from light.

Solution A: 45 volumes of *acetonitrile* and 55 volumes of a 1.35% w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 3.0 with *orthophosphoric acid*.

(1) After 15 minutes withdraw a sample of the medium and filter. Dilute with the dissolution medium, if necessary, to produce a solution expected to contain 0.01% w/v of Pivmecillinam Hydrochloride.

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(2) 0.01% w/v of *pivmecillinam hydrochloride EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 0.55 g of *tetraethylammonium hydrogen sulfate* and 1.0 g of *tetramethylammonium hydrogen sulfate* in solution A and dilute to 1000 mL with solution A.

DETERMINATION OF CONTENT

Calculate the total content of $C_{21}H_{34}ClN_3O_5S$,HCl in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{34}ClN_3O_5S$,HCl in *pivmecillinam hydrochloride EPCRS*.

LIMITS

The amount of pivmecillinam hydrochloride released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A as described under Dissolution. Prepare the solutions immediately before use and protected from light.

(1) Disperse with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Pivmecillinam Hydrochloride with 100 mL. Mix and filter through a 0.45-µm filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.01% w/v each of *pivmecillinam hydrochloride EPCRS* and *pivmecillinam impurity C EPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, allowing the chromatography to proceed for three times the retention time of pivmecillinam.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to pivmecillinam (retention time about 5 minutes) is: impurity C, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to pivmecillinam and impurity C is at least 3.5.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A as described under Dissolution. Prepare the solutions immediately before use and protected from light.

(1) Disperse with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 0.5 g of Pivmecillinam Hydrochloride with sufficient solvent to produce 250 mL. Filter through a 0.45-µm filter (Whatman GF/C is suitable) and dilute 1 volume of the filtrate to 20 volumes.
(2) 0.01% w/v of *pivmecillinam hydrochloride EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{34}ClN_3O_5S$,HCl in the tablets from the chromatograms obtained and using the declared content of $C_{21}H_{34}ClN_3O_5S$,HCl in *pivmecillinam hydrochloride EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Pivmecillinam Hydrochloride.

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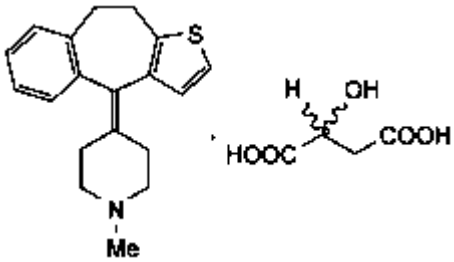
Pizotifen Malate

General Notices



$C_{19}H_{21}NS,C_4H_6O_5$ 429.5 *5189-11-7*

Action and use

Serotonin (5HT) receptor partial agonist; prophylaxis of migraine.

Preparation

Pizotifen Tablets

DEFINITION

Pizotifen Malate is 9,10-dihydro-4-(1-methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene hydrogen malate. It contains not less than 98.5% and not more than 101.5% of $C_{19}H_{21}NS,C_4H_6O_5$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or slightly yellowish white, crystalline powder.

Very slightly soluble in *water*; slightly soluble in *ethanol (96%)*; sparingly soluble in *methanol*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of pizotifen malate *(RS 277)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (5).

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 70 volumes of *isopropyl ether*, 25 volumes of *anhydrous formic acid* and 5 volumes of *water* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) dissolve 30 mg of the substance being examined in 1 mL of *ethanol (80%)*, heating if necessary. Solution (2) contains 1% w/v of *malic acid* in *ethanol (80%)*. After removal of the plate, dry it at 100° for 30 minutes, cool, spray

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with 0.02M *potassium permanganate* and dry in a current of warm air for about 1 minute. The chromatogram obtained with solution (1) exhibits a spot corresponding in position, colour and size to the spot in the chromatogram obtained with solution (2).

TESTS

Clarity and colour of solution

A 1.0% w/v solution in a mixture of equal volumes of *ethanol (96%)* and *water* is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* BY_6, Appendix IV B, Method II.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 100 volumes of *toluene*, 60 volumes of *butan-1-ol*, 40 volumes of *hexane* and 3 volumes of 13.5M *ammonia* as the mobile phase. Apply separately to the plate 5 µL of each of five solutions in a mixture of 9 volumes of *dichloromethane* and 1 volume of *methanol* containing (1) 2.0% w/v, (2) 0.20% w/v, (3) 0.010% w/v and (4) 0.0050% w/v of the substance being examined and (5) 0.20% w/v of *pizotifen malate BPCRS*. After removal of the plate, dry it in a current of cold air for 5 minutes, spray with a mixture of 1 volume of *potassium iodobismuthate solution* and 10 volumes of 2M *acetic acid* and then with *hydrogen peroxide solution (10 vol)*, cover immediately with a glass plate and examine in daylight. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (4). Disregard any yellow spot or band remaining on the line of application.

Loss on drying

When dried to constant weight at 100° to 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.2%, Appendix IX A, Method II. Use the residue obtained in the test for Loss on drying.

ASSAY

Dissolve 0.35 g in 60 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 42.95 mg of $C_{19}H_{21}NS,C_4H_6O_5$.

STORAGE

Pizotifen Malate should be protected from light.

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Pizotifen Tablets

General Notices

Action and use

Serotonin (5HT) receptor partial agonist; prophylaxis of migraine.

DEFINITION

Pizotifen Tablets contain Pizotifen Malate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pizotifen, $C_{19}H_{21}NS$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing the equivalent of 10 mg of pizotifen add 50 mL of *water*, mix with the aid of ultrasound for 15 minutes and centrifuge. Make the clear supernatant liquid alkaline with 5M *sodium hydroxide* and extract with three 25 mL quantities of *ether*, washing each extract with the same 20 mL of *water*. Combine the ether extracts, dry with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pizotifen (*RS 276*).

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (1) corresponds to the spot in the chromatogram obtained with solution (2).

C. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to pizotifen in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of 3 volumes of 13.5M *ammonia*, 100 volumes of *chloroform* and 200 volumes of *methanol* (solvent A).

(1) Mix a quantity of the powdered tablets containing the equivalent of 6 mg of pizotifen with 60 mL of solvent A for 20 minutes, centrifuge, evaporate 50 mL of the clear supernatant liquid to dryness at 40° at a pressure of 2 kPa and dissolve the residue in 2 mL of solvent A. Centrifuge and use the supernatant liquid.

(2) 0.36% w/v of *pizotifen malate BPCRS* in solvent A.

(3) Dilute 1 volume of solution (1) to 100 volumes with solvent A.

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(4) Dilute 1 volume of solution (3) to 2 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of warm air for 5 minutes, spray with a mixture of 1 volume of *potassium iodobismuthate solution* and 10 volumes of 2M *acetic acid* and then with *hydrogen peroxide solution* (*10 vol*), cover immediately with a glass plate and examine in daylight.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 15 volumes of *absolute ethanol* and 85 volumes of *toluene*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (1%) and not more than two such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.5%). Disregard any spots with Rf values lower than 0.1.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of pizotifen comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add sufficient mobile phase to one tablet to produce a solution containing the equivalent of 0.0050% w/v of pizotifen, mix with the aid of ultrasound until the tablet has disintegrated, stir for 15 minutes and centrifuge.

(2) 0.0073% w/v of *pizotifen malate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable) and a pre-column (1 cm × 4.6 mm) packed with the same material placed between the pump and the injector.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 256 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.3 volume of *triethylamine*, 45 volumes of *water* and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{21}NS$ in each tablet using the declared content of $C_{19}H_{21}NS$ in *pizotifen malate BPCRS*.

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ASSAY

Calculate the content of $C_{19}H_{21}NS$ using the average of the individual results determined in the test for Uniformity of content.

STORAGE

Pizotifen Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of pizotifen.

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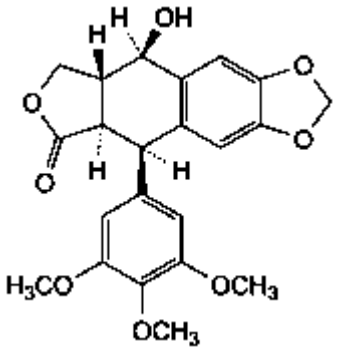
Podophyllotoxin

General Notices

(Ph. Eur. monograph 2750)



$C_{22}H_{22}O_8$ 414.4 *518-28-5*

Action and use

Inhibitor of DNA topoisomerase type II.

Ph Eur

DEFINITION

(5*R*,5a*R*,8a*R*,9*R*)-9-Hydroxy-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in acetone, soluble in methanol.

It shows polymorphism (*5.9*).

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About 184 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *podophyllotoxin CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Specific optical rotation (*2.2.7*)

-112 to -107 (anhydrous substance).

Dissolve 0.200 g in *anhydrous ethanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in 10.0 mL of the mobile phase using sonication for 30 min and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *podophyllotoxin for system suitability CRS* (containing impurities A and C) in 5 mL of the mobile phase.

Reference solution (c) Dissolve 25.0 mg of *podophyllotoxin CRS* in 10.0 mL of the mobile phase using sonication for 30 min and dilute to 25.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase Mix 40 volumes of a 1.0 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.5 with *phosphoric acid R*, and 60 volumes of *methanol R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

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Injection 5 µL of the test solution and reference solutions (a) and (b).

Run time Twice the retention time of podophyllotoxin.

Identification of impurities Use the chromatogram supplied with *podophyllotoxin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to podophyllotoxin (retention time = about 8 min): impurity A = about 0.9; impurity C = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to podophyllotoxin and impurity C.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity C = 0.4;

— for each impurity, use the concentration of podophyllotoxin in reference solution (a).

Limits:

— *impurities A, C*: for each impurity, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{22}H_{22}O_8$ taking into account the assigned content of *podophyllotoxin CRS*.

STORAGE

Protected from light, at a temperature not exceeding 30 °C.

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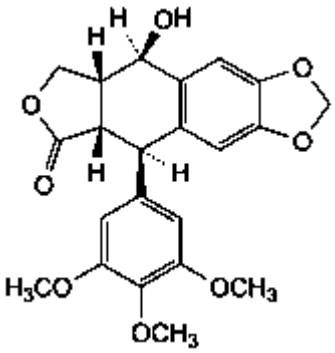
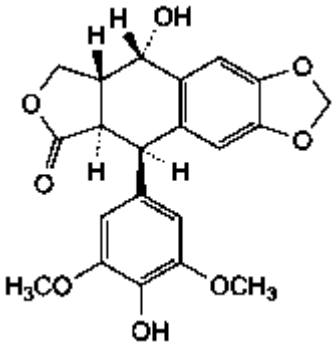
IMPURITIES

Specified impurities A, C.

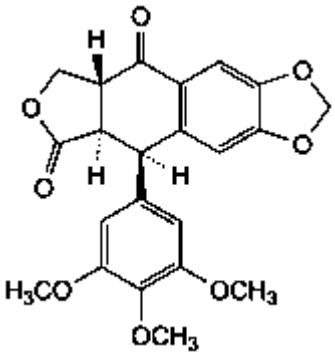
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. (5*R*,5a*S*,8a*R*,9*R*)-9-hydroxy-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (picropodophyllotoxin),



B. (5*R*,5a*R*,8a*R*,9*S*)-9-hydroxy-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (4′-demethylepipodophyllotoxin),



C. (5a*R*,8a*R*,9*R*)-9-(3,4,5-trimethoxyphenyl)-5a,6,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-5,8-dione (podophyllotoxone).

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Pollens for Allergen Products

General Notices

(Ph. Eur. monograph 2627)

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DEFINITION

Pollens for allergen products come primarily from anemophilous plants and secondarily from a few entomophilous plants. They may be processed (e.g. defatted with organic solvents) or unprocessed pollen and they contain soluble substances, including proteins, whose functional activity is unrelated to any antigenic and allergenic properties they may have.

PRODUCTION

Pollens for allergen products are defined by their species and geographic location. Species identification is carried out on the parent plant from which the pollen is collected. The field characteristics and any treatments are specified for cultivated species. Where pollen is collected from wild species, the nature of collection areas is specified. The methods of collection are described and must ensure the origin, quality, consistency and traceability of the pollen. Where applicable, reference is made to good agricultural and collection practice (GACP). The collection, handling and further processing of the pollen are such that a consistent composition of the source material is ensured from batch to batch.

Pollen may be defatted using organic solvents. The content of relevant pesticides, heavy metals and residual solvents is monitored and determined on a number of batches according to a justified sampling plan. Pesticides, heavy metals and residual solvents are limited according to the principles defined in general chapters *2.8.13. Pesticide residues*, *2.4.27. Heavy metals in herbal drugs and herbal drug preparations* and *2.4.24. Identification and control of residual solvents*, respectively.

Where major changes to the production of the pollens for allergen products take place (e.g. when a new process or supplier of pollen source material is introduced), such changes are qualified.

Microbial contamination of the pollen may be unavoidable and should be monitored on a representative number of batches of pollens for allergen products (e.g. defined by collection year and location) according to a justified sampling plan and each time a new supplier and/or a new process for production is introduced; if a determination of microbial contamination is not applicable, this must be justified. Microbial contamination values and potential increases in microbial contamination are monitored during stability studies, in order to assess this aspect along with the pollen characteristics upon storage.

Control methods and acceptance criteria relating to identity and purity of the pollen are established. The acceptance criteria must ensure the consistency of the pollens for allergen products from a qualitative and quantitative point of view. Pollens for allergen products are stored under controlled conditions justified by stability data. The collection and production, as well as the handling of the pollen, are such that consistent quality is ensured from batch to batch.

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POLLENS FOR ALLERGEN PRODUCTS REFERENCE BATCH

An appropriate reference batch is established for each species. The nature of the reference batch depends on the testing approach to verify batch-to-batch consistency and to establish acceptable quality. The reference batch may be, for example, an internal reference preparation (if available), a source material extract or a sample of a production batch. Its characterisation must be described. The extent of characterisation of the reference batch depends on the pollen, knowledge of the allergenic components and availability of suitable reagents. The reference batch is stored under controlled conditions ensuring its stability.

BATCH-TO-BATCH CONSISTENCY

To establish batch-to-batch consistency, one or more of the following tests are performed on each batch. If the microbial contamination test is performed, at least one other test is to be used. The choice of tests must be justified. Variations between different batches are to be expected due to, for example, geographic location of the harvest areas or different climates during the growth period.

Total protein (*2.5.33*)

Protein profile

Determined by using suitable electrophoresis methods (*2.2.31*, *2.2.54*).

Allergen profile

Relevant allergenic components are identified by means of suitable techniques using allergen-specific antibodies.

Major allergen content

Determined by using suitable immunochemical methods (*2.7.1*) such as enzyme-linked immunosorbent assay (ELISA).

Total allergenic activity

Determined by testing inhibition of the binding capacity of specific immunoglobulin E antibodies or by a suitable equivalent *in vitro* method.

Microbial contamination (*2.6.12*)

CHARACTERS

Pollens for allergen products are supplied as coloured powders and consist of grains in a great variety of shapes, densities and sizes depending on the species. Detailed specifications for each type of pollen grain are established.

IDENTIFICATION

Tests on identity are performed on each individual batch of pollen using adequate methods (e.g. microscopy). Specific characteristics, such as colour, size, shape, number and position of apertures, are described and compared with those of a reference batch or reference documents.

Additional tests may be performed as complementary identification determination.

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TESTS

Foreign pollen

The content of pollen from other species is limited to 1 per cent of total mixed pollens and 0.5 per cent of any individual pollen as determined by a microscopic particle count.

Foreign matter

Particles of plant origin (determined by microscopic examination), other than pollen are kept to a minimum but in any case do not exceed 10 per cent unless otherwise justified and authorised. The sum of all non-plant particles (e.g. soil) must not exceed 1 per cent. Detectable mould spores must not exceed 1 per cent.

Water (*2.5.12* or *2.5.32*) or loss on drying (*2.2.32*)

The water content of dried material is determined; specification limits must be supported by batch analysis and stability data.

STORAGE

Pollens for allergen products are stored under controlled conditions justified by stability data.

LABELLING

The label states the species of the pollen.

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Poloxamers

General Notices

(Ph. Eur. monograph 1464)

Action and use

Non-ionic surfactant.

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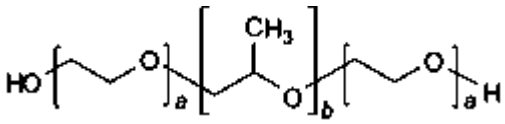
DEFINITION

Synthetic block copolymer of ethylene oxide (oxirane) and propylene oxide (methyloxirane), represented by the following general formula:



Poloxamer type	Ethylene oxide units *a*	Propylene oxide units *b*	Content of oxyethylene units (per cent)	Average relative molecular mass
124	10 - 15	18 - 23	44.8 - 48.6	2090 - 2360
188	75 - 85	25 - 30	79.9 - 83.7	7680 - 9510
237	60 - 68	35 - 40	70.5 - 74.3	6840 - 8830
338	137 - 146	42 - 47	81.4 - 84.9	12 700 - 17 400
407	95 - 105	54 - 60	71.5 - 74.9	9840 - 14 600

A suitable antioxidant may be added.

CHARACTERS

Appearance

— *poloxamer 124*: colourless or almost colourless liquid;

— *poloxamers 188, 237, 338, 407*: white or almost white, waxy powder, microbeads or flakes.

Solubility

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— *poloxamers 124, 237, 338, 407*: very soluble in water and in ethanol (96 per cent), practically insoluble in light petroleum (bp: 50-70 °C);

— *poloxamer 188*: soluble in water and in ethanol (96 per cent).

mp

About 50 °C for poloxamers 188, 237, 338 and 407.

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison Ph. Eur. chemical reference substance corresponding to the type of poloxamer to be examined.

B. Average relative molecular mass (see Tests).

C. Oxypropylene:oxyethylene ratio (see Tests).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

pH (*2.2.3*)

5.0 to 7.5 for solution S.

Ethylene oxide, propylene oxide and dioxan

Head-space gas chromatography (*2.2.28*).

Ethylene oxide stock solution Introduce 0.5 mL of ethylene oxide stock solution R2 into a vial and dilute to 50.0 mL with *dimethyl sulfoxide R1*. Mix carefully.

Ethylene oxide solution Dilute 1.0 mL of the ethylene oxide stock solution to 250 mL with *dimethyl sulfoxide R1*.

Propylene oxide stock solution Introduce about 7 mL of *methylene chloride R* into a volumetric flask, add 0.500 g (*m*) of *propylene oxide R* and dilute to 10.0 mL with *methylene chloride R*. Dilute 0.5 mL of this solution to 50.0 mL with *dimethyl sulfoxide R1*. Mix carefully. Calculate the exact concentration of propylene oxide, in milligrams per millilitre, using the following expression:

$$\frac{m \times 1000 \times 0.5}{10 \times 50}$$

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Propylene oxide solution Dilute 1.0 mL of the propylene oxide stock solution to 50.0 mL with *dimethyl sulfoxide R1*.

Calculate the exact concentration of propylene oxide, in micrograms per millilitre, using the following expression:

$$\frac{C \times 1000 \times 1}{50}$$

C = concentration of the propylene oxide stock solution, in milligrams per millilitre.

Dioxan solution Introduce 0.100 g (*m*) of *dioxan R* into a flask and dilute to 50.0 mL with *dimethyl sulfoxide R1*. Dilute 2.50 mL of this solution to 100.0 mL with *dimethyl sulfoxide R1*.

Calculate the exact concentration of dioxan, in micrograms per millilitre, using the following expression:

$$\frac{m \times 2.50 \times 1000 \times 1000}{50 \times 100}$$

Mixture solution Dilute a mixture of 6.0 mL of the ethylene oxide solution, 6.0 mL of the propylene oxide solution and 2.5 mL of the dioxan solution to 25.0 mL with *dimethyl sulfoxide R1*.

Test solution To 1.000 g of the substance to be examined in a head-space vial, add 4.0 mL of *dimethyl sulfoxide R1* and close the vial immediately.

Reference solution To 1.000 g of the substance to be examined in a head-space vial, add 2.0 mL of *dimethyl sulfoxide R1* and 2.0 mL of the mixture solution. Close the vial immediately.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.4 mL/min.

Static head-space conditions:

— *equilibrium temperature*: 110 °C;

— *equilibration time*: 30 min;

— *transfer-line temperature*: 140 °C;

— *pressurisation time*: 1 min;

— *injection time*: 0.05 min.

Temperature:

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	Time (min)	Temperature (°C)
	0 - 10	70
Column	10 - 27	70 → 240
Injection port		250
Detector		250

Detection Flame ionisation.

Injection Inject a suitable volume of the gaseous phase, for example 1 mL.

Relative retention With reference to ethylene oxide (retention time = about 6 min): propylene oxide = about 1.3; methylene chloride = about 1.6; dioxan = about 3.0; dimethyl sulfoxide = about 3.7.

Limits:

— *ethylene oxide*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (1 ppm);

— *propylene oxide*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (5 ppm);

— *dioxan*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm).

Average relative molecular mass

Weigh 15 g (*m*) of the substance to be examined into a 250 mL ground-glass-stoppered flask, add 25.0 mL of *phthalic anhydride solution R* and a few glass beads and swirl to dissolve. Boil gently under a reflux condenser for 1 h, allow to cool and add 2 quantities, each of 10 mL, of *pyridine R*, through the condenser. Add 10 mL of *water R*, mix and allow to stand for 10 min. Add 40.0 mL of *0.5 M sodium hydroxide* and 0.5 mL of a 10 g/L solution of *phenolphthalein R* in *pyridine R*. Titrate with *0.5 M sodium hydroxide* to a light pink endpoint that persists for 15 s and record the volume of sodium hydroxide used (*S*). Prepare a blank. Record the volume of sodium hydroxide used (*B*).

Calculate the average relative molecular mass using the following expression:

$$\frac{4000_m}{B - S}$$

Oxypropylene:oxyethylene ratio

Nuclear magnetic resonance spectrometry (*2.2.33*).

Use a 100 g/L solution of the substance to be examined in *deuterated chloroform R*. Record the average area of the doublet appearing at about 1.08 ppm due to the methyl groups of the oxypropylene units (A_1) and the average area of the composite band from 3.2 ppm to

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3.8 ppm due to CH_2O groups of both the oxyethylene and oxypropylene units and the CHO groups of the oxypropylene units (A_2) with reference to the internal standard.

Calculate the percentage of oxyethylene, by weight, in the sample being examined using the following expression:

$$\frac{3300\alpha}{33\alpha+58}$$

where $\alpha = \frac{A_2}{A_1} - 1$

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.000 g.

Total ash (*2.4.16*)

Maximum 0.4 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

LABELLING

The label states the type of poloxamer.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for poloxamers used as dispersing agents or vehicles (type 124).

Viscosity (*2.2.9*)

About 400 mPa·s, determined at 25 °C, for the undiluted poloxamer.

The following characteristics may be relevant for poloxamers used as solubilising agents (types 188 and 237).

Viscosity (*2.2.9*)

Typically less than 50 mPa·s, determined at 25 °C.

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Dissolve 25.0 g in 100.0 mL of *water R*.

Oxypropylene:oxyethylene ratio

(see Tests).

The following characteristics may be relevant for poloxamers used as solubilising agents (type 407).

Viscosity (2.2.9)

Typically less than 75 mPa·s, determined at 5 °C.

Dissolve 25.0 g in 100.0 mL of *water R*.

Oxypropylene:oxyethylene ratio

(see Tests).

The following characteristics may be relevant for poloxamers used as wetting agents (types 188 and 407).

Particle-size distribution (2.9.31)

Oxypropylene:oxyethylene ratio

(see Tests).

The following characteristic may be relevant for poloxamers used as viscosity-increasing agents or suspending agents (types 338 and 407).

Gel formation

Dissolve 25.0 g in 100 mL of cold *water R* (5-8 °C) and stir overnight in a refrigerator until dissolution is complete. The viscous solution obtained forms a thermoreversible gel after heating to 37 °C and does not flow in a capillary tube (2.2.9) or flows only very slowly (flow time greater than 10 min).

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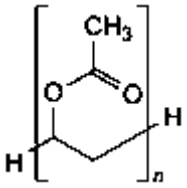
Poly(vinyl acetate)

General Notices

(Ph. Eur. monograph 1962)



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DEFINITION

Poly(vinyl acetate) is a thermoplastic polymer obtained by polymerisation of vinyl acetate using a suitable starter, without solvent or with water or 2-propanol. The vast majority of the acetate moieties are attached to non-neighbouring carbon atoms of the chain.

The index *n* is about 100-17 000. The relative molecular mass lies between 10 000 and 1500 000. The viscosity is 4 mPa·s to 250 mPa·s. The ester value, which characterises the degree of hydrolysis, is 615 to 675.

CHARACTERS

Appearance

White or almost white powder or colourless granules or beads.

Solubility

Practically insoluble in water, freely soluble in ethyl acetate, soluble in ethanol (96 per cent). It is hygroscopic and swells in water.

It softens at temperatures above 40-50 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs prepared as follows: dissolve about 200 mg in 5 mL of *acetone R*, place 100 µL on a *potassium bromide R* disc and dry to evaporate the solvent. Alternatively, the spectrum may be recorded directly by attenuated total reflectance (ATR).

Comparison *poly(vinyl acetate) CRS*.

B. Viscosity (see Tests).

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C. Saponify (2.5.6) 0.500 g in a mixture of 25.0 mL of *0.5 M alcoholic potassium hydroxide* and 25.0 mL of *water R*. 0.15 mL of the solution obtained gives reaction (b) of acetates (2.3.1).

TESTS

Solution S

Suspend 50.0 g in 100 mL of *ethyl acetate R* in a borosilicate glass flask with a ground-glass neck. Heat under a reflux condenser with constant stirring for 30 min. Allow to cool. Filter through a sintered-glass filter (16) (2.1.2), wash the residue with 50.0 mL of *ethyl acetate R* and pour the filtrate into a 250 mL graduated flask. Dilute to 250 mL with *ethyl acetate R*.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method I*).

Viscosity (*2.2.49, Method A*)

85 per cent to 115 per cent of the value stated on the label.

Determine the viscosity immediately after preparation of solution S at 20 ± 0.1 °C by using a falling ball viscometer.

Acid value (2.5.1)

Maximum 2.0, determined on 5.0 g dissolved in 50 mL of *ethanol (96 per cent) R* by shaking for 3 h.

Ester value (2.5.2)

615 to 675.

Saponify (2.5.6) 0.500 g in a mixture of 25.0 mL of *0.5 M alcoholic potassium hydroxide* and 25.0 mL of *water R*.

Residual peroxides

Maximum 100 ppm, calculated as hydrogen peroxide.

Place 0.85 g in a borosilicate glass flask with a ground-glass neck. Add 10 mL of *ethyl acetate R* and heat under a reflux condenser with constant agitation. Allow to cool. Replace the air in the container with *oxygen-free nitrogen R* and add a solution of 1 mL of *glacial acetic acid R* and 0.5 g of *sodium iodide R* in 40 mL of *water R*. Shake thoroughly and allow to stand protected from light for 20 min. Titrate with *0.005 M sodium thiosulfate* until the yellow colour is discharged. Carry out a blank titration. The difference between the titration volumes is not greater than 1.0 mL.

Vinyl acetate

Head-space gas chromatography (2.2.28).

Test solution (a) Place 0.200 g of the substance to be examined in a 20 mL vial and add 1.0 mL of *dimethylformamide R*. Close the vial and secure the stopper. Shake, avoiding contact between the stopper and the liquid.

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Test solution (b) Place 0.200 g of the substance to be examined in a 20 mL vial and add 1.0 mL of the reference solution. Close the vial and secure the stopper. Shake, avoiding contact between the stopper and the liquid.

Reference solution Place 15.0 mL of *dimethylformamide R* in a 20 mL vial, add 45 µL of *vinyl acetate R* and 50 µL of *butanal R* and dilute to volume with *dimethylformamide R*. Dilute 1.0 mL of the solution to 10.0 mL with *dimethylformamide R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: *vinyl(1)phenyl(5)methyl(94)polysiloxane R* (film thickness 0.32 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 20 mL/min.

Static head-space conditions that may be used:

— *equilibration temperature*: 60 °C;

— *equilibration time*: 20 min;

— *transfer-line temperature*: 120 °C;

— *carrier gas*: *nitrogen for chromatography R*.

Temperature:

— *column*: 155 °C;

— *injection port*: 120 °C;

— *detector*: 180 °C.

Detection Flame ionisation.

Injection 1.6 mL of the gaseous phase of test solutions (a) and (b).

System suitability Test solution (b):

— *resolution*: minimum 2.0 between the peaks due to vinyl acetate and butanal;

— *signal-to-noise ratio*: minimum 5 for the peak due to vinyl acetate.

Calculate the percentage content of vinyl acetate using the following expression:

$$\frac{V \times S_1 \times 0.931}{\left(m_1 S_2 - m_2 S_1\right) \times 2000}$$

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S_1	=	area (or height) of the peak due to vinyl acetate in the chromatogram obtained with test solution (a);
S_2	=	area (or height) of the peak due to vinyl acetate in the chromatogram obtained with test solution (b);
m_1	=	mass of the substance to be examined used to prepare test solution (a), in grams;
m_2	=	mass of the substance to be examined used to prepare test solution (b), in grams;
0.931	=	density of vinyl acetate, in grams per millilitre;
V	=	volume of vinyl acetate used to prepare the reference solution, in microlitres.

Limit:

— *vinyl acetate*: maximum 0.3 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

LABELLING

The label states:

— the nominal relative molecular mass;

— the viscosity.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

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The following characteristics may be relevant for poly(vinyl acetate) used as matrix former in prolonged-release dosage forms or film former.

Viscosity

(see Tests).

Solubility of a film

Place 3 mL of solution S on a glass plate and dry. Place the film obtained in 50 mL of *phosphate buffer solution pH 6.8 R* whilst stirring continuously. The film does not dissolve within 30 min.

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Poly(vinyl acetate) Dispersion 30 per cent

General Notices

(Ph. Eur. monograph 2152)

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DEFINITION

Dispersion in water of poly(vinyl acetate) having a mean relative molecular mass of about 450 000. It may contain *Povidone (0685)* and a suitable surface-active agent, such as *Sodium laurilsulfate (0098)*, as stabilisers.

Content

25.0 per cent to 30.0 per cent of poly(vinyl acetate).

CHARACTERS

Appearance

Opaque, white or almost white, slightly viscous liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

It is sensitive to spoilage by microbial contaminants.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dry 1 mL *in vacuo*, dissolve the residue in *acetone R*, and spread 1 drop of the solution between 2 sodium chloride R plates; remove 1 plate and allow the solvent to evaporate.

Comparison Repeat the operation using *poly(vinyl acetate) dispersion 30 per cent CRS*.

B. Place 3 mL on a glass plate and allow to dry. A clear film is formed.

C. 50 mg gives the reaction of acetyl (*2.3.1*).

TESTS

Agglomerates

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Filter 100.0 g through a tared stainless steel sieve (90). Rinse with *water R* until a clear filtrate is obtained and dry to constant mass at 100-105 °C. The mass of the residue is not greater than 0.5 g.

Vinyl acetate

Liquid chromatography (*2.2.29*).

Test solution Introduce 0.250 g into a 10 mL volumetric flask and add about 1 mL of *methanol R*. Sonicate. Add about 8 mL of *water R*. Sonicate and dilute to 10.0 mL with *water R*. Centrifuge for about 10 min and filter.

Reference solution (a) Dissolve 5.0 mg of *vinyl acetate CRS* in *methanol R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) To 5 mg of *vinyl acetate R* and 5 mg of *1-vinylpyrrolidin-2-one R*, add 10 mL of *methanol R* and sonicate. Dilute to 50 mL with mobile phase A. Dilute 1 mL of the solution to 20 mL with mobile phase A.

A precolumn containing *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) may be used if a matrix effect is observed.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, *methanol R2*, *water for chromatography R* (5:5:90 *V/V/V*);

— *mobile phase B*: *methanol R2*, *acetonitrile R1*, *water for chromatography R* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 26	100 → 80	0 → 20
26 - 27	80 → 0	20 → 100
27 - 30	0 → 100	100 → 0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL.

System suitability Reference solution (b):

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— *resolution*: minimum 5.0 between the peaks due to vinyl acetate and 1-vinylpyrrolidin-2-one.

Limit:

— *vinyl acetate*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (100 ppm).

Povidone

Maximum 4.0 per cent.

Carry out the determination of nitrogen by sulfuric acid digestion (2.5.9), using 0.25 g. Calculate the percentage content of povidone using the following expression:

$$\frac{N}{0.126}$$

N = percentage content of nitrogen.

Acetic acid

Liquid chromatography (2.2.29).

Test solution Mix 0.200 g with *water R*. Sonicate for about 10 min and dilute to 10.0 mL with *water R*.

Reference solution Dissolve 30.0 mg of *acetic acid R* and 30 mg of *citric acid monohydrate R* in the mobile phase. Shake gently to dissolve and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *0.005 M sulfuric acid*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL; after each injection, rinse the column with a mixture of equal volumes of *acetonitrile R1* and *0.005 M sulfuric acid*.

Retention time Acetic acid = about 6 min; citric acid = about 8 min.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to acetic acid and citric acid.

Limit:

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— *acetic acid*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (1.5 per cent).

Residue on evaporation

28.5 per cent to 31.5 per cent, determined on 1.000 g at 110 °C for 5 h.

Sulfated ash

Maximum 0.5 per cent, determined on 1.0 g.

Heat a silica crucible to redness for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.00 g of the preparation to be examined in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 ± 25 °C, until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting with “Moisten the substance to be examined...”.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

ASSAY

Determine the saponification value (*2.5.6*) on 1.5 g and calculate the percentage content of poly(vinyl acetate) using the following expression:

$$I_s \times 0.1534$$

I_s = saponification value.

STORAGE

At a temperature of 5 °C to 30 °C. Handle the substance so as to minimise microbial contamination.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

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The following characteristics may be relevant for poly(vinyl acetate) dispersion 30 per cent used in the manufacture of modified-release dosage forms and to mask taste.

Solubility of a film

Place the film obtained in identification test B in 50 mL of *phosphate buffer solution pH 6.8 R* whilst stirring continuously. The film does not dissolve within 30 min.

Apparent viscosity (*2.2.10*)

Maximum 100 mPa·s, determined using a rotating viscometer at 20 °C and a shear rate of 100 s^{-1}.

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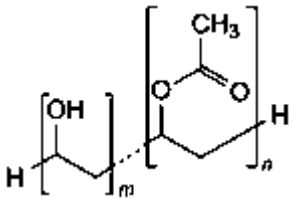
Poly(vinyl alcohol)

General Notices

(Ph. Eur. monograph 1961)



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DEFINITION

Poly(vinyl alcohol) is obtained by polymerisation of vinyl acetate, followed by partial or almost complete hydrolysis of poly(vinyl acetate) in the presence of catalytic amounts of alkali or mineral acids.

Poly(vinyl alcohol) polymers comply with the following indices:

$$0 \leq \frac{n}{m} \leq 0.35$$

The mean relative molecular mass lies between 20 000 and 150 000. The viscosity is 3 mPa·s to 70 mPa·s. The ester value, which characterises the degree of hydrolysis, is not greater than 280.

CHARACTERS

Appearance

Yellowish-white powder or translucent granules.

Solubility

Soluble in water, slightly soluble in anhydrous ethanol, practically insoluble in acetone.

Various grades of poly(vinyl alcohol) are available. They differ in their degree of polymerisation and their degree of hydrolysis which determine the physical properties of the different grades. They are characterised by the viscosity and the ester value of the substance.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *poly(vinyl alcohol) CRS*.

The intensities of the absorption bands at about 1720 cm^{-1} and 1260 cm^{-1} are inversely proportional to the degree of hydrolysis.

B. Viscosity (see Tests).

TESTS

Solution S

Heat on a water-bath 250 mL of *water R* in a borosilicate round-bottomed flask attached to a reflux condenser with stirrer, add 10.0 g of the substance to be examined (correcting for the loss on drying) and continue heating for 30 min with continuous stirring. Remove the flask from the water-bath and continue stirring until room temperature is reached.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

pH (2.2.3)

4.5 to 6.5 for solution S.

Viscosity (2.2.49, *Method A*)

85 per cent to 115 per cent of the value stated on the label.

Determine the viscosity using a falling ball viscometer immediately after preparation of solution S at 20 ± 0.1 °C.

Acid value

Maximum 3.0.

Add 1 mL of *phenolphthalein solution R* to 50 mL of solution S and titrate with *0.05 M potassium hydroxide* until the pink colour persists for 15 s. Calculate the acid value using the following expression:

$$\frac{2.805V}{2}$$

V = volume of *0.05 M potassium hydroxide* used, in millilitres.

Ester value (2.5.2)

90 per cent to 110 per cent of the value stated on the label.

Saponify (2.5.6) 1.00 g in a mixture of 25.0 mL of *0.5 M alcoholic potassium hydroxide* and 25.0 mL of *water R*.

Loss on drying (2.2.32)

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Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.0 g.

LABELLING

The label states:

— the viscosity for a 40 g/L solution;

— the ester value.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for poly(vinyl alcohol) used as viscosity-increasing agent, binder or film former.

Viscosity

(see Tests).

Ester value

(see Tests).

Infrared absorption spectrophotometry

(see Identification A).

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Polyacrylate Dispersion (30 per cent)

General Notices

(Ph. Eur. monograph 0733)

Action and use

Excipient.

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DEFINITION

Dispersion in water of a copolymer of ethyl acrylate and methyl methacrylate having a mean relative molecular mass of about 800 000.

Content

28.5 per cent to 31.5 per cent (residue on evaporation).

It may contain a suitable emulsifier.

CHARACTERS

Appearance

Opaque, white or almost white, slightly viscous liquid.

Solubility

Miscible with water, soluble in acetone, in anhydrous ethanol and in 2-propanol.

IDENTIFICATION

First identification: A.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of polyacrylate*.

B. To 1 g add 5 mL of *water R* and mix; the mixture remains opaque. Take 3 portions of 1 g and mix separately with 5 g of *anhydrous ethanol R*, 5 g of *acetone R* and 5 g of *2-propanol R*. Transparent solutions are obtained.

C. To 1 g add 10 mL of *0.1 M sodium hydroxide*. The mixture remains opaque.

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D. Appearance of a film (see Tests).

E. Dry 4 g in a Petri dish at 60 °C in an oven for 4 h and transfer the resulting clear film to a small test-tube (100 mm × 12 mm). Heat over a flame and collect the fumes that evolve in a 2nd test-tube held over the mouth of the 1st tube. The condensate gives the reaction of esters (2.3.1).

TESTS

Relative density (2.2.5)

1.037 to 1.047.

Viscosity (2.2.10)

Maximum 50 mPa·s, determined using a rotating viscometer at 20 °C and a shear rate of 10 s^{-1}.

Appearance of a film

Pour 1 mL on a glass plate and allow to dry. A clear elastic film is formed.

Particulate matter

Filter 100.0 g through a tared stainless steel sieve (90). Rinse with *water R* until a clear filtrate is obtained and dry at 80 °C to constant mass. The residue weighs not more than 0.500 g.

Residual monomers

Liquid chromatography (2.2.29).

Test solution Dissolve 1.00 g of the substance to be examined in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent. To 5.0 mL of a 35 g/L solution of *sodium perchlorate R* add 10.0 mL of the solution dropwise whilst stirring continuously. Centrifuge and filter the clear supernatant. Dilute 5.0 mL of this solution to 10.0 mL with *water R*.

Reference solution Dissolve 10 mg of *ethyl acrylate R* and 10 mg of *methyl methacrylate R* in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *tetrahydrofuran R*. To 10.0 mL of the solution add 5.0 mL of a 35 g/L solution of *sodium perchlorate R* and mix. Dilute 5.0 mL of the mixture to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.12 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase *acetonitrile R1*, *water for chromatography R* (15:85 *V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 205 nm.

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Injection About 50 µL.

Limit:

— *residual monomers*: maximum 100 ppm.

Sulfated ash (2.4.14)

Maximum 0.4 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

ASSAY

Dry 1.000 g at 110 °C for 3 h and weigh the residue.

STORAGE

At a temperature of 5 °C to 25 °C, protected from freezing.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for polyacrylate dispersion 30 per cent used as film former or matrix former in prolonged-release dosage forms.

Viscosity

(see Tests).

Appearance of a film

(see Tests).

Solubility of a film

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Take a piece of the film obtained in the test for appearance of a film and place it in a flask containing a 10.3 g/L solution of *hydrochloric acid R* with stirring. It does not dissolve within 2 h. Take another piece of the film and place it in a flask containing *0.33 M phosphate buffer solution pH 7.5 R* with stirring. It also does not dissolve within 2 h.

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Polymyxin and Bacitracin Ointment

General Notices

Action and use

Antibacterial and polypeptide antibacterial.

DEFINITION

Polymyxin and Bacitracin Ointment contains Polymyxin B Sulfate and Bacitracin Zinc in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 20 mL of *chloroform* to a quantity of the ointment containing 2500 IU of Bacitracin Zinc and shake. Add 5 mL of 0.1M *hydrochloric acid*, shake vigorously, centrifuge and use the aqueous layer.

(2) 0.13% w/v of *polymyxin B sulfate BPCRS* in 0.1M *hydrochloric acid*.

(3) 0.75% w/v of *bacitracin zinc EPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it at 105°, spray with a 0.5% w/v solution of *ninhydrin* in *butan-1-ol* and heat at 105° for 15 minutes.

MOBILE PHASE

10 volumes of 13.5M *ammonia*, 40 volumes of *water* and 60 volumes of *propan-2-ol*.

CONFIRMATION

The two principal spots in the chromatogram obtained with solution (1) correspond to those in the chromatograms obtained with solutions (2) and (3).

TESTS

Related substances (polymyxin B sulfate)

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Disperse a quantity of the ointment containing 40,000 IU of Polymyxin B Sulfate with 10 mL of *hexane* by warming gently for a few minutes. Extract with two 10-mL quantities of *water* whilst still warm and filter the resulting solution through a Whatman GF/C filter and then through a 0.45-µm nylon filter.

(2) 0.03% w/v of *polymyxin B sulfate BPCRS* in *water*.

(3) Dilute 1 volume of solution (2) to 100 volumes with *water*.

(4) 0.025% w/v of *bacitracin zinc EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 3.0 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 1.4 times the retention time of polymyxin B1.

MOBILE PHASE

20 volumes of *acetonitrile R1* and 80 volumes of a solution prepared by dissolving 4.46 g of *anhydrous sodium sulfate* in 900 mL of *water*, adjusting the pH to 2.3 with *dilute orthophosphoric acid* and diluting to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of polymyxin B1 is about 35 minutes. The retention times relative to polymyxin B1 are: about 0.5 (polymyxin B2); about 0.6 (polymyxin B3); about 0.8 (polymyxin B1-I).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to polymyxin B2 and polymyxin B3 is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 3.0% by *normalisation*;

the sum of the areas of any such peaks is not greater than 17.0% by *normalisation*.

Disregard (a) any peak with an area less than 0.7 times the area of the peak due to polymyxin B1 in the chromatogram obtained with solution (3) (0.7%), (b) any peaks due to polymyxins B1, B2, B3 and B1-1 and (c) any peaks corresponding to the peaks in the chromatogram obtained with solution (4).

Impurity E (bacitracin zinc)

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

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(1) Disperse a quantity of the ointment containing 2000 IU of Bacitracin Zinc in 20 mL of *dichloromethane*. Extract with two 10-mL quantities of a 0.446% w/v solution of *anhydrous sodium sulfate*, the pH of which has been adjusted to 2.3 with 2M *orthophosphoric acid*, and filter the aqueous layer through a glass-fibre filter paper (Whatman GF/C is suitable) and then through a 0.45-µm membrane filter.

(2) Dissolve 20 mg of *bacitracin zinc EPCRS* in 10 mL of a 4% w/v solution of *sodium edetate*, the pH of which has been adjusted to 7.0 with 2M *sodium hydroxide*.

(3) Dilute 5 volumes of solution (1) to 100 volumes with *water*.

(4) Dissolve 50 mg of *bacitracin zinc EPCRS* in 25 mL of a 4% w/v solution of *sodium edetate*, the pH of which has been adjusted to 7.0 with 2M *sodium hydroxide*. Heat in a boiling water bath for 30 minutes and allow to cool to room temperature (generation of impurity E).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC-pack ODS-A is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

40 volumes of *acetonitrile*, 100 volumes of a 3.48% w/v solution of *dipotassium hydrogen orthophosphate*, the pH of which has been adjusted to pH 6.0 with a 2.72% w/v solution of *potassium dihydrogen orthophosphate*, 300 volumes of *water* and 520 volumes of *methanol*.

Use the chromatogram obtained with solution (4) to identify the peak due to impurity E. When the chromatograms are recorded under the prescribed conditions the retention time of bacitracin A is about 40 minutes and the retentions relative to bacitracin A are: bacitracin B1, about 0.6; bacitracin B3, about 0.8; impurity E, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *peak-to-valley ratio* is at least 1.2 where H_p is the height above the baseline of the peak due to bacitracin B1 and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bacitracin B2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 1.2 times the area of the peak due to bacitracin A in the chromatogram obtained with solution (3) (6%).

Related peptides (bacitracin zinc)

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

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(1) Disperse a quantity of the ointment containing 2000 IU of Bacitracin Zinc in 20 mL of *dichloromethane*. Extract with two 10-mL quantities of a 0.446% w/v solution of *anhydrous sodium sulfate*, the pH of which has been adjusted to 2.3 with 2M *orthophosphoric acid*, and filter the aqueous layer through a glass-fibre filter paper (Whatman GF/C is suitable) and then through a 0.45-µm membrane filter.

(2) Dissolve 20 mg of *bacitracin zinc EPCRS* in 10 mL of a 4% w/v solution of *sodium edetate*, the pH of which has been adjusted to 7.0 with 2M *sodium hydroxide*.

(3) Dilute 5 volumes of solution (1) to 100 volumes with *water* and further dilute 1 volume to 10 volumes with *water*.

(4) 4% w/v of *sodium edetate*, the pH of which has been adjusted to 7.0 with 2M *sodium hydroxide* (blank solution).

(5) 0.03% w/v of *polymyxin B sulfate BPCRS* in solution (4).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Impurity E may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *peak-to-valley ratio* is at least 1.2 where H_p is the height above the baseline of the peak due to bacitracin B1 and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bacitracin B2.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* eluting before the peak due to bacitracin B1 is not greater than 20% by *normalisation*.

Disregard any peaks corresponding to the peaks in the chromatograms obtained with solutions (4) and (5) and any peak with an area less than that of the peak due to bacitracin A in the chromatogram obtained with solution (3) (0.5%).

ASSAY

For polymyxin B sulfate

To a quantity of the ointment containing 10,000 IU of Polymyxin B Sulfate add 15 mL of *chloroform* and 40 mL of sterile *phosphate buffer pH 6.0*, mix thoroughly, centrifuge and discard the chloroform layer. Using the aqueous layer, carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated number of IU of Polymyxin B Sulfate.

For bacitracin zinc

To a quantity of the ointment containing 500 IU of Bacitracin Zinc add 15 mL of *chloroform* and 40 mL of 0.01M *hydrochloric acid*, mix thoroughly, centrifuge and discard the chloroform layer. Using the aqueous layer, carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated number of IU of Bacitracin Zinc.

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LABELLING

The strength is stated as the number of IU (Units) of Polymyxin B Sulfate per g and the number of IU (Units) of Bacitracin Zinc per g.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Bacitracin Zinc.

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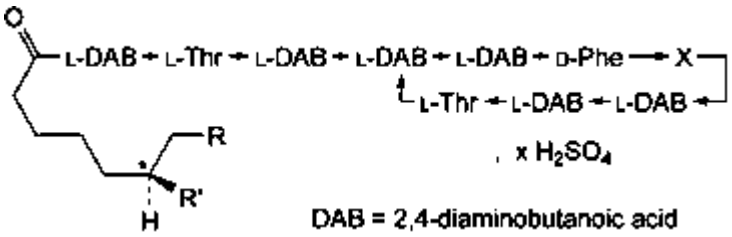
Polymyxin B Sulfate

General Notices

Polymyxin B Sulphate

(Ph. Eur. monograph 0203)



Polymyxin	R	R′	X	Molecular formula	M_r
B1	CH_3	CH_3	L-Leu	$C_{56}H_{98}N_{16}O_{13}$	1203
B2	H	CH_3	L-Leu	$C_{55}H_{96}N_{16}O_{13}$	1189
B3	CH_3	H	L-Leu	$C_{55}H_{96}N_{16}O_{13}$	1189
B1-I	CH_3	CH_3	L-Ile	$C_{56}H_{98}N_{16}O_{13}$	1203

Action and use

Antibacterial.

Preparation

Polymyxin and Bacitracin Ointment

Ph Eur

DEFINITION

Mixture of the sulfates of polypeptides produced by the growth of certain strains of *Paenibacillus polymyxa*, the main component being polymyxin B1.

Potency

Minimum 6500 IU/mg (dried substance).

CHARACTERS

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Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in 1 mL of a mixture of equal volumes of *hydrochloric acid R* and *water R*. Heat at 135 °C in a sealed tube for 5 h. Evaporate to dryness on a water-bath and continue the heating until the hydrochloric acid has evaporated. Dissolve the residue in 0.5 mL of *water R*.

Reference solution (a) Dissolve 20 mg of *leucine R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *threonine R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (c) Dissolve 20 mg of *phenylalanine R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (d) Dissolve 20 mg of *serine R* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Carry out the following procedures protected from light.

Mobile phase *water R*, *phenol R* (25:75 *V/V*).

Application 5 µL as bands of 10 mm, then place the plate in the chromatographic tank so that it is not in contact with the mobile phase, and allow it to become impregnated with the vapour of the mobile phase for at least 12 h.

Development Over 2/3 of the plate using the same mobile phase.

Drying At 100-105 °C.

Detection Spray with *ninhydrin solution R1* and heat at 110 °C for 5 min.

Results The chromatogram obtained with the test solution shows zones corresponding to those in the chromatograms obtained with reference solutions (a), (b) and (c), but shows no zone corresponding to that in the chromatogram obtained with reference solution (d); the chromatogram obtained with the test solution also shows a zone with a very low R_F value (2,4-diaminobutyric acid).

B. Examine the chromatograms obtained in the test for composition.

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Results The peaks due to polymyxins B1, B2, B3 and B1-I in the chromatogram obtained with the test solution are similar in retention time to the corresponding peaks in the chromatogram obtained with reference solution (a).

C. Dissolve about 2 mg in 5 mL of *water R* and add 5 mL of a 100 g/L solution of *sodium hydroxide R*. Shake and add dropwise 0.25 mL of a 10 g/L solution of *copper sulfate pentahydrate R*, shaking after each addition. A reddish-violet colour develops.

D. It gives reaction (a) of sulfates (*2.3.1*).

TESTS

pH (*2.2.3*)

5.0 to 7.0.

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Composition

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Solvent mixture *acetonitrile R*, *water R* (20:80 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *polymyxin B sulfate CRS* in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (b) Dilute 1 mL of reference solution (a) to 100 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 20 volumes of *acetonitrile R1* and 80 volumes of a solution prepared as follows: dissolve 4.46 g of *anhydrous sodium sulfate R* in 900 mL of *water for chromatography R*, adjust to pH 2.3 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 1.4 times the retention time of polymyxin B1.

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Identification of peaks Use the chromatogram supplied with *polymyxin B sulfate CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to polymyxins B1, B2, B3 and B1-I.

Relative retention With reference to polymyxin B1 (retention time = about 35 min): polymyxin B2 = about 0.5; polymyxin B3 = about 0.6; polymyxin B1-I = about 0.8.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to polymyxin B2 and polymyxin B3 in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 20 for the peak due to polymyxin B1 in the chromatogram obtained with reference solution (b).

Limits:

— *polymyxin B1-I*: maximum 15.0 per cent;

— *polymyxin B3*: maximum 6.0 per cent;

— *sum of polymyxins B1, B2, B3 and B1-I*: minimum 80.0 per cent;

— *reporting threshold*: 0.40 per cent.

Related substances

Liquid chromatography (*2.2.29*) as described in the test for composition.

Limits:

— *any impurity*: for each impurity, maximum 3.0 per cent;

— *total*: maximum 17.0 per cent;

— *reporting threshold*: 0.40 per cent.

Sulfate

15.5 per cent to 17.5 per cent (dried substance).

Dissolve 0.250 g in 100 mL of *water R* and adjust the solution to pH 11 with *concentrated ammonia R*. Add 10.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate*, adding 50 mL of *ethanol (96 per cent) R* when the colour of the solution begins to change and continuing the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of SO_4.

Loss on drying (*2.2.32*)

Maximum 6.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0,7 kPa for 3 h.

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Sulfated ash (*2.4.14*)

Maximum 0.75 per cent, determined on 1.0 g.

Pyrogens (*2.6.8*)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject, per kilogram of the rabbit's mass, 1 mL of a solution in *water for injections R* containing 1.5 mg of the substance to be examined per millilitre.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *polymyxin B sulfate for microbiological assay CRS* as the chemical reference substance.

STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Polyoxyl Castor Oil

General Notices

(Macrogolglycerol Ricinoleate, Ph. Eur. monograph 1082)

Action and use

Excipient.

Ph Eur

DEFINITION

Contains mainly ricinoleyl glycerol ethoxylated with 30-50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate and of the corresponding free glycols. It results from the reaction of castor oil with ethylene oxide.

CHARACTERS

Appearance

Clear, yellow viscous liquid or semi-solid.

Solubility

Freely soluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 per cent).

Relative density

About 1.05.

Viscosity

500 mPa·s to 800 mPa·s at 25 °C.

IDENTIFICATION

A. Iodine value (see Tests).

B. Saponification value (see Tests).

C. Thin-layer chromatography (*2.2.27*).

Test solution To 1 g of the substance to be examined add 100 mL of a 100 g/L solution of *potassium hydroxide R* and boil under a reflux condenser for 30 min. Allow to cool. Acidify the solution with 20 mL of *hydrochloric acid R*. Shake the mixture with 50 mL of *ether R* and allow to stand until separation of the layers is obtained. Transfer the clear upper layer to a suitable tube, add 5 g of *anhydrous sodium*

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sulfate R, close the tube and allow to stand for 30 min. Filter and evaporate the filtrate to dryness on a water-bath. Dissolve 50 mg of the residue in 25 mL of *ether R*.

Reference solution Dissolve 50 mg of *ricinoleic acid R* in *methylene chloride R* and dilute to 25 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel plate R*.

Mobile phase *methylene chloride R*, *glacial acetic acid R*, *acetone R* (10:40:50 *V/V/V*).

Application 2 µL.

Development Over a path of 8 cm.

Drying In a current of cold air.

Detection Spray with an 80 g/L solution of *phosphomolybdic acid R* in *2-propanol R* and heat at 120 °C for 1-2 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and colour to the principal spot in the chromatogram obtained with the reference solution.

D. Place about 2 g of the substance to be examined in a test-tube and add 0.2 mL of *sulfuric acid R*. Close the tube using a stopper fitted with a glass tube bent twice at right angles. Heat the tube until white fumes appear. Collect the fumes in 1 mL of *mercuric chloride solution R*. A white precipitate is formed and the fumes turn a filter paper impregnated with *alkaline potassium tetraiodomercurate solution R* black.

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*). If intended for use in the manufacture of parenteral preparations, solution S is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Alkalinity

Dissolve 2.0 g in a hot mixture of 10 mL of *water R* and 10 mL of *ethanol (96 per cent) R*. Add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid value (*2.5.1*)

Maximum 2.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

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See Table 1082.-1.

Iodine value (*2.5.4*)

25 to 35.

Saponification value (*2.5.6*)

See Table 1082.-1.

Table 1082.-1

Ethylene oxide units per molecule (nominal value)	Hydroxyl value	Saponification value
30 - 35	65 - 82	60 - 75
50	48 - 68	38 - 52

Residual ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of residual ethylene oxide and 10 ppm of residual dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 2.000 g.

Total ash (*2.4.16*)

Maximum 0.3 per cent, determined on 2.0 g.

STORAGE

Protected from light.

LABELLING

The label states:

— the amount of ethylene oxide reacted with castor oil (nominal value),

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Polyoxypropylene Stearyl Ether

General Notices

(Ph. Eur. monograph 2602)

Ph Eur

DEFINITION

Mixture of ethers of polyoxypropylene with linear alcohols, mainly stearyl alcohol, obtained by the reaction of stearyl alcohol with propylene oxide. It may contain some free polyoxypropylene and various amounts of free stearyl alcohol. The number of moles of propylene oxide reacted per mole of stearyl alcohol is 11 (nominal value). A suitable antioxidant may be added.

CHARACTERS

Appearance

Colourless or pale yellow, clear or slightly turbid liquid.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent), in mineral oils and in 2-propanol, practically insoluble in propylene glycol and in glycerol.

Relative density

About 0.94 at 25 °C.

Refractive index

About 1.448 at 25 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *polyoxypropylene stearyl ether CRS*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Viscosity (*2.2.9*): 83 mPa·s to 95 mPa·s.

TESTS

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Acid value (2.5.1)

Maximum 2.0.

Hydroxyl value (2.5.3, Method A)

60 to 77.

Iodine value (2.5.4, Method A)

Maximum 3.0.

Peroxide value (2.5.5, Method A)

Maximum 5.0.

Saponification value (2.5.6)

Maximum 3.0.

Propylene oxide

Head-space gas chromatography (2.2.28).

Propylene oxide stock solution Weigh 45 g of cold macrogol 200 R1 and add 1.000 g (*m*) of propylene oxide R. Mix carefully by swirling to ensure a homogeneous solution. Add more macrogol 200 R1 until the total weight is 50.0 g and mix again. [NOTE: the solution is stable for 1 month if stored at -20 °C]. Allow to reach room temperature. Dilute 0.50 g of this solution to 100.0 mL with water R.

Propylene oxide standard solution Dilute 10.0 mL of propylene oxide stock solution to 100.0 mL with water R.

Propionaldehyde stock solution Weigh 0.1 g of propionaldehyde R into a volumetric flask and dilute to 100.0 mL with water R.

Test solution (a) Weigh 1.00 g of the substance to be examined into a 20 mL head-space vial. Add 0.5 mL of cold water R and seal the vial immediately with a polytetrafluoroethylene-coated silicon membrane and an aluminium cap. Mix carefully.

Test solution (b) Weigh 1.00 g of the substance to be examined into a 20 mL head-space vial. Add 0.5 mL of cold propylene oxide standard solution and seal the vial immediately with a polytetrafluoroethylene-coated silicon membrane and an aluminium cap. Mix carefully.

Reference solution Introduce 50.0 mL of cold propylene oxide standard solution into a volumetric flask, add 0.5 mL of cold propionaldehyde stock solution and dilute to 100.0 mL with water R. Introduce 0.5 mL of this solution into a 20 mL head-space vial.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.32 mm;

— *stationary phase*: methylpolysiloxane R (film thickness 5 µm).

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Carrier gas helium for chromatography R.

Flow rate 2.6 mL/min.

Split ratio 10:1.

Static head-space conditions that may be used:

— *equilibration temperature*: 90 °C;

— *equilibration time*: 45 min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	50
	5 - 31	50 → 180
	31 - 32.7	180 → 230
	32.7 - 37.7	230
Injection port		150
Detector		250

Detection Flame ionisation.

Injection A suitable volume, for example 1.0 mL, of the gaseous phase of test solutions (a) and (b) and of the reference solution.

Identification of peaks Use the chromatogram obtained with the reference solution to identify the peaks due to propylene oxide and propionaldehyde.

Relative retention With reference to propylene oxide (retention time = about 10.4 min): propionaldehyde = about 0.96.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to propionaldehyde and propylene oxide;

— *signal-to-noise ratio*: minimum 10 for the peak due to propylene oxide.

Calculate the content of propylene oxide in parts per million using the following expression:

$$\frac{A_1 \times m \times 5}{(A_2 \times M_1) - (A_1 \times M_2)}$$

A_1 = area of the peak due to propylene oxide in the chromatogram obtained with test solution (a);

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A_2 = area of the peak due to propylene oxide in the chromatogram obtained with test solution (b);

M_1 = mass of the substance to be examined in test solution (a), in grams;

M_2 = mass of the substance to be examined in test solution (b), in grams;

m = mass of propylene oxide used to prepare the propylene oxide stock solution, in grams.

Limit:

— *propylene oxide*: maximum 5 ppm.

Water (2.5.12)

Maximum 0.7 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.3 per cent.

Ignite a suitable crucible at 600 ± 25 °C for 30 min, allow to cool in a desiccator over silica gel or other suitable desiccant and weigh. Place 1.0 g of the substance to be examined in the crucible and weigh. Carefully ignite and char the substance using a gas burner in a fume cupboard. Carry out the test for sulfated ash (2.4.14) on the residue obtained, starting from “Moisten the substance to be examined…”.

STORAGE

In an airtight container.

LABELLING

The label states the number of moles of propylene oxide reacted per mole of stearyl alcohol (nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for polyoxypropylene stearyl ether used as solvent or emollient in preparations for cutaneous application.

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Viscosity

(see Identification).

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This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Polysorbate 20

General Notices

Polyoxyethylene 20 Sorbitan Monolaurate

(Ph. Eur. monograph 0426)

Action and use

Non-ionic surfactants.

Ph Eur

DEFINITION

Mixture of partial esters of fatty acids, mainly lauric (dodecanoic) acid, with sorbitol and its anhydrides ethoxylated with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

CHARACTERS

Appearance

Oily, yellow or brownish-yellow, clear or slightly opalescent liquid.

Solubility

Soluble in water, in anhydrous ethanol, in ethyl acetate and in methanol, practically insoluble in fatty oils and in liquid paraffin.

Relative density

About 1.10.

Viscosity

About 400 mPa·s at 25 °C.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D, E.

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of polysorbate 20*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

E. Dissolve 0.1 g in 5 mL of *methylene chloride R*. Add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R*. Stir with a glass rod. The solution becomes blue.

TESTS

Acid value (2.5.1)

Maximum 2.0.

Dissolve 5.0 g in 50 mL of the prescribed solvent mixture.

Hydroxyl value (2.5.3, Method A)

96 to 108.

Peroxide value

Maximum 10.0.

Introduce 10.0 g into a 100 mL beaker and dissolve with 20 mL of *glacial acetic acid R*. Add 1 mL of *saturated potassium iodide solution R*, mix and allow to stand for 1 min. Add 50 mL of *carbon dioxide-free water R* and a magnetic stirring bar. Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration. If the result of the blank determination exceeds 0.1 mL of titration reagent, replace the reagents and repeat the determination.

Determine the peroxide value using the following expression:

$$\frac{\left(n_1 - n_2\right) \times M \times 1000}{m}$$

n_1 = volume of *0.01 M sodium thiosulfate* required for the substance to be examined, in millilitres;

n_2 = volume of *0.01 M sodium thiosulfate* required for the blank titration, in millilitres;

M = molarity of the sodium thiosulfate solution, in moles per litre;

m = mass of the substance to be examined, in grams.

Saponification value (2.5.6)

40 to 50, determined on 4.0 g.

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Use 15.0 mL of *0.5 M alcoholic potassium hydroxide* and dilute with 50 mL of *ethanol (96 per cent) R* before carrying out the titration. Heat under reflux for 60 min.

Composition of fatty acids (*2.4.22, Method C*)

Prepare reference solution (a) as indicated in Table 2.4.22.-2.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 50 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 14	80 → 220
	14 - 54	220
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Composition of the fatty-acid fraction of the substance:

— *caproic acid*: maximum 1.0 per cent;

— *caprylic acid*: maximum 10.0 per cent;

— *capric acid*: maximum 10.0 per cent;

— *lauric acid*: 40.0 per cent to 60.0 per cent;

— *myristic acid*: 14.0 per cent to 25.0 per cent;

— *palmitic acid*: 7.0 per cent to 15.0 per cent;

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— *stearic acid*: maximum 7.0 per cent;

— *oleic acid*: maximum 11.0 per cent;

— *linoleic acid*: maximum 3.0 per cent.

Ethylene oxide and dioxan (*2.4.25, Method A*)

Maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

Maximum 0.25 per cent, determined on 2.0 g.

STORAGE

In an airtight container, protected from light.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for polysorbate 20 used as emulsifier or solubiliser in liquid dosage forms and in semi-solid preparations.

Hydroxyl value

(see Tests).

Composition of fatty acids

(see Tests).

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Polysorbate 40

General Notices

Polyoxyethylene 20 Sorbitan Monopalmitate

(Ph. Eur. monograph 1914)

Action and use

Non-ionic surfactants.

Ph Eur

DEFINITION

Mixture of partial esters of fatty acids, mainly *Palmitic acid (1904)*, with sorbitol and its anhydrides ethoxylated with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

CHARACTERS

Appearance

Oily, viscous, yellowish or brownish-yellow liquid.

Solubility

Miscible with water, with anhydrous ethanol, with ethyl acetate and with methanol, practically insoluble in fatty oils and in liquid paraffin.

Relative density

About 1.10.

Viscosity

About 400 mPa·s at 30 °C.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D, E.

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of polysorbate 40*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

E. Dissolve 0.1 g in 5 mL of *methylene chloride R*. Add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R*. Stir with a glass rod. The solution becomes blue.

TESTS

Acid value (2.5.1)

Maximum 2.0.

Dissolve 5.0 g in 50 mL of the prescribed solvent mixture.

Hydroxyl value (2.5.3, Method A)

89 to 105.

Peroxide value

Maximum 10.0.

Introduce 10.0 g into a 100 mL beaker and dissolve with 20 mL of *glacial acetic acid R*. Add 1 mL of *saturated potassium iodide solution R*, mix and allow to stand for 1 min. Add 50 mL of *carbon dioxide-free water R* and a magnetic stirring bar. Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration. If the result of the blank determination exceeds 0.1 mL of titration reagent, replace the reagents and repeat the determination.

Determine the peroxide value using the following expression:

$$\frac{\left(n_1 - n_2\right) \times M \times 1000}{m}$$

n_1 = volume of *0.01 M sodium thiosulfate* required for the substance to be examined, in millilitres;

n_2 = volume of *0.01 M sodium thiosulfate* required for the blank titration, in millilitres;

M = molarity of the sodium thiosulfate solution, in moles per litre;

m = mass of the substance to be examined, in grams.

Saponification value (2.5.6)

41 to 52, determined on 4.0 g.

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Use 15.0 mL of *0.5 M alcoholic potassium hydroxide* and dilute with 50 mL of *ethanol (96 per cent) R* before carrying out the titration. Heat under reflux for 60 min.

Composition of fatty acids (*2.4.22, Method C*)

Prepare reference solution (a) as indicated in Table 2.4.22.-1.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 50 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 14	80 → 220
	14 - 54	220
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Composition of the fatty-acid fraction of the substance:

— *palmitic acid*: minimum 92.0 per cent.

Ethylene oxide and dioxan (*2.4.25, Method A*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

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Maximum 0.25 per cent, determined on 2.0 g.

STORAGE

In an airtight container, protected from light.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for polysorbate 40 used as emulsifier or solubiliser in liquid dosage forms and in semi-solid preparations.

Hydroxyl value

(see Tests).

Composition of fatty acids

(see Tests).

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Polysorbate 60

General Notices

Polyoxyethylene 20 Sorbitan Monostearate

(Ph. Eur. monograph 0427)

Action and use

Non-ionic surfactants.

Ph Eur

DEFINITION

Mixture of partial esters of fatty acids, mainly *Stearic acid 50 (1474)*, with sorbitol and its anhydrides ethoxylated with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

CHARACTERS

Appearance

Yellowish-brown gelatinous mass which becomes a clear liquid at temperatures above 25 °C.

Solubility

Soluble in water, in anhydrous ethanol, in ethyl acetate and in methanol, practically insoluble in fatty oils and in liquid paraffin.

Relative density

About 1.10.

Viscosity

About 400 mPa·s at 30 °C.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D, E.

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of polysorbate 60*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

E. Dissolve 0.1 g in 5 mL of *methylene chloride R*. Add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R*. Stir with a glass rod. The solution becomes blue.

TESTS

Acid value (2.5.1)

Maximum 2.0.

Dissolve 5.0 g in 50 mL of the prescribed solvent mixture.

Hydroxyl value (2.5.3, Method A)

81 to 96.

Peroxide value

Maximum 10.0.

Introduce 10.0 g into a 100 mL beaker and dissolve with 20 mL of *glacial acetic acid R*. Add 1 mL of *saturated potassium iodide solution R*, mix and allow to stand for 1 min. Add 50 mL of *carbon dioxide-free water R* and a magnetic stirring bar. Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration. If the result of the blank determination exceeds 0.1 mL of titration reagent, replace the reagents and repeat the determination.

Determine the peroxide value using the following expression:

$$\frac{\left(n_1 - n_2\right) \times M \times 1000}{m}$$

n_1 = volume of *0.01 M sodium thiosulfate* required for the substance to be examined, in millilitres;

n_2 = volume of *0.01 M sodium thiosulfate* required for the blank titration, in millilitres;

M = molarity of the sodium thiosulfate solution, in moles per litre;

m = mass of the substance to be examined, in grams.

Saponification value (2.5.6)

45 to 55, determined on 4.0 g.

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Use 15.0 mL of *0.5 M alcoholic potassium hydroxide* and dilute with 50 mL of *ethanol (96 per cent) R* before carrying out the titration. Heat under reflux for 60 min.

Composition of fatty acids (*2.4.22, Method C*)

Prepare reference solution (a) as indicated in Table 2.4.22.-1.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 50 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 14	80 → 220
	14 - 54	220
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Composition of the fatty-acid fraction of the substance:

— *stearic acid*: 40.0 per cent to 60.0 per cent;

— *sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent.

Ethylene oxide and dioxan (*2.4.25, Method A*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.00 g.

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Total ash (*2.4.16*)

Maximum 0.25 per cent, determined on 2.0 g.

STORAGE

In an airtight container, protected from light.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for polysorbate 60 used as emulsifier or solubiliser in liquid and dosage forms and in semi-solid preparations.

Hydroxyl value

(see Tests).

Composition of fatty acids

(see Tests).

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Polysorbate 80[1]

General Notices

Polyoxyethylene 20 Sorbitan Mono-oleate

(Ph. Eur. monograph 0428)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture of partial esters of fatty acids, mainly *Oleic acid (0799)*, with sorbitol and its anhydrides ethoxylated with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

♦ CHARACTERS

Appearance

Oily, colourless or brownish-yellow, clear or slightly opalescent liquid.

Solubility

Dispersible in water, in anhydrous ethanol, in ethyl acetate and in methanol, practically insoluble in fatty oils and in liquid paraffin.

Relative density

About 1.10.

Viscosity

About 400 mPa·s at 25 °C.♦

IDENTIFICATION

First identification: ♦ *A*♦ *, D.*

◊ *Second identification: B, C, D, E.*◊

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♦ A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of polysorbate 80*.♦

◊ B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).◊

D. Composition of fatty acids (see Tests).

◊ E. Dissolve 0.1 g in 5 mL of *methylene chloride R*. Add 0.1 g of *cobalt nitrate R* and 0.1 g of *potassium thiocyanate R*. Stir with a glass rod. The solution becomes blue.◊

TESTS

Acid value (2.5.1)

Maximum 2.0.

Dissolve 5.0 g in 50 mL of the prescribed mixture of solvents.

Hydroxyl value (2.5.3, Method A)

65 to 80.

Peroxide value

Maximum 10.0.

Introduce 10.0 g into a 100 mL beaker and dissolve with 20 mL of *glacial acetic acid R*. Add 1 mL of *saturated potassium iodide solution R*, mix and allow to stand for 1 min. Add 50 mL of *carbon dioxide-free water R* and a magnetic stirring bar. Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

Determine the peroxide value using the following expression:

$$\frac{\left(n_1 - n_2\right) \times M \times 1000}{m}$$

n_1 = volume of *0.01 M sodium thiosulfate* required for the substance to be examined, in millilitres;

n_2 = volume of *0.01 M sodium thiosulfate* required for the blank titration, in millilitres;

M = molarity of the sodium thiosulfate solution, in moles per litre;

m = mass of the substance to be examined, in grams.

Saponification value (2.5.6)

45 to 55, determined on 4.0 g.

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Use 30.0 mL of *0.5 M alcoholic potassium hydroxide*, heat under reflux for 60 min and add 50 mL of *anhydrous ethanol R* before carrying out the titration.

Composition of fatty acids (*2.4.22, Method C*)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 50 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 14	80 → 220
	14 - 54	220
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Composition of the fatty-acid fraction of the substance:

— *myristic acid*: maximum 5.0 per cent;

— *palmitic acid*: maximum 16.0 per cent;

— *palmitoleic acid*: maximum 8.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: minimum 58.0 per cent;

— *linoleic acid*: maximum 18.0 per cent;

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— *linolenic acid*: maximum 4.0 per cent.

Ethylene oxide and dioxan

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Head-space gas chromatography (*2.2.28*).

Ethylene oxide stock solution Dilute 0.5 mL of a commercially available solution of ethylene oxide in methylene chloride (50 mg/mL) to 50.0 mL with *water R*. [NOTE: the solution is stable for 3 months, if stored in vials with polytetrafluoroethylene-coated silicone membrane crimp caps at -20 °C]. Allow to reach room temperature. Dilute 1.0 mL of this solution to 250.0 mL with *water R*.

Dioxan stock solution Dilute 1.0 mL of *dioxan R* to 200.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Acetaldehyde stock solution Weigh about 0.100 g of *acetaldehyde R* into a 100 mL volumetric flask and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Standard solution To 6.0 mL of ethylene oxide stock solution add 2.5 mL of dioxan stock solution and dilute to 25.0 mL with *water R*.

Test solution (a) Weigh 1.00 g of the substance to be examined into a 10 mL head-space vial. Add 2.0 mL of *water R*, seal the vial immediately with a polytetrafluoroethylene-coated silicon membrane and an aluminum cap. Mix carefully.

Test solution (b) Weigh 1.00 g of the substance to be examined into a 10 mL head-space vial. Add 2.0 mL of standard solution, seal the vial immediately with a polytetrafluoroethylene-coated silicon membrane and an aluminum cap. Mix carefully.

Reference solution Introduce 2.0 mL of acetaldehyde stock solution and 2.0 mL of ethylene oxide stock solution into a 10 mL head-space vial and seal the vial immediately with a polytetrafluoroethylene-coated silicon membrane and an aluminum cap. Mix carefully.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.53 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 4.0 mL/min.

Split ratio 1:3.5.

Static head-space conditions that may be used:

— *equilibration temperature*: 80 °C;

— *equilibration time*: 30 min.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 18	70 → 250
	18 - 23	250
Injection port		85
Detector		250

Detection Flame ionisation.

Injection 1.0 mL of test solutions (a) and (b) and of the reference solution.

Relative retention With reference to ethylene oxide (retention time = about 6.5 min): acetaldehyde = about 0.9; dioxan = about 1.9.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to acetaldehyde and ethylene oxide.

Calculate the content of ethylene oxide in ppm using the following expression:

$$\frac{2\,C_{EO} \times A_a}{A_b - A_a}$$

C_{EO} = concentration of added ethylene oxide in test solution (b), in micrograms per millilitre;

A_a = peak area of ethylene oxide in the chromatogram obtained with test solution (a);

A_b = peak area of ethylene oxide in the chromatogram obtained with test solution (b).

Calculate the content of dioxan in ppm using the following expression:

$$\frac{2 \times 1.03 \times C_D \times A_{a'}}{A_{b'} - A_{a'}} \times 1000$$

C_D = concentration of added dioxan in test solution (b), in microlitres per millilitre;

1.03 = density of dioxan, in grams per millilitre;

$A_{a'}$ = peak area of dioxan in the chromatogram obtained with test solution (a);

$A_{b'}$ = peak area of dioxan in the chromatogram obtained with test solution (b).

Water (2.5.12)

Maximum 3.0 per cent, determined on 1.00 g.

Total ash (2.4.16)

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Maximum 0.25 per cent, determined on 2.0 g.

STORAGE

In an airtight container, protected from light.

◊ *FUNCTIONALITY-RELATED CHARACTERISTICS*

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for polysorbate 80 used as emulsifier or solubiliser in liquid dosage forms and in semi-solid preparations.

Hydroxyl value

(see Tests).

Composition of fatty acids

(see Tests).◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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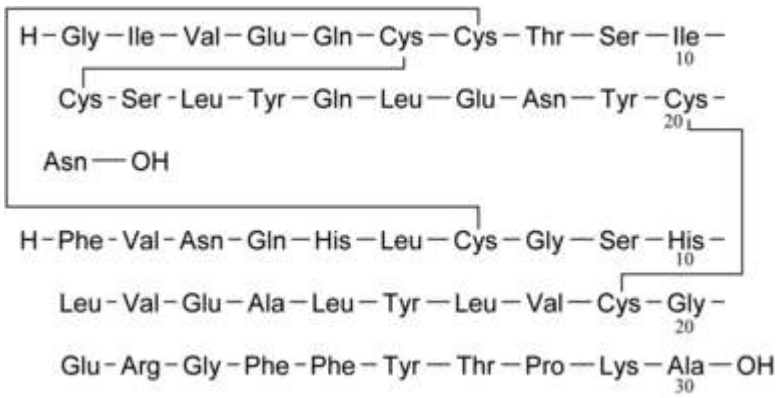
Porcine Insulin

General Notices

(Ph. Eur. monograph 1638)



$C_{256}H_{381}N_{65}O_{76}S_6$ 5778

Action and use

Hormone; treatment of diabetes mellitus.

Preparation

Insulin Preparations

Ph Eur

DEFINITION

Porcine insulin is the natural antidiabetic principle obtained from pork pancreas and purified.

Content

— *sum of porcine insulin ($C_{256}H_{381}N_{65}O_{76}S_6$) and A21 desamido porcine insulin*: 95.0 per cent to 105.0 per cent (dried substance).

By convention, for the purpose of labelling insulin preparations, 0.0345 mg of porcine insulin is equivalent to 1 IU of insulin.

PRODUCTION

The animals from which porcine insulin is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

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Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute mineral acids and with decomposition in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The retention time of the principal peak in the chromatogram obtained with the test solution corresponds to that of the principal peak in the chromatogram obtained with reference solution (b).

B. Peptide mapping.

Test solution Prepare a 2.0 mg/mL solution of the substance to be examined in *0.01 M hydrochloric acid* and transfer 500 µL of this solution to a clean tube. Add 2.0 mL of *HEPES buffer solution pH 7.5 R* and 400 µL of a 1 mg/mL solution of *Staphylococcus aureus strain V8 protease, type XVII-B R*. Cap the tube and incubate at 25 °C for 6 h. Stop the reaction by adding 2.9 mL of *sulfate buffer solution pH 2.0 R*.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *insulin porcine for system suitability CRS* instead of the substance to be examined.

Examine the digests by liquid chromatography (*2.2.29*).

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 100 mL of *acetonitrile for chromatography R*, 700 mL of *water for chromatography R* and 200 mL of *sulfate buffer solution pH 2.0 R*; filter and degas;

— *mobile phase B*: mix 400 mL of *acetonitrile for chromatography R*, 400 mL of *water for chromatography R* and 200 mL of *sulfate buffer solution pH 2.0 R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	90 → 30	10 → 70
60 - 65	30 → 0	70 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
65 - 70	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 15 min. Carry out a blank run using the above-mentioned gradient.

Injection 50 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of porcine insulin digest supplied with *insulin porcine for system suitability CRS*. In the chromatogram obtained with the reference solution, identify the peaks due to digest fragments I, II and III. The symmetry factor of the peaks due to fragments II and III is not greater than 1.5, and the resolution between the 2 peaks is at least 1.9.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

NOTE: the retention time of fragment I is the same for porcine insulin and for human insulin. The retention times of fragments II and IV are the same for all insulins. The retention time of fragment III is the same for bovine insulin and for porcine insulin.

TESTS

Impurities with molecular masses greater than that of insulin

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure. *Maintain the solutions at 2-10 °C and use within 7 days. If an automatic injector is used, maintain the temperature at 2-10 °C.*

Test solution Dissolve 4 mg of the substance to be examined in 1.0 mL of *0.01 M hydrochloric acid*.

Resolution solution Use a solution of insulin (approximately 4 mg/mL), containing more than 0.4 per cent of high molecular mass proteins. An injectable insulin preparation, whether a solution or a suspension, that has been clarified with a sufficient amount of *6 M hydrochloric acid R*, containing the indicated percentage of high molecular mass proteins, or a solution prepared from insulin, dissolved in *0.01 M hydrochloric acid*, may be used. Insulin containing the indicated percentage of high molecular mass proteins may be prepared by allowing insulin powder to stand at room temperature for about 10 days.

Column:

— *size*: *l* = 0.3 m, Ø = at least 7.5 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5-10 µm), of a grade suitable for the separation of insulin monomer from dimer and polymers.

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Mobile phase Mix 15 volumes of *glacial acetic acid R*, 20 volumes of *acetonitrile R* and 65 volumes of a 1.0 g/L solution of *arginine R*; filter and degas.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 276 nm.

Equilibration Before using a new column for chromatographic analysis, equilibrate by repeated injections of an insulin solution containing high molecular mass proteins. This can be done by at least 3 injections of the resolution solution. The column is equilibrated when repeatable results are obtained from 2 subsequent injections.

Injection 100 µL.

Run time About 35 min.

Retention times Polymeric insulin complexes = 13 min to 17 min; covalent insulin dimer = about 17.5 min; insulin monomer = about 20 min; salts = about 22 min.

System suitability Resolution solution:

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

Limits The sum of the areas of any peaks with a retention time less than that of the principal peak is not greater than 1.0 per cent of the total area of the peaks; disregard any peak with a retention time greater than that of the insulin peak.

Related proteins

Liquid chromatography (2.2.29) as described under Assay, following the elution conditions as described in the table below.

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	42	58
30 - 44	42 → 11	58 → 89
44 - 50	11	89

Maintain the solutions at 2-10 °C and use within 24 h.

Perform a system suitability test (resolution, linearity) as described under Assay. If necessary, the relative proportions of the mobile phases may be adjusted to ensure complete elution of A21 desamido porcine insulin before commencement of the gradient. The profile of the gradient may also be adjusted to ensure complete elution of all insulin related impurities.

Inject 20 µL of reference solution (b) and 20 µL of the test solution. If necessary, adjust the injection volume to between 10 µL and 20 µL in accordance with the results obtained in the test for linearity as described under Assay. Record the chromatograms for approximately 50 min. In the chromatogram obtained with reference solution (b), A21 desamido porcine insulin appears as a small peak after the principal

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peak and has a relative retention of about 1.3 with reference to the principal peak. In the chromatogram obtained with the test solution, the area of the peak due to A21 desamido porcine insulin is not greater than 2.0 per cent of the total area of the peaks; the sum of the areas of all the peaks, apart from those due to porcine insulin and A21 desamido porcine insulin, is not greater than 2.0 per cent of the total area of the peaks.

Porcine proinsulin-like immunoreactivity (PLI)

Maximum 10 ppm (dried substance).

Use a suitably sensitive immunochemical method (*2.7.1*) such as radio-immunoassay, using the International Reference Reagent for porcine proinsulin to calibrate the method.

Zinc

Maximum 1.0 per cent (dried substance).

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 50.0 mg of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 25.0 mL with the same acid. Dilute if necessary to a suitable concentration (for example, 0.4 µg to 1.6 µg of Zn per millilitre) with *0.01 M hydrochloric acid*.

Reference solutions Use solutions containing 0.40 µg, 0.80 µg, 1.00 µg, 1.20 µg and 1.60 µg of Zn per millilitre, freshly prepared by diluting *zinc standard solution (5 mg/mL Zn) R* with *0.01 M hydrochloric acid*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Flame Air-acetylene flame of suitable composition (for example, 11 L of air and 2 L of acetylene per minute).

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 0.200 g by drying in an oven at 105 °C for 24 h.

Sulfated ash (*2.4.14*)

Maximum 2.5 per cent, determined on 0.200 g (dried substance).

Bacterial endotoxins (*2.6.14*)

Less than 10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 40.0 mg of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 10.0 mL with the same solvent.

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Reference solution (a) Dissolve the contents of a vial of *human insulin CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4.0 mg/mL.

Reference solution (b) Dissolve the contents of a vial of *porcine insulin CRS* in *0.01 M hydrochloric acid* to obtain a concentration of 4.0 mg/mL.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with *0.01 M hydrochloric acid*.

Resolution solution Mix 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b).

Maintain the solutions at 2-10 °C and use within 48 h. If an automatic injector is used, maintain the temperature at 2-10 °C.

Column:

— *size*: *l* = 0.25, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 42 volumes of mobile phase A and 58 volumes of mobile phase B, adjusting the composition of the mixture if necessary.

Prepare and maintain the following solutions at a temperature of at least 20 °C:

— *mobile phase A*: dissolve 28.4 g of *anhydrous sodium sulfate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; add 2.7 mL of *phosphoric acid R*; adjust to pH 2.3, if necessary, with *ethanolamine R*; filter and degas;

— *mobile phase B*: mix 550 mL of mobile phase A with 450 mL of *acetonitrile R*; warm the solution to a temperature of at least 20 °C in order to avoid precipitation (mixing of mobile phase A with acetonitrile is endothermic); filter and degas.

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

System suitability:

— *resolution*: inject 20 µL of the resolution solution and 20 µL of reference solution (b). Record the chromatogram of the resolution solution until the peak corresponding to the principal peak in the chromatogram obtained with reference solution (b) is clearly visible. In the chromatogram obtained with the resolution solution, identify the peaks due to porcine insulin and human insulin. The test is not valid unless the resolution between the peaks due to human insulin and porcine insulin is at least 1.2. If necessary, adjust the concentration of acetonitrile in the mobile phase until this resolution is achieved.

— *linearity*: inject 20 µL each of reference solutions (b) and (c). The test is not valid unless the area of the principal peak in the chromatogram obtained with reference solution (b) is 10 ± 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c). If this test fails, adjust the injection volume to between 10 µL and 20 µL, in order that the responses are within the linearity range of the detector.

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Injection 20 µL of the test solution.

Calculate the content of porcine insulin $C_{256}H_{381}N_{65}O_{76}S_6$ plus A21 desamido porcine insulin from the area of the principal peak and the area of the peak due to A21 desamido porcine insulin in the chromatograms obtained with the test solution and reference solution (b) and the declared content of porcine insulin plus A21 desamido porcine insulin in *porcine insulin CRS*.

STORAGE

In an airtight container, protected from light, at -20 °C until released by the manufacturer. When thawed, insulin may be stored at 5 ± 3 °C and used for manufacturing preparations within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

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Potassium Acetate

General Notices

(Ph. Eur. monograph 1139)

$C_2H_3KO_2$ 98.1 *127-08-2*

Action and use

Used in solutions for dialysis.

Preparation

Potassium Acetate Sterile Concentrate

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, deliquescent.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives reaction (a) of acetates (*2.3.1*).

B. It gives reaction (a) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

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Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

7.5 to 9.0.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Reducing substances

Dilute 10 mL of solution S to 100 mL with *water R*. Add 5 mL of *dilute sulfuric acid R* and 0.5 mL of a 0.32 g/L solution of *potassium permanganate R*. Mix and boil gently for 5 min. The solution remains pink.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Aluminium (*2.4.17*)

Maximum 1 ppm, if intended for use in the manufacture of peritoneal dialysis solutions, haemofiltration solutions or haemodialysis solutions.

Prescribed solution Dissolve 2.0 g in 50 mL of *water R* and add 5 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 1 mL of *aluminium standard solution (2 ppm Al) R*, 5 mL of *acetate buffer solution pH 6.0 R* and 49 mL of *water R*.

Blank solution Mix 5 mL of *acetate buffer solution pH 6.0 R* and 50 mL of *water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Sodium

Maximum 0.5 per cent.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluted as necessary with *water R*.

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Wavelength 589 nm.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 80.0 mg in 20 mL of *anhydrous acetic acid R*. Add 0.2 mL of *naphtholbenzein solution R*. Titrate with *0.1 M perchloric acid*. Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 9.81 mg of $C_2H_3KO_2$.

STORAGE

In an airtight container.

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Potassium Acetate Sterile Concentrate

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in Parenteral Nutrition Solutions.

DEFINITION

Potassium Acetate Sterile Concentrate is a sterile solution of Potassium Acetate in a suitable solvent.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements. Where appropriate, the concentrate also complies with the requirements stated under Unlicensed Medicines.

Content of potassium acetate, $C_2H_3KO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields reaction A characteristic of *potassium salts* and reaction A characteristic of *acetates*, Appendix VI.

TESTS

Acidity or alkalinity

pH of the concentrate, diluted to contain 1% w/v of Potassium Acetate, 6.5 to 8.5, Appendix V L.

Sodium

Not more than 0.25%, calculated with respect to the content of potassium acetate, when determined by the following method.

Carry out the method for *atomic emission spectrophotometry,* Appendix II D, Method II, using the following solutions and measuring at 589 nm.

(1) Dilute the concentrate with *water* to produce a solution containing 1% w/v of Potassium Acetate.

(2) Prepare the standard solutions using *sodium standard solution (200 ppm Na)*, diluted as necessary with *water*.

ASSAY

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Dilute a quantity of the concentrate with sufficient *water* to produce a solution containing 1% w/v of Potassium Acetate. Evaporate a volume of the resulting solution containing 80 mg of Potassium Acetate to dryness, dissolve the residue in 20 mL of *anhydrous acetic acid* and carry out Method I for non-aqueous titration, Appendix VIII A, using 0.2 mL of *1-naphtholbenzein solution* as indicator. Carry out a blank titration using *water* in place of the preparation being examined.

Each mL of 0.1M *perchloric acid* is equivalent to 9.81 mg of $C_2H_3KO_2$.

LABELLING

The strength is stated as the percentage w/v of Potassium Acetate and as the approximate concentration of potassium ions, in mmol, in a suitable volume.

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Potassium Ascorbate Eye Drops

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in the treatment of chemical corneal burns.

DEFINITION

Potassium Ascorbate Eye Drops are a sterile solution of potassium ascorbate, prepared by the interaction of Potassium Hydroxide and Ascorbic Acid, in Purified Water containing a suitable antioxidant.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of potassium ascorbate, calculated as ascorbic acid, $C_6H_8O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a suitable volume of the eye drops with *water* to produce a solution containing the equivalent of 0.1% w/v of ascorbic acid. Dilute 1 volume of this solution to 100 volumes with 0.01M *hydrochloric acid*. The *light absorption* of the resulting solution, Appendix II B, in the range 210 to 350 nm exhibits a maximum only at 244 nm.

B. Dilute a suitable volume of the eye drops with *water* to produce a solution containing the equivalent of 1.0% w/v of ascorbic acid. To 5 mL of this solution add 0.05 mL of a freshly prepared 5.0% w/v solution of *sodium nitroprusside* and 2.0 mL of 2M *sodium hydroxide*. Add 0.6 to 0.7 mL of *hydrochloric acid*, dropwise, with stirring. The yellow colour turns blue.

TESTS

Acidity

pH, 5.5 to 6.5, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.001M *DL-homocysteine*.

(1) Dilute a volume of the eye drops, if necessary, to produce a solution containing the equivalent of 0.01% w/v of ascorbic acid.

(2) 0.01% w/v of *ascorbic acid BPCRS*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Platinum™ EPS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

A 0.05M solution of *cetrimide* in 40 volumes of *methanol* and 60 volumes of a buffer solution prepared in the following manner. Mix 77.8 mL of a 0.908% w/v solution of *potassium dihydrogen orthophosphate* and 122.2 mL of a 2.38% w/v solution of *anhydrous disodium hydrogen orthophosphate* and adjust the pH to 7.8 with 1M *sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_8O_6$ in the eye drops using the declared content of $C_6H_8O_6$ in *ascorbic acid BPCRS*.

STORAGE

Potassium Ascorbate Eye Drops should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ascorbic acid.

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Potassium Bicarbonate

General Notices

(Potassium Hydrogen Carbonate, Ph. Eur. monograph 1141)

$KHCO_3$ 100.1 *298-14-6*

Action and use

Excipient.

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

When heated in the dry state or in solution, it is gradually converted to potassium carbonate.

IDENTIFICATION

A. To 5 mL of solution S (see Tests) add 0.1 mL of *phenolphthalein solution R*. A pale pink colour is produced. Heat; gas is evolved and the colour becomes red.

B. It gives the reaction of carbonates and bicarbonates (*2.3.1*).

C. 1 mL of solution S gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in 90 mL of *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

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Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Carbonates

The pH (2.2.3) of freshly prepared solution S is not greater than 8.6.

Chlorides (2.4.4)

Maximum 150 ppm.

Dilute 7 mL of solution S to 15 mL with *dilute nitric acid R*.

Sulfates (2.4.13)

Maximum 150 ppm.

Dilute 10 mL of solution S to 15 mL with *acetic acid R*. Prepare the standard using a mixture of 7.5 mL of *sulfate standard solution (10 ppm SO_4) R* and 7.5 mL of *distilled water R*.

Ammonium (2.4.1)

Maximum 20 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Calcium (2.4.3)

Maximum 100 ppm.

Dilute 10 mL of solution S to 15 mL with *acetic acid R*. Prepare the standard using a mixture of 5 mL of *calcium standard solution (10 ppm Ca) R* and 10 mL of *distilled water R*.

Iron (2.4.9)

Maximum 20 ppm, determined on solution S.

Sodium

Maximum 0.5 per cent.

Atomic emission spectrometry (2.2.22, Method II).

Test solution Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluted as necessary with *water R*.

Wavelength 589 nm.

ASSAY

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Dissolve 0.800 g in 50 mL of *carbon dioxide-free water R*. Titrate with *1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*). Read the volume added at the 2nd point of inflection, or at the point of inflection if only 1 point is detected.

1 mL of *1 M hydrochloric acid* is equivalent to 0.1001 g of $KHCO_3$.

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Potassium Bromide

General Notices

(Ph. Eur. monograph 0184)

KBr 119.0 *7758-02-3*

Ph Eur

DEFINITION

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water and in glycerol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives reaction (a) of bromides (*2.3.1*).

B. Solution S (see Tests) gives the reactions of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

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Bromates

To 10 mL of solution S add 1 mL of *starch solution R*, 0.1 mL of a 100 g/L solution of *potassium iodide R* and 0.25 mL of *0.5 M sulfuric acid* and allow to stand protected from light for 5 min. No blue or violet colour develops.

Chlorides and sulfates

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 0.400 g of the substance to be examined in 50 mL of *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 25.0 mL of test solution (a) to 50.0 mL with *water for chromatography R*.

Reference solution (a) To 25.0 mL of test solution (a) add 1.0 mL of *sulfate standard solution (10 ppm SO_4) R* and 12.0 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (b) Dilute 10 mL of test solution (a) to 100 mL with *water for chromatography R*. To 2 mL of this solution add 8 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 20 mL with *water for chromatography R*.

Blank solution *water for chromatography R*.

Column:

— *size*: *l* = 0.25 m, Ø = 2 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R2* (13 µm).

Mobile phase Dissolve 0.600 g of *potassium hydroxide R* in *water for chromatography R* and dilute to 1000 mL with the same solvent.

Flow rate 0.4 mL/min.

Detection Conductivity detector equipped with a suitable ion suppressor.

Injection 50 µL of test solution (b), reference solutions (a) and (b) and the blank solution.

Run time 2.5 times the retention time of bromide.

Retention time Chloride = about 5 min; bromide = about 8 min; sulfate = about 16 min.

System suitability Reference solution (b):

— *resolution*: minimum 8.0 between the peaks due to chloride and bromide.

Calculation of percentage contents:

— for chlorides, use the concentration of chloride in reference solution (a); correct the area of the peak due to chloride in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to chloride in the chromatogram obtained with test solution (b);

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— for sulfates, use the concentration of sulfate in reference solution (a); correct the area of the peak due to sulfate in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to sulfate in the chromatogram obtained with test solution (b).

Limits:

— *chlorides*: maximum 0.6 per cent;

— *sulfates*: maximum 0.01 per cent.

Iodides

To 5 mL of solution S add 0.15 mL of *ferric chloride solution R1* and 2 mL of *methylene chloride R*. Shake and allow to separate. The lower layer is colourless (*2.2.2, Method I*).

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium and alkaline-earth metals (*2.4.7*)

Maximum 200 ppm, calculated as Ca.

10.0 g complies with the test for magnesium and alkaline-earth metals. The volume of *0.01 M sodium edetate* used does not exceed 5.0 mL.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 100.0 mg in *water R*, add 5 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 11.90 mg of KBr.

Calculate the percentage content of KBr using the following expression:

$$a - 3.357\,b$$

a	=	percentage content of KBr and KCl obtained in the assay and calculated as KBr;
b	=	percentage content of Cl obtained in the test for chlorides.

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Potassium Carbonate

General Notices

(Ph. Eur. monograph 1557)

K_2CO_3 138.2 *584-08-7*

Action and use

Excipient.

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white granular powder, hygroscopic.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in 10 mL of *water R*. The solution is strongly alkaline (*2.2.4*).

B. 2 mL of the solution prepared for identification test A gives the reaction of carbonates and bicarbonates (*2.3.1*).

C. 1 mL of the solution prepared for identification test A gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in 25 mL of *distilled water R*. Slowly add 14 mL of *hydrochloric acid R*. When the effervescence has ceased, boil for a few minutes. Allow to cool and dilute to 50 mL with *distilled water R*.

Appearance of solution

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Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Chlorides (2.4.4)

Maximum 100 ppm.

Dissolve 0.50 g in 10 mL of *water R*. Carefully add dropwise 1 mL of *nitric acid R*. Boil. Cool, add 5 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 100 ppm.

Dilute 7.50 mL of solution S to 15 mL with *distilled water R*.

Calcium (2.4.3)

Maximum 100 ppm.

To 5 mL of solution S add 1 mL of *concentrated ammonia R*. Boil. Cool. Dilute to 15 mL with *distilled water R*.

Iron (2.4.9)

Maximum 10 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 0.300 g by drying in an oven at 120-125 °C for 5 h.

ASSAY

Dissolve 0.500 g in 50 mL of *carbon dioxide-free water R*. Carry out a potentiometric titration (2.2.20), using *1 M hydrochloric acid*. Read the volume added at the 2nd point of inflexion.

1 mL of *1 M hydrochloric acid* is equivalent to 69.1 mg of K_2CO_3.

STORAGE

In an airtight container.

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Potassium Chloride

General Notices

(Ph. Eur. monograph 0185)

KCl 74.5 *7447-40-7*

Action and use

Used in prevention and treatment of potassium deficiency and electrolyte imbalance.

Preparations

Bumetanide and Potassium Prolonged-release Tablets

Oral Rehydration Salts

Magnesium Sulfate, Potassium Chloride and Sodium Chloride Infusion

Potassium Chloride and Glucose Infusion

Potassium Chloride and Sodium Chloride Infusion

Potassium Chloride, Sodium Chloride and Glucose Infusion

Potassium Chloride Oral Solution

Potassium Chloride Sterile Concentrate

Potassium Chloride Prolonged-release Tablets

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent of KCl (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

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Freely soluble in water, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. It gives reaction (a) of chlorides (2.3.1).

B. Solution S (see Tests) gives the reactions of potassium (2.3.1).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 50 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromides

Maximum 0.1 per cent.

Dilute 1.0 mL of solution S to 50 mL with *water R*. To 5.0 mL of the solution add 2.0 mL of *phenol red solution R2* and 1.0 mL of *chloramine solution R1* and mix immediately. After exactly 2 min add 0.15 mL of *0.1 M sodium thiosulfate*, mix and dilute to 10.0 mL with *water R*. The absorbance (2.2.25) of the solution measured at 590 nm, using *water R* as the compensation liquid, is not greater than that of a standard prepared at the same time and in the same manner using 5 mL of a 3.0 mg/L solution of *potassium bromide R*.

Iodides

Moisten 5 g by the dropwise addition of a freshly prepared mixture of 0.15 mL of *sodium nitrite solution R*, 2 mL of *0.5 M sulfuric acid*, 25 mL of *iodide-free starch solution R* and 25 mL of *water R*. After 5 min, examine in daylight. The substance shows no blue colour.

Sulfates (2.4.13)

Maximum 300 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Aluminium (2.4.17)

Maximum 1.0 ppm, if intended for use in the manufacture of haemodialysis solutions.

Prescribed solution Dissolve 4 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

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Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium and alkaline-earth metals (*2.4.7*)

Maximum 200 ppm, calculated as Ca and determined on 10.0 g using 0.15 g of *mordant black 11 triturate R*. The volume of *0.01 M sodium edetate* used is not more than 5.0 mL.

Sodium

Maximum 0.1 per cent, if intended for use in the manufacture of parenteral preparations or haemodialysis solutions.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions by diluting as required a solution containing 200 µg of Na per millilitre, prepared as follows: dissolve in *water R* 0.5084 g of *sodium chloride R*, previously dried at 105 °C for 3 h, and dilute to 1000.0 mL with the same solvent.

Wavelength 589 nm.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 60.0 mg in *water R*, add 5 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 7.45 mg of KCl.

LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

— where applicable, that the substance is suitable for use in the manufacture of haemodialysis solutions.

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Potassium Chloride and Glucose Infusion

General Notices

Potassium Chloride and Dextrose Injection; Potassium Chloride and Dextrose Infusion; Potassium Chloride and Dextrose Intravenous Infusion; Potassium Chloride and Glucose Injection; Potassium Chloride and Glucose Intravenous Infusion

DEFINITION

Potassium Chloride and Glucose Infusion is a sterile solution containing Potassium Chloride and either Glucose or Glucose Monohydrate. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of potassium chloride, KCl

95.0 to 105.0% of the stated amount.

Content of anhydrous glucose, $C_6H_{12}O_6$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or faintly straw-coloured solution.

IDENTIFICATION

A. When heated with *cupri-tartaric solution R1* a copious precipitate of copper(I) oxide is produced.

B. The residue on evaporation yields the reactions characteristic of *potassium salts* and of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 3.5 to 6.5, Appendix V L.

5-Hydroxymethylfurfural and related substances

Dilute a volume containing 1.0 g of glucose, $C_6H_{12}O_6$, to 500 mL with *water*. The *absorbance* of the resulting solution at the maximum at 284 nm is not more than 0.25, Appendix II B.

Sodium

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The content of Na is not more than 1.0% of the content of K, calculated from the content of potassium chloride determined in the Assay. Determine the content of Na by Method II for *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm and using *sodium standard solution* (*200 ppm Na*), diluted if necessary with *water*, to prepare the standard solutions.

Bacterial endotoxins

The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C.

ASSAY

For potassium chloride

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 767 nm and using *potassium standard solution* (*600 ppm K*), suitably diluted with *water*, to prepare the standard solutions.

For glucose

To a quantity containing the equivalent of 2 to 5 g of glucose, $C_6H_{12}O_6$, add 0.2 mL of 5M *ammonia* and sufficient *water* to produce 100 mL. Mix well, allow to stand for 30 minutes and measure the *optical rotation* in a 2-dm tube, Appendix V F. The observed rotation in degrees multiplied by 0.9477 represents the weight in g of glucose, $C_6H_{12}O_6$, in the quantity of the intravenous infusion taken for assay.

LABELLING

The strength is stated as the percentages w/v of Potassium Chloride and of glucose, $C_6H_{12}O_6$.

When the preparation is intended for intravenous infusion, the label also states (1) that rapid infusion may be harmful; (2) the approximate concentrations, in millimoles per litre, of the potassium ions and the chloride ions and the number of grams per litre of glucose, $C_6H_{12}O_6$.

For a preparation containing 0.3% w/v of Potassium Chloride, the concentration of each ion is stated as 40 millimoles per litre.

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Potassium Chloride and Sodium Chloride Infusion

General Notices

Potassium Chloride and Sodium Chloride Injection; Potassium Chloride and Sodium Chloride Intravenous Infusion

DEFINITION

Potassium Chloride and Sodium Chloride Infusion is a sterile solution containing Potassium Chloride and Sodium Chloride. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of potassium chloride, KCl

95.0 to 105.0% of the stated amount.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

The residue on evaporation yields the reactions characteristic of *potassium salts*, the reactions characteristic of *sodium salts* and the reactions characteristic of *chlorides*, Appendix VI.

Bacterial endotoxins

The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C.

ASSAY

For potassium chloride

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 767 nm and using *potassium standard solution* (*600 ppm K*), suitably diluted with *water*, to prepare the standard solutions.

For sodium chloride

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm and using *sodium standard solution* (*200 ppm Na*), suitably diluted with *water*, to prepare the standard solutions.

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LABELLING

The strength is stated as the percentages w/v of Potassium Chloride and of Sodium Chloride.

When the preparation is intended for intravenous infusion, the label also states (1) that rapid infusion may be harmful; (2) the approximate concentrations, in millimoles per litre, of the potassium ions, the sodium ions and the chloride ions.

For a preparation containing 0.3% w/v of Potassium Chloride and 0.9% w/v of Sodium Chloride, the concentrations of the ions are stated as 40 millimoles of potassium, 150 millimoles of sodium and 190 millimoles of chloride per litre.

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Potassium Chloride Effervescent Tablets

General Notices

Effervescent Potassium Chloride Tablets

DEFINITION

Potassium Chloride Effervescent Tablets contain potassium ions and chloride ions in an effervescent basis. The proportion of chloride ions to potassium ions may vary, but the stated molar proportion of chloride ions should be not less than 66% of that of potassium ions.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of potassium ions, K^+

95.0 to 105.0% of the stated amount.

Content of chloride ions, Cl^-

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The powdered tablets yield the reactions characteristic of *potassium salts* and of *chlorides*, Appendix VI.

B. Effervesce on the addition of *water*.

TESTS

Disintegration

The requirement for Disintegration does not apply to Potassium Chloride Effervescent Tablets.

Solution

One tablet dissolves in 100 mL of *water* at 20° with brisk effervescence in not more than 3 minutes. The resulting solution is not more than faintly opalescent.

ASSAY

Weigh and powder 20 tablets.

For potassium ions

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Dissolve a quantity of the powder containing 35 mg of potassium ions in sufficient *water* to produce 500 mL. Dilute 5 mL of the resulting solution to 100 mL with a 0.6% w/v solution of *strontium chloride* and determine the content of potassium by Method I for *atomic emission spectrophotometry*, Appendix II D, measuring at 767 nm and using *potassium standard solution* (*600 ppm K*), suitably diluted with a 0.6% w/v solution of *strontium chloride*, to prepare the standard solutions.

For chloride ions

Dissolve a quantity of the powder containing 0.12 g of chloride ions in *water*, dilute to 50 mL with *water* and titrate with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 3.545 mg of Cl.

LABELLING

The label states the content of potassium ions and the content of chloride ions in terms of the weight and the number of millimoles of ion present in each tablet.

When Potassium Chloride Effervescent Tablets are prescribed or demanded, the amount of potassium required in each tablet must be specified.

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Potassium Chloride Oral Solution

General Notices

Action and use

Used in the prevention and treatment of potassium deficiency and electrolyte imbalance.

DEFINITION

Potassium Chloride Oral Solution is a solution of Potassium Chloride in Purified Water.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of potassium chloride, KCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields the reactions characteristic of *potassium salts* and the reactions characteristic of *chlorides*, Appendix VI.

Acidity or alkalinity

pH, 5.0 to 7.5, Appendix V L.

ASSAY

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 767 nm and using *potassium standard solution* (*600 ppm K*), suitably diluted with *water*, to prepare the standard solutions.

When Potassium Chloride Oral Solution for paediatric or neonatal use is prescribed or demanded, a solution containing 1 mmol/mL or 2 mmol/mL shall be dispensed or supplied.

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Potassium Chloride Prolonged-release Tablets

General Notices

Prolonged-release Potassium Chloride Tablets

Potassium Chloride Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

DEFINITION

Potassium Chloride Prolonged-release Tablets contain Potassium Chloride and are formulated so as to release the medicament over a period of several hours. They are coated.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of potassium chloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of potassium chloride, KCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Stir 3 tablets in successive 20 mL portions of *water* until the outer coating is removed and separate the cores from the water. The powdered cores comply with the following tests.

A. Yield reaction A characteristic of *chlorides*, Appendix VI.

B. Yield the reactions characteristic of *potassium salts*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *water* and rotate the paddle at 50 revolutions per minute. Withdraw a sample of 10 mL of the medium after 1, 2 and 6 hours and treat each sample in the following manner. Add 25 mL of *water*, 5 mL of a 25% v/v solution of *glacial acetic acid* and 0.1 mL of a saturated solution of *potassium sulfate* and titrate with *0.01M silver nitrate VS* determining the end point potentiometrically. Each mL of *0.01M silver nitrate VS* is equivalent to 0.7455 mg of KCl. The amount of potassium chloride released

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after 1 hour is not more than 50%, after 2 hours is not less than 25% and not more than 75%, and after 6 hours is not less than 75%, calculated with reference to the declared content of Potassium Chloride.

ASSAY

Shake 10 whole tablets with 400 mL of *water* for 30 minutes then heat on a water bath for 45 minutes. Cool, add sufficient *water* to produce 500 mL and allow to stand for 24 hours. Filter and dilute to give a suitable concentration. Carry out the method for *atomic emission spectrophotometry*, Appendix II D, measuring at 766.5 nm and using *potassium standard solution* (*600 ppm K*), suitably diluted with *water*, to prepare the standard solutions. Each mg of potassium is equivalent to 1.908 mg of KCl.

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Potassium Chloride, Sodium Chloride and Glucose Infusion

General Notices

Potassium Chloride, Sodium Chloride and Dextrose Infusion; Potassium Chloride, Sodium Chloride and Dextrose Injection; Potassium Chloride, Sodium Chloride and Dextrose Intravenous Infusion; Potassium Chloride, Sodium Chloride and Glucose Injection; Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion

DEFINITION

Potassium Chloride, Sodium Chloride and Glucose Infusion is a sterile solution containing Potassium Chloride, Sodium Chloride and either Glucose or Glucose Monohydrate. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of potassium chloride, KCl

95.0 to 105.0% of the stated amount.

Content of sodium chloride, NaCl

0.17 to 0.19% w/v.

Content of anhydrous glucose, $C_6H_{12}O_6$

3.8 to 4.2% w/v.

CHARACTERISTICS

A colourless or faintly straw-coloured solution.

IDENTIFICATION

A. When heated with *cupri-tartaric solution R1* a copious precipitate of copper(I) oxide is produced.

B. The residue on evaporation and ignition yields reaction B characteristic of *potassium salts*, reaction B characteristic of *sodium salts* and reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 3.5 to 6.5, Appendix V L.

5-Hydroxymethylfurfural and related substances

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Dilute 25 mL to 500 mL with *water*. The *absorbance* of the resulting solution at the maximum at 284 nm is not more than 0.25, Appendix II B.

Bacterial endotoxins

The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C.

ASSAY

For potassium chloride

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 767 nm and using *potassium standard solution* (*600 ppm K*), suitably diluted with *water*, to prepare the standard solutions.

For sodium chloride

Dilute appropriately with *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm and using *sodium standard solution* (*200 ppm Na*), suitably diluted with *water*, to prepare the standard solutions.

For glucose

To a quantity containing the equivalent of 2 to 5 g of glucose, $C_6H_{12}O_6$, add 0.2 mL of 5M *ammonia* and sufficient *water* to produce 100 mL. Mix well, allow to stand for 30 minutes and measure the *optical rotation* in a 2-dm tube, Appendix V F. The observed rotation in degrees multiplied by 0.9477 represents the weight in g of glucose, $C_6H_{12}O_6$, in the quantity of the infusion taken for assay.

STORAGE

During storage, the separation of small solid particles from a glass container may occur. A solution containing such particles must not be used.

LABELLING

The label states (1) the content of Potassium Chloride as a percentage w/v and that the preparation contains 0.18% w/v of Sodium Chloride and 4.0% w/v of glucose, $C_6H_{12}O_6$; (2) the concentration of Potassium Chloride in grams per litre and the approximate concentration of potassium ions in millimoles per litre; (3) that the preparation contains 1.8 grams per litre of Sodium Chloride, equivalent to approximately 30 millimoles of sodium ions per litre; (4) the approximate quantity of chloride ions present, in millimoles per litre; (5) that the preparation contains 40 grams per litre of glucose, $C_6H_{12}O_6$; (6) that rapid infusion may be harmful; (7) that solutions containing visible solid particles must not be used.

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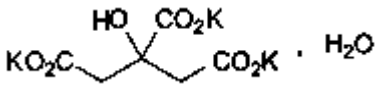
Potassium Citrate

General Notices

(Ph. Eur. monograph 0400)



$C_6H_5K_3O_7,H_2O$ 324.4 *6100-05-6*

Action and use

Alkalisation of urine.

Preparation

Potassium Citrate Mixture

Ph Eur

DEFINITION

Tripotassium 2-hydroxypropane-1,2,3-tricarboxylate monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, granular powder or transparent crystals, hygroscopic.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. To 1 mL of solution S (see Tests) add 4 mL of *water R*. The solution gives the reaction of citrates (*2.3.1*).

B. 0.5 mL of solution S gives reaction (b) of potassium (*2.3.1*).

TESTS

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Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. Not more than 0.2 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Readily carbonisable substances

To 0.20 g of the powdered substance to be examined add 10 mL of *sulfuric acid R* and heat in a water-bath at 90 ± 1 °C for 60 min. Cool rapidly. The solution is not more intensely coloured than reference solution Y_2 or GY_2 (*2.2.2, Method II*).

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Oxalates

Maximum 300 ppm.

Dissolve 0.50 g in 4 mL of *water R*, add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules and heat on a water-bath for 1 min. Allow to stand for 2 min, decant the liquid into a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of *potassium ferricyanide solution R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 4 mL of a 0.05 g/L solution of *oxalic acid R*.

Sulfates (*2.4.13*)

Maximum 150 ppm.

To 10 mL of solution S add 2 mL of *hydrochloric acid R1* and dilute to 15 mL with *distilled water R*.

Sodium

Maximum 0.3 per cent.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution To 10 mL of solution S add 1 mL of *dilute hydrochloric acid R* and dilute to 100 mL with *distilled water R*.

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Reference solutions Prepare the reference solutions using a solution of *sodium chloride R* containing 1 mg of Na per millilitre diluted as necessary with *distilled water R*.

Wavelength 589 nm.

Water (*2.5.12*)

4.0 per cent to 7.0 per cent, determined on 0.250 g. Use a mixture of 1 volume of *formamide R* and 2 volumes of *methanol R* as solvent. After adding the substance to be examined, stir for 15 min before titrating.

ASSAY

Dissolve 0.150 g in 20 mL of *anhydrous acetic acid R*, heating to about 50 °C. Allow to cool. Titrate with *0.1 M perchloric acid* using 0.25 mL of *naphtholbenzein solution R* as indicator until a green colour is obtained.

1 mL of *0.1 M perchloric acid* is equivalent to 10.21 mg of $C_6H_5K_3O_7$.

STORAGE

In an airtight container.

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Potassium Citrate Mixture

General Notices

Potassium Citrate Oral Solution

DEFINITION

Potassium Citrate Mixture is an *oral solution* containing 30% w/v of Potassium Citrate and 5% w/v of Citric Acid Monohydrate in a suitable vehicle with a lemon flavour. It is intended to be diluted with water before use.

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of citric acid monohydrate, $C_6H_8O_7,H_2O$

4.75 to 5.25% w/v.

Content of potassium citrate, $C_6H_5K_3O_7,H_2O$

28.5 to 31.5% w/v.

IDENTIFICATION

A. Yields reaction A characteristic of *potassium salts*, Appendix VI.

B. Yields reaction B characteristic of *citrates*, Appendix VI.

ASSAY

For citric acid monohydrate

To 5 mL add 100 mL of *water*, boil, cool and titrate with carbonate-free *0.1M sodium hydroxide VS* using *thymol blue solution* as indicator. Each mL of carbonate-free *0.1M sodium hydroxide VS* is equivalent to 7.005 mg of $C_6H_8O_7,H_2O$.

For potassium citrate

To 1 g add 5 mL of *acetic anhydride* and 20 mL of *anhydrous acetic acid*, heat on a water bath for 20 minutes, allow to cool and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 10.81 mg of $C_6H_5K_3O_7,H_2O$. Determine the *weight per mL* of the mixture, Appendix V G, and calculate the content of $C_6H_5K_3O_7,H_2O$, weight in volume.

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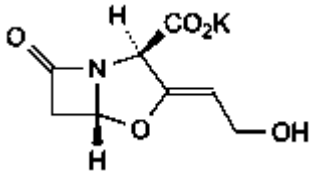
Potassium Clavulanate

General Notices

(Ph. Eur. monograph 1140)



$C_8H_8KNO_5$ 237.3 *61177-45-5*

Action and use

Beta-lactamase inhibitor, potentiation of the action of amoxicillin and ticarcillin.

Preparations

Co-amoxiclav Injection

Co-amoxiclav Oral Suspension

Co-amoxiclav Tablets

Co-amoxiclav Dispersible Tablets

Ticarcillin and Clavulanic Acid Infusion

Ph Eur

DEFINITION

Potassium (2*R*,3*Z*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate, the potassium salt of a substance produced by the growth of certain strains of *Streptomyces clavuligerus* or obtained by any other means.

Content

96.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

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Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in acetone.

PRODUCTION

The methods of production, extraction and purification are such that clavam-2-carboxylate is eliminated or present at a level not exceeding 0.01 per cent.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of potassium clavulanate*.

B. It gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 0.400 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

pH (*2.2.3*)

5.5 to 8.0.

Dilute 5 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

+ 53 to + 63 (anhydrous substance), determined on solution S.

Polymeric impurities and other impurities absorbing at 278 nm

Dissolve 50.0 mg in *0.1 M phosphate buffer solution pH 7.0 R* and dilute to 50.0 mL with the same buffer solution. Measure the absorbance immediately.

The absorbance (*2.2.25*) of the solution determined at 278 nm is not greater than 0.40.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Test solution Dissolve 0.250 g of the substance to be examined in mobile phase A and dilute to 25.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

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Reference solution (b) Dissolve 10 mg of *lithium clavulanate CRS* and 10 mg of *amoxicillin trihydrate CRS* in mobile phase A and dilute to 100 mL with mobile phase A.

Reference solution (c) Dissolve 2 mg of *potassium clavulanate impurity G CRS* in 20 mL of mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 7.8 g/L solution of *sodium dihydrogen phosphate R*, adjusted to pH 4.0 with *phosphoric acid R*;

— *mobile phase B*: a mixture of equal volumes of *methanol R1* and mobile phase A;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 15	100 → 50	0 → 50
15 - 18	50	50

Flow rate 1 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to clavulanate (retention time = about 3 min): impurity E = about 2.3; impurity G = about 3.6.

System suitability Reference solution (b):

— *resolution*: minimum 13 between the peaks due to clavulanate (1st peak) and amoxicillin (2nd peak).

Limits:

— *impurities E, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

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— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Aliphatic amines

Gas chromatography (2.2.28).

The method shown below can be used to determine the following aliphatic amines: 1,1-dimethylethylamine; tetramethylethylenediamine; 1,1,3,3-tetramethylbutylamine; *N*,*N*′-diisopropylethylenediamine; 2,2′-oxybis(*N*,*N*)dimethylethylamine.

Internal standard solution Dissolve 50 µL of *3-methylpentan-2-one R* in *water R* and dilute to 100.0 mL with the same solvent.

Test solution Weigh 1.00 g of the substance to be examined into a centrifuge tube. Add 5.0 mL of the internal standard solution, 5.0 mL of *dilute sodium hydroxide solution R*, 10.0 mL of *water R*, 5.0 mL of *2-methylpropanol R* and 5 g of *sodium chloride R*. Shake vigorously for 1 min. Centrifuge to separate the layers.

Reference solution Dissolve 80.0 mg of each of the following amines: *1,1-dimethylethylamine R*; *tetramethylethylenediamine R*; *1,1,3,3-tetramethylbutylamine R*; *N,N'-diisopropylethylenediamine R* and *2,2'-oxybis(N,N-dimethylethylamine) R* in *dilute hydrochloric acid R* and dilute to 200.0 mL with the same acid. Introduce 5.0 mL of this solution into a centrifuge tube. Add 5.0 mL of the internal standard solution, 10.0 mL of *dilute sodium hydroxide solution R*, 5.0 mL of *2-methylpropanol R* and 5 g of *sodium chloride R*. Shake vigorously for 1 min. Centrifuge to separate the layers.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.53 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 8 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 7	35
	7 - 10.8	35 → 150
	10.8 - 25.8	150
Injection port		200

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	Time (min)	Temperature (°C)
Detector		250

Detection Flame ionisation.

Injection 1 µL of the upper layers obtained from the test solution and the reference solution.

Relative retention With reference to 3-methylpentan-2-one (retention time = about 11.4 min): impurity H = about 0.55; impurity J = about 1.07; impurity K = about 1.13; impurity L = about 1.33; impurity M = about 1.57.

Limit:

— *total of aliphatic amines*: maximum 0.2 per cent.

2-Ethylhexanoic acid (2.4.28)

Maximum 0.8 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Bacterial endotoxins (2.6.14)

Less than 0.03 IU/mg if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 50.0 mg of the substance to be examined in a 4.1 g/L solution of *sodium acetate R* previously adjusted to pH 6.0 with *glacial acetic acid R*, and dilute to 50.0 mL with the same solution.

Reference solution (a) Dissolve 50.0 mg of *lithium clavulanate CRS* in a 4.1 g/L solution of *sodium acetate R* previously adjusted to pH 6.0 with *glacial acetic acid R* and dilute to 50.0 mL with the same solution.

Reference solution (b) Dissolve 10 mg of *amoxicillin trihydrate CRS* in 10 mL of reference solution (a).

Column:

— *size*: *l* = 0.3 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Mix 5 volumes of *methanol R1* and 95 volumes of a 15 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 4.0 with *dilute phosphoric acid R*.

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Flow rate 1 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to clavulanate (1st peak) and amoxicillin (2nd peak).

1 mg of clavulanate ($C_8H_9NO_5$) is equivalent to 1.191 mg of $C_8H_8KNO_5$.

STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Test for related substances

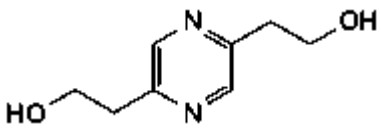
A, B, C, D, E, F, G.

Test for aliphatic amines

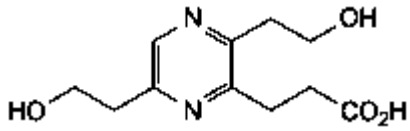
H, J, K, L, M.

Specified impurities *E, G, H, J, K, L, M.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, F.*



A. 2,2′-(pyrazine-2,5-diyl)diethanol,



B. 3-[3,6-bis(2-hydroxyethyl)pyrazin-2-yl]propanoic acid,

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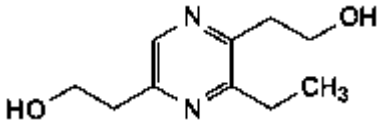
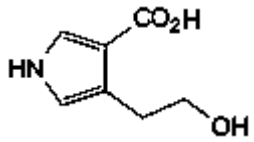
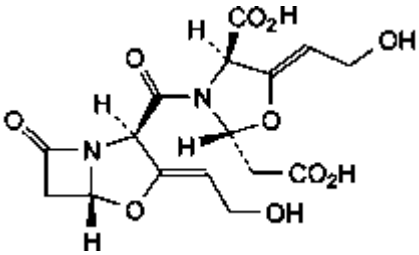


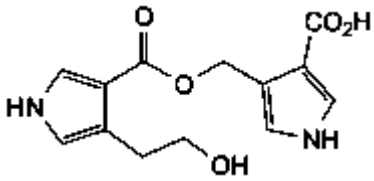
C. 2,2′-(3-ethylpyrazine-2,5-diyl)diethanol,



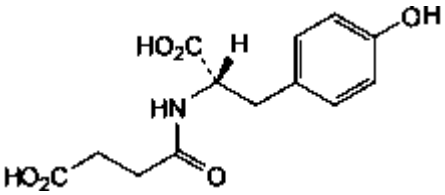
D. 4-(2-hydroxyethyl)-1*H*-pyrrole-3-carboxylic acid,



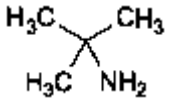
E. (2*R*,4*R*,5*Z*)-2-(carboxymethyl)-5-(2-hydroxyethylidene)-3-[[(2*R*,3*Z*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxazolidine-4-carboxylic acid,



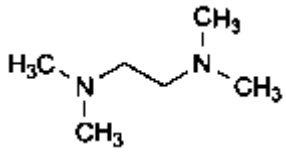
F. 4-[[[[4-(2-hydroxyethyl)-1*H*-pyrrol-3-yl]carbonyl]oxy]methyl]-1*H*-pyrrole-3-carboxylic acid,



G. 4-[[(1*S*)-1-carboxy-2-(4-hydroxyphenyl)ethyl]amino]-4-oxobutanoic acid (*N*-(hydrogensuccinyl)tyrosine),



H. 2-methylpropan-2-amine (2-amino-2-methylpropane, *tert*-butylamine, 1,1-dimethylethylamine),



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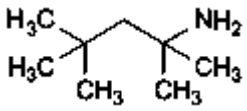
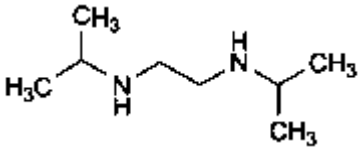
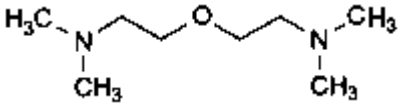
J. *N,N,N′,N′*-tetramethylethane-1,2-diamine (1,2-bis(dimethylamino)ethane, *N,N,N′,N′*-tetramethylethylenediamine),



K. 2,4,4-trimethylpentan-2-amine (2-amino-2,4,4-trimethylpentane, 1,1,3,3-tetramethylbutylamine),



L. *N,N′*-diisopropylethane-1,2-diamine (*N,N′*-bis(1-methylethyl)ethane-1,2-diamine),



M. 2,2′-oxybis(*N,N*-dimethylethanamine) (bis[2-(dimethylamino)ethyl] ether, *N,N,N′,N′*-tetramethyl(oxydiethylene)diamine).

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Potassium Dihydrogen Phosphate

General Notices

(Ph. Eur. monograph 0920)

KH_2PO_4 136.1 *7778-77-0*

Preparations

Potassium Dihydrogen Phosphate Sterile Concentrate

Potassium Dihydrogen Phosphate Oral Solution

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DEFINITION

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly acid (*2.2.4*).

B. Solution S gives reaction (b) of phosphates (*2.3.1*).

C. 0.5 mL of solution S gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

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Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.2 to 4.5.

To 5 mL of solution S add 5 mL of *carbon dioxide-free water R*.

Reducing substances

To 5 mL of solution S add 5 mL of *dilute sulfuric acid R* and 0.25 mL of *0.02 M potassium permanganate*. Heat on a water-bath for 5 min. The colour of the permanganate is not completely discharged.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

To 5 mL of solution S add 0.5 mL of *hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Arsenic (*2.4.2, Method A*)

Maximum 2 ppm, determined on 0.5 g.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Sodium

Maximum 0.1 per cent, if intended for use in the manufacture of parenteral preparations.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using the following solution, diluted as necessary with *water R*: dissolve 0.5084 g of *sodium chloride R*, previously dried at 100-105 °C for 3 h, in *water R* and dilute to 1000.0 mL with the same solvent (200 µg of Na per millilitre).

Wavelength 589 nm.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 125-130 °C.

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ASSAY

Dissolve 1.000 g in 50 mL of *carbon dioxide-free water R*. Titrate with carbonate-free *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 0.1361 g of KH_2PO_4.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Potassium Dihydrogen Phosphate Oral Solution

General Notices

Potassium Acid Phosphate Oral Solution

NOTE: This monograph has been developed to cover unlicensed formulations.

DEFINITION

Potassium Dihydrogen Phosphate Oral Solution is a 13.6% w/v solution of Potassium Dihydrogen Phosphate in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of potassium dihydrogen phosphate, KH_2PO_4

12.9 to 14.3% w/v.

IDENTIFICATION

The oral solution yields the reactions characteristic of *potassium salts* and the reactions characteristic of *phosphates,* Appendix VI.

TESTS

Acidity

pH, 3.5 to 5.0, Appendix V L.

ASSAY

Titrate 10 mL of the oral solution, saturated with *sodium chloride,* with *0.5M sodium hydroxide VS* using *phenolphthalein solution* as indicator. Each mL of *0.5M sodium hydroxide VS* is equivalent to 68.05 mg of KH_2PO_4.

LABELLING

The label states: (1) the strength as a percentage w/v of Potassium Dihydrogen Phosphate; (2) the approximate concentration of the potassium ions and the phosphate ions in millimoles in a suitable volume.

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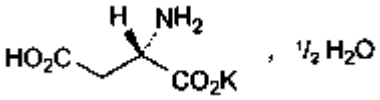
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Potassium Hydrogen Aspartate Hemihydrate

General Notices

(Ph. Eur. monograph 2076)



$C_4H_6KNO_4,½H_2O$ 180.2

Action and use

Excipient.

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DEFINITION

Potassium hydrogen (2*S*)-2-aminobutanedioate hemihydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, powder or crystalline powder, or colourless crystals.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Examine the chromatograms obtained in the test for ninhydrin-positive substances.

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Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. It gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 7.5 for solution S.

Specific optical rotation (*2.2.7*)

+ 18.0 to + 20.5 (anhydrous substance).

Dissolve 0.50 g in a mixture of equal volumes of *hydrochloric acid R* and *water R* and dilute to 25.0 mL with the same mixture of solvents.

Ninhydrin-positive substances

Thin-layer chromatography (*2.2.27*).

Test solution (a) Solution S.

Test solution (b) Dilute 1.0 mL of solution S to 10.0 mL with *water R*.

Reference solution (a) Dissolve 25 mg of *potassium hydrogen aspartate hemihydrate CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (b) to 20.0 mL with *water R*.

Reference solution (c) Dissolve 10 mg of *glutamic acid CRS* and 10 mg of the substance to be examined in *water R* and dilute to 25 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

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Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated principal spots.

Limits Test solution (a):

— *any impurity*: any spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Chlorides (*2.4.4*)

Maximum 200 ppm.

To 10 mL of solution S add 5 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

To 12 mL of solution S add 3 mL of *distilled water R*.

Ammonium (*2.4.1, Method B*)

Maximum 200 ppm, determined on 50 mg.

Prepare the standard using 0.1 mL of *ammonium standard solution (100 ppm NH_4) R*.

Iron (*2.4.9*)

Maximum 30 ppm.

In a separating funnel, dissolve 0.33 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. The aqueous layer complies with the limit test for iron.

Water (*2.5.12*)

4.0 per cent to 6.0 per cent, determined on 0.200 g.

Dissolve the substance to be examined in 10 mL of *formamide R1* and add 10 mL of *anhydrous methanol R*.

ASSAY

Dissolve 70.0 mg in 5 mL of *anhydrous formic acid R*, add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

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1 mL of *0.1 M perchloric acid* is equivalent to 8.56 mg of $C_4H_6KNO_4$.

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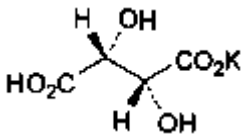
Potassium Hydrogen Tartrate

General Notices

Cream of Tartar

(Ph. Eur. monograph 1984)



$C_4H_5KO_6$ 188.2 *868-14-4*

Action and use

Excipient.

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DEFINITION

Potassium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of mineral acids and alkali hydroxides.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Suspend 0.5 g in 50 mL of *water R* and boil until dissolution is complete. Allow to cool (solution A). To 5 mL of solution A, add 0.1 mL of *methyl red solution R*. The solution is red.

C. Solution A gives reaction (a) of tartrates (*2.3.1*).

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D. Solution A gives reaction (b) of potassium (*2.3.1*).

TESTS

Specific optical rotation (*2.2.7*)

+ 8.0 to + 9.2 (dried substance).

Dissolve 2.50 g in 20 mL of *1 M hydrochloric acid* with heating. Allow to cool. Dilute to 25.0 mL with *water R*.

Oxalic acid

Maximum 500 ppm.

Dissolve 0.43 g in 4 mL of *water R*. Add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules and boil for 1 min. Allow to stand for 2 min. Collect the liquid in a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of a 50 g/L solution of *potassium ferricyanide R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 1 mL of *water R* and 3 mL of a 0.1 g/L solution of *oxalic acid R*.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dissolve 1.0 g with heating in a mixture of 3 mL of *dilute nitric acid R* and 50 mL of *water R*. Dilute to 100 mL with *water R*. Dilute 10 mL of the solution to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

Suspend 0.30 g in 3.0 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*. Heat until dissolution is complete.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.170 g in 100 mL of *water R* at 100 °C. Titrate the hot solution with *0.1 M sodium hydroxide*, using 0.3 mL of *phenolphthalein solution R* as indicator.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.82 mg of $C_4H_5KO_6$.

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Potassium Hydroxide

General Notices

Caustic Potash

(Ph. Eur. monograph 0840)

KOH 56.11 *1310-58-3*

Preparations

Potassium Ascorbate Eye Drops

Potassium Hydroxide Solution

Ph Eur

DEFINITION

Content

85.0 per cent to 100.5 per cent of total alkali, calculated as KOH.

CHARACTERS

Appearance

White or almost white, crystalline, hard masses, supplied as sticks, pellets or irregularly shaped pieces, deliquescent, absorbing carbon dioxide.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. pH (2.2.3): minimum 10.5.

Dissolve 0.1 g in 10 mL of *water R* (solution A used for identification test B). Dilute 1 mL of this solution to 100 mL with *water R*.

B. 1 mL of solution A prepared in identification test A gives reaction (b) of potassium (2.3.1).

TESTS

Solution S1

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Dissolve 2.5 g in 10 mL of *water R*. Carefully add 2 mL of *nitric acid R* while cooling, and dilute to 25 mL with *dilute nitric acid R*.

Solution S2

Dissolve 10 g in 15 mL of *distilled water R*. Carefully add 12 mL of *hydrochloric acid R* while cooling, and dilute to 50 mL with *dilute hydrochloric acid R*.

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Carbonates

Maximum 2.0 per cent, calculated as K_2CO_3 as determined in the assay.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S1 to 15 mL with *water R*.

Phosphates (*2.4.11*)

Maximum 100 ppm.

Dilute 1 mL of solution S1 to 100 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 5 mL of solution S2 to 20 mL with *distilled water R*.

Aluminium (*2.4.17*)

Maximum 0.2 ppm, if intended for use in the manufacture of haemodialysis solutions.

Prescribed solution Dissolve 20 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Iron (*2.4.9*)

Maximum 10 ppm.

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Dilute 5 mL of solution S2 to 10 mL with *water R*.

Sodium

Maximum 1.0 per cent.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dissolve 1.00 g in 50 mL of *water R*, add 5 mL of *sulfuric acid R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluting with *water R*.

Source Sodium hollow-cathode lamp.

Wavelength 589 nm.

Atomisation device Air-acetylene flame.

ASSAY

Dissolve 2.000 g in 25 mL of *carbon dioxide-free water R*. Add 25 mL of freshly prepared *barium chloride solution R1* and 0.3 mL of *phenolphthalein solution R*. Add slowly, while shaking, 25.0 mL of *1 M hydrochloric acid* and continue the titration with *1 M hydrochloric acid* until the colour changes from pink to colourless. Add 0.3 mL of *bromophenol blue solution R* and continue the titration with *1 M hydrochloric acid* until the colour changes from violet-blue to yellow.

1 mL of *1 M hydrochloric acid* used in the 2nd part of the titration is equivalent to 69.11 mg of K_2CO_3.

1 mL of *1 M hydrochloric acid* used in the combined titrations is equivalent to 56.11 mg of total alkali, calculated as KOH.

STORAGE

In an airtight, non-metallic container.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of haemodialysis solutions.

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Potassium Hydroxide Solution

General Notices

Potash Solution

DEFINITION

Potassium Hydroxide Solution is a solution of Potassium Hydroxide in Purified Water.

Content of total alkali, calculated as KOH

4.9 to 5.1% w/v.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

Strongly alkaline and when neutralised with 2M *hydrochloric acid* yields the reactions characteristic *of potassium salts*, Appendix VI.

Weight per mL

1.040 to 1.050 g, Appendix V G.

ASSAY

Titrate 20 mL with *1M hydrochloric acid VS* using *methyl orange solution* as indicator. Each mL of *1M hydrochloric acid VS* is equivalent to 56.11 mg of total alkali, calculated as KOH.

STORAGE

Potassium Hydroxide Solution should be kept in a well-closed container of lead-free glass or of a suitable plastic.

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Potassium Hydroxyquinoline Sulfate

General Notices

Potassium Hydroxyquinoline Sulphate

Action and use

Used in treatment of acne.

Preparation

Potassium Hydroxyquinoline Sulfate and Benzoyl Peroxide Cream.

DEFINITION

Potassium Hydroxyquinoline Sulfate is an equimolecular mixture of quinolin-8-ol sulfate monohydrate, $(C_9H_7NO)_2,H_2SO_4,H_2O$, and potassium sulfate, K_2SO_4. It contains not less than 50.6% and not more than 52.6% of quinolin-8-ol, C_9H_7NO, and not less than 29.5% and not more than 32.5% of K_2SO_4, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A pale yellow, microcrystalline powder. It partly liquefies between 172° and 184°.

Freely soluble in *water*; insoluble in *ether*. On extraction with hot *absolute ethanol* a residue of potassium sulfate and a solution of quinolin-8-ol sulfate are obtained.

IDENTIFICATION

A. To 5 mL of a 5% w/v solution add drop wise, with shaking, 5M *sodium hydroxide* until a heavy precipitate is produced. Filter, wash with *water* and dry at a pressure not exceeding 0.7 kPa for 3 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of quinolin-8-ol *(RS 310)*.

B. To 5 mL of a 5% w/v solution add 0.5 mL of *iron(III) chloride solution R1*. A dark green colour is produced.

C. Yields reaction A characteristic of *potassium salts*, Appendix VI.

D. Yields reaction A characteristic of *sulfates*, Appendix VI.

TESTS

Water

Not more than 5.0% w/w, Appendix IX C. Use 0.5 g.

ASSAY

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For quinolin-8-ol

Dissolve 0.35 g in 50 mL of *water* and 20 mL of *hydrochloric acid*, add 50 mL of *0.05M bromine VS*, stopper the flask and shake for 15 minutes. Allow to stand for 15 minutes, add 80 mL of *water* and 10 mL of *dilute potassium iodide solution* and titrate with 0.1M *sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of bromine required. Each mL of *0.05M bromine VS* is equivalent to 3.629 mg of C_9H_7NO.

For potassium sulfate

Prepare a solution of suitable concentration with *water*. Carry out the method for *atomic emission spectrophotometry*, Appendix II D, measuring at 766.5 nm and using *potassium standard solution (600 ppm K)*, suitably diluted with *water*, to prepare the standard solutions. Each mg of potassium is equivalent to 2.2284 mg of K_2SO_4.

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Potassium Hydroxyquinoline Sulfate and Benzoyl Peroxide Cream

General Notices

Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream

Action and use

Used topically in the treatment of acne.

DEFINITION

Potassium Hydroxyquinoline Sulfate and Benzoyl Peroxide Cream contains Potassium Hydroxyquinoline Sulfate and Hydrous Benzoyl Peroxide in a suitable astringent basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of potassium hydroxyquinoline sulfate, $(C_9H_7NO)_2,H_2SO_4:K_2SO_4$

90.0 to 110.0% of the stated amount.

Content of anhydrous benzoyl peroxide, $C_{14}H_{10}O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the preparation being examined containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 10 mL of *dichloromethane* and filter.

(2) 0.5% w/v of *benzoyl peroxide* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 2 volumes of *dichloromethane* and 50 volumes of *toluene*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Add 20 mL of *methanol* to a quantity of the cream containing 10 mg of Potassium Hydroxyquinoline Sulfate, heat in a water bath, shaking occasionally, cool and filter through *anhydrous sodium sulfate*. To 10 mL of the filtrate add 5 mL of a 0.5% w/v solution of *iron(II) sulfate* in *methanol* (*70%*). A dark blue or green colour is produced immediately.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 0.1 volumes of *acetic acid* and 999.9 volumes of *acetonitrile*

(1) Add 1 mL of Solvent A to a quantity of the cream containing the equivalent of 25 mg of anhydrous benzoyl peroxide. Mix using a vortex mixer until a uniform suspension is obtained. Add three 1-mL quantities of *acetonitrile* and mix using a vortex mixer between each addition. Add a further 15 mL of *acetonitrile* and mix with the aid of ultrasound for 3 minutes. Add sufficient *acetonitrile* to produce 100 mL. Dilute 1 volume to 10 volumes with *acetonitrile*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.

(3) 0.003% w/v of *benzoic acid*, 0.0003% w/v of *ethyl benzoate* and 0.0003% w/v of *benzaldehyde* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *polar endcapped ether-linked phenyl for chromatography* (4 µm) (Phenomenex Synergi Polar RP is suitable) fitted with a suitable stainless steel guard column packed with *octadecylsilyl silica gel for chromatography*.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.00042% v/v *phosphoric acid*.

Mobile phase B *acetonitrile*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	65	35	isocratic
5-15	65→15	35→85	linear gradient
15-18	15	85	isocratic
18-20	15→65	85→35	linear gradient
20-31	65	35	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to benzoyl peroxide (retention time about 14.5 minutes) are: benzoic acid, about 0.3; benzaldehyde, about 0.5 and ethyl benzoate, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to benzoic acid and benzaldehyde is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify the peaks due to benzoic acid, benzaldehyde and ethyl benzoate using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: benzoic acid, 1.50; benzaldehyde, 1.74; and ethyl benzoate, 1.72.

the area of any peak corresponding to benzoic acid is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (10%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

For potassium hydroxyquinoline sulfate

Shake vigorously a quantity of the cream containing 35 mg of Potassium Hydroxyquinoline Sulfate with 50 mL of *chloroform* and 10 mL of 13.5M *ammonia* for 5 minutes. Separate and reserve the chloroform layer and extract the aqueous layer with a further 50 mL of *chloroform*. Extract the combined chloroform layers with two 50 mL quantities of 3.5M *hydrochloric acid*, combine the extracts, wash gently with three 50 mL quantities of *chloroform* and discard the chloroform layers. Add 50 mL of *0.01M bromine VS*, stopper the flask, shake for 20 minutes and allow to stand for 20 minutes. Add 10 mL of *dilute potassium iodide solution* and titrate with 0.02M *sodium thiosulfate VS* using *starch solution*, added towards the end of the titration, as indicator. Repeat the titration using 100 mL of 3.5M *hydrochloric acid* and beginning at the words ‘Add 50 mL...’. The difference between the titrations represents the amount of bromine required. Each mL of *0.01M bromine VS* is equivalent to 1.407 mg of $(C_9H_7NO)_2,H_2SO_4:K_2SO_4$.

For benzoyl peroxide

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Shake gently a quantity of the cream containing the equivalent of 0.4 g of anhydrous benzoyl peroxide with 50 mL of *chloroform* until the cream has dispersed and filter the lower layer excluding any solid matter that separates at the interface. Repeat the extraction with two further 50 mL quantities of *chloroform*, wash the filter with *chloroform*, combine the extracts and washings and dilute to 250 mL with *chloroform*. To 25 mL of the chloroform extract add 40 mL of a 0.0005% w/v solution of *iron(III) chloride hexahydrate* in *glacial acetic acid* and 10 mL of *dilute potassium iodide solution* and shake for 20 minutes protected from light. Add 60 mL of *water* and titrate with 0.0125M *sodium thiosulfate VS* using *starch solution*, added towards the end of the titration, as indicator. Repeat the titration using 25 mL of *chloroform* in place of the chloroform extract. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.0125M *sodium thiosulfate VS* is equivalent to 1.514 mg of $C_{14}H_{10}O_4$.

LABELLING

The content of Hydrous Benzoyl Peroxide is stated in terms of the equivalent amount of anhydrous benzoyl peroxide.

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Potassium Iodate

General Notices

KIO_3 214.0 *7758-05-6*

Action and use

Iodine supplement for emergency use.

Preparation

Potassium Iodate Tablets

DEFINITION

Potassium Iodate contains not less than 99.0% and not more than 101.0% of KIO_3, calculated with reference to the dried substance.

CHARACTERISTICS

A white crystalline powder.

Slowly soluble in water; insoluble in ethanol (96%).

Dissolve 10 g of the substance being examined in sufficient water to produce 200 mL (solution S1).

Add 25 mL of *hydrochloric acid* to 6 g of the substance being examined, evaporate to dryness and repeat. Heat until iodine is removed. Dissolve the residue in 2.5 mL of a 25% v/v solution of *hydrochloric acid* and dilute to 50 mL with *water* (solution S2).

IDENTIFICATION

A. 1 mL of solution S1 yields reaction B characteristic of *potassium salts*, Appendix VI.

B. Dissolve 0.1 g in 5 mL of *water*. Add 1 mL of *silver nitrate solution* followed by 1 mL of *sulfur dioxide solution*. A yellow precipitate is produced immediately.

TESTS

Acidity or alkalinity

pH of solution S1, 5.0 to 8.0, Appendix V L.

Clarity and colour of solution

Solution S1 is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

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Chloride, chlorate, bromide, bromate

Dilute 5 mL of solution S1 to 15 mL with *water*, add 20 mL of *sulfur dioxide solution* and heat on a water bath for 30 minutes. Heat to boiling, cool, add 10 mL of 18M *ammonia* and 20 mL of *silver nitrate solution R2* and dilute to 70 mL with *water*. Filter, transfer 35 mL of the filtrate to a *Nessler cylinder* and acidify with 6 mL of *nitric acid*. After 5 minutes, any opalescence, when viewed vertically, is not greater than that produced by treating 5 mL of a 0.00165% w/v solution of *sodium chloride* at the same time and in the same manner (0.02%).

Iodide

Add 1 mL of 1.8M *sulfuric acid* to 25 mL of solution S1 and shake with 1 mL of *chloroform*. Any violet colour produced is not more intense than that of a solution prepared at the same time and in the same manner but using 5 mL of solution S1 and 2 mL of *iodide standard solution (10 ppm I)* (20 ppm).

Sulfate

Add 1 mL of a 25% w/v solution of *barium chloride* to 1.5 mL of *sulfate standard solution (10 ppm SO_4)*, shake and allow to stand for 1 minute. Add 12.5 mL of solution S2 diluted to 15 mL with *distilled water* and 0.5 mL of 5M *acetic acid* and allow to stand for 5 minutes. Any opalescence produced is not more intense than that of a standard prepared in the same manner but using 7.5 mL of *sulfate standard solution (10 ppm SO_4)* diluted to 15 mL with *distilled water* in place of the solution being examined (50 ppm).

Loss on drying

When dried at 130° for 1 hour, loses not more than 0.5% of its weight. Use 1 g.

ASSAY

To 1.5 g add sufficient *water* to produce 250 mL. To 25 mL of the resulting solution in an iodine flask add 3 g of *potassium iodide*, 100 mL of *water* and 10 mL of *hydrochloric acid*. Close the flask and stand in the dark for 5 minutes. Titrate the solution with 0.1M *sodium thiosulfate VS* to a light straw colour and then complete the titration to a colourless end point using *starch mucilage* as indicator. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 3.567 mg of KIO_3.

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Potassium Iodate Tablets

General Notices

DEFINITION

Potassium Iodate Tablets contain Potassium Iodate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of potassium iodate, KIO_3

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.4 g of Potassium Iodate with 10 mL of *water* and filter (solution A). 1 mL of solution A yields reaction B characteristic of *potassium salts*, Appendix VI.

B. Add 1 g of *potassium iodide* and 1 mL of *hydrochloric acid* to 5 mL of solution A and shake. A brown colour is produced.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *water* and rotating the basket at 100 revolutions per minute. Filter the medium after first wetting the filter paper with *water* and note the volume of filtrate. Treat the filtrate as described under Assay beginning at the words 'To 50 mL of the filtrate ...'. Repeat the assay procedure without the dissolution medium. Calculate the total content of potassium iodate, KIO_3, in the dissolution medium from the difference between the titrations.

Iodide

Shake a quantity of the powdered tablets containing 2.5 g of Potassium Iodate with 50 mL *water* and filter (solution B). Add 1 mL of 1.8M *sulfuric acid* and 1 mL of *chloroform* to 25 mL of solution B and shake. Any violet colour produced is not more intense than that of a solution prepared at the same time and in the same manner but using 5 mL of solution B and 2 mL of *iodide standard solution (10 ppm I)* (20 ppm).

ASSAY

Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing 0.3 g of Potassium Iodate to an iodine flask, add 100 mL of *water*, shake and filter. To 50 mL of the filtrate add 3 g of *potassium iodide* followed by 50 mL of 2M *hydrochloric acid*. Stopper the flask, mix and stand in the dark for 5 minutes. Titrate the resulting solution with 0.1M *sodium thiosulfate VS* to a light straw colour and then complete the titration to a colourless end point using *starch solution* as indicator. Repeat the titration without the powdered tablets. The

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difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 3.567 mg of KIO_3.

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Potassium Iodide

General Notices

(Ph. Eur. monograph 0186)

KI 166.0 *7681-11-0*

Action and use

Antithyroid.

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals.

Solubility

Very soluble in water, freely soluble in glycerol, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives the reactions of iodides (*2.3.1*).

B. Solution S gives the reactions of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

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Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Alkalinity

To 12.5 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Iodates

To 10 mL of solution S add 0.25 mL of *iodide-free starch solution R* and 0.2 mL of *dilute sulfuric acid R* and allow to stand protected from light for 2 min. No reddish-brown colour develops.

Sulfates (*2.4.13*)

Maximum 150 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Thiosulfates

To 10 mL of solution S add 0.1 mL of *starch solution R* and 0.1 mL of *0.005 M iodine*. A reddish-brown colour is produced.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.00 g of previously powdered substance by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 1.500 g in *water R* and dilute to 100.0 mL with the same solvent. To 20.0 mL of the solution add 40 mL of *hydrochloric acid R* and titrate with *0.05 M potassium iodate* until the colour changes from red to yellow. Add 5 mL of *chloroform R* and continue the titration, shaking vigorously, until the chloroform layer is decolourised.

1 mL of *0.05 M potassium iodate* is equivalent to 16.60 mg of KI.

STORAGE

Protected from light.

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Potassium Metabisulfite

General Notices

Potassium Metabisulphite

(Ph. Eur. monograph 2075)

$K_2S_2O_5$ 222.3 *16731-55-8*

Action and use

Preservative.

Ph Eur

DEFINITION

Potassium metabisulfite (dipotassium disulfite).

Content

95.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white powder, or colourless crystals.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. pH (see Tests).

B. To 5 mL of solution S (see Tests), add 0.5 mL of *0.05 M iodine*. The mixture is colourless and gives reaction (a) of sulfates (*2.3.1*).

C. Solution S gives reaction (a) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

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Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method I*).

pH (*2.2.3*)

3.0 to 4.5 for solution S.

Thiosulfates

To 2.00 g add 25 mL of a 42.5 g/L solution of *sodium hydroxide R* and 75 mL of *water R*. Shake until dissolved and add 10 mL of *formaldehyde R* and 10 mL of *acetic acid R*. After 5 min, titrate with *0.05 M iodine* using 1 mL of *starch solution R*. Carry out a blank titration. The difference between the volumes consumed in the 2 titrations is not more than 0.15 mL.

Iron

Maximum 10 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 20 mL of solution S to 50 mL with *water R*.

Reference solutions Prepare the reference solutions using *iron standard solution (20 ppm Fe) R*, diluting with *water R*.

Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Zinc

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 20 mL of solution S to 50 mL with *water R*.

Reference solutions Prepare the reference solutions using *zinc standard solution (100 ppm Zn) R*, diluting with *water R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame.

ASSAY

In a 500 mL conical flask containing 50.0 mL of *0.05 M iodine* introduce 0.150 g and add 5 mL of *hydrochloric acid R*. Titrate the excess of iodine with *0.1 M sodium thiosulfate* using 0.1 mL of *starch solution R*, added towards the end of the titration, as indicator.

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1 mL of *0.05 M iodine* is equivalent to 5.558 mg of $K_2S_2O_5$.

STORAGE

In an airtight container, protected from light.

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Potassium Nitrate

General Notices

(Ph. Eur. monograph 1465)

KNO_3 101.1 *7757-79-1*

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, very soluble in boiling water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives the reaction of nitrates (*2.3.1*).

B. Solution S (see Tests) gives the reactions of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

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Reducible substances

To 10 mL of solution S, add 0.5 mL of *dilute sulfuric acid R* and 2 mL of *zinc iodide and starch solution R*. The solution does not become blue within 2 min.

Chlorides (*2.4.4*)

Maximum 20 ppm, if intended for ophthalmic use.

Dissolve 2.5 g in *water R* and dilute to 15 mL with the same solvent.

Sulfates (*2.4.13*)

Maximum 150 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Ammonium (*2.4.1*)

Maximum 100 ppm, determined in 1 mL of solution S; maximum 50 ppm if intended for ophthalmic use.

Calcium (*2.4.3*)

Maximum 100 ppm; maximum 50 ppm if intended for ophthalmic use.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 20 ppm; maximum 10 ppm if intended for ophthalmic use.

Dilute 5 mL of solution S to 10 mL with *water R*.

Sodium

Maximum 0.1 per cent.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluting with *water R*.

Wavelength 589 nm.

Loss on drying

(*2.2.32*)Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

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Prepare a chromatography column 0.3 m long and 10 mm in internal diameter and filled with 10 g of *strongly acidic ion-exchange resin R* covered with *carbon dioxide-free water R*. Maintain a 1 cm layer of liquid above the resin at all times. Allow 100 mL of *dilute hydrochloric acid R* to run through the column at a flow rate of about 5 mL/min. Wash the column (with the tap completely open) with *carbon dioxide-free water R* until neutral to *blue litmus paper R*. Dissolve 0.200 g of the substance to be examined in 2 mL of *carbon dioxide-free water R* in a beaker and transfer it to the column reservoir, allow the solution to run through the column at a flow rate of about 3 mL/min and collect the eluate. Wash the beaker with 10 mL of *carbon dioxide-free water R* and transfer this solution at the same flow rate to the column before it runs dry. Finally wash the column with 200 mL of *carbon dioxide-free water R* (with the tap completely open) until neutral to *blue litmus paper R*. Titrate the combined eluate and washings with *0.1 M sodium hydroxide*, using 1 mL of *phenolphthalein solution R* as indicator.

1 mL of *0.1 M sodium hydroxide* is equivalent to 10.11 mg of KNO_3.

LABELLING

The label states, where applicable, that the substance is suitable for ophthalmic use.

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Potassium Perchlorate

General Notices

(Ph. Eur. monograph 1987)

$KClO_4$ 138.6 *7778-74-7*

Action and use

Diagnostic aid; treatment of hyperthyroidism.

Ph Eur

DEFINITION

Content

99.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 0.1 g in 5 mL of *water R*. Add 5 mL of *indigo carmine solution R* and heat to boiling. The colour of the solution does not disappear.

B. Chlorates and chlorides (see Tests).

C. Heat 10 mg over a flame for 2 min. Dissolve the residue in 2 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

D. Dissolve 50 mg with heating in 5 mL of *water R*. Allow to cool to room temperature. The solution gives reaction (a) of potassium (*2.3.1*).

TESTS

Solution S

Suspend 5.0 g in 90 mL of *distilled water R* and heat to boiling. Allow to cool. Filter. Dilute the filtrate to 100 mL with *carbon dioxide-free water R*.

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Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.20 g in *water R* and dilute to 20 mL with the same solvent.

Acidity or alkalinity

To 5 mL of solution S add 5 mL of *water R* and 0.1 mL of *phenolphthalein solution R*. Not more than 0.25 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator. To 5 mL of solution S, add 5 mL of *water R* and 0.1 mL of *bromocresol green solution R*. Not more than 0.25 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Chlorates and chlorides (*2.4.4*)

Maximum 100 ppm (calculated as chlorides).

To 5 mL of solution S, add 5 mL of *water R* and heat to boiling. Add 1 mL of *nitric acid R* and 0.1 g of *sodium nitrite R*. Allow to cool to room temperature. Dilute to 15 mL with *water R*. The solution complies with the limit test for chlorides. Prepare the standard using 5 mL of *chloride standard solution (5 ppm Cl) R* and 10 mL of *water R*, and adding only 1 mL of *dilute nitric acid R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Prepare the standard using a mixture of 7.5 mL of *sulfate standard solution (10 ppm SO_4) R* and 7.5 mL of *water R*.

Calcium (*2.4.3*)

Maximum 100 ppm, determined on solution S.

Prepare the standard using a mixture of 7.5 mL of *calcium standard solution (10 ppm Ca) R*, 1 mL of *dilute acetic acid R* and 7.5 mL of *distilled water R*.

ASSAY

Prepare a chromatography column 0.3 m long and 10 mm in internal diameter and filled with 10 g of *strongly acidic ion-exchange resin R* covered with *carbon dioxide-free water R*. Maintain a 1 cm layer of liquid above the resin throughout the determination. Allow 100 mL of *dilute hydrochloric acid R* to run through the column at a flow rate of about 5 mL/min. Wash the column (with the tap completely open) with *carbon dioxide-free water R* until the eluate is neutral to *blue litmus paper R*. Dissolve 0.100 g of the substance to be examined in 10 mL of *carbon dioxide-free water R* in a beaker and transfer it to the column reservoir, allow the solution to run through the column at a flow rate of about 3 mL/min and collect the eluate. Wash the beaker 3 times with 10 mL of *carbon dioxide-free water R* and transfer this solution at the same flow rate to the column before it runs dry. Finally, wash the column with 200 mL of *carbon dioxide-free water R* (with the tap completely open) until the eluate is neutral to *blue litmus paper R*. Titrate the combined eluate and washings with *0.1 M sodium hydroxide*, using 1 mL of *phenolphthalein solution R* as indicator.

1 mL of *0.1 M sodium hydroxide* is equivalent to 13.86 mg of $KClO_4$.

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Potassium Permanganate

General Notices

(Ph. Eur. monograph 0121)

$KMnO_4$ 158.0 *7722-64-7*

Action and use

Antiseptic.

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

Dark purple or brownish-black, granular powder or dark purple or almost black crystals, usually having a metallic lustre.

Solubility

Soluble in cold water, freely soluble in boiling water.

It decomposes on contact with certain organic substances.

IDENTIFICATION

A. Dissolve about 50 mg in 5 mL of *water R* and add 1 mL of *ethanol (96 per cent) R* and 0.3 mL of *dilute sodium hydroxide solution R*. A green colour develops. Heat to boiling. A dark brown precipitate is formed.

B. Filter the mixture obtained in identification test A. The filtrate gives reaction (b) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 0.75 g in 25 mL of *distilled water R*, add 3 mL of *ethanol (96 per cent) R* and boil for 2-3 min. Cool, dilute to 30 mL with *distilled water R* and filter.

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Appearance of solution

Solution S is colourless (*2.2.2, Method II*).

Substances insoluble in water

Maximum 1.0 per cent.

Dissolve 0.5 g in 50 mL of *water R* and heat to boiling. Filter through a tared sintered-glass filter (16) (*2.1.2*). Wash with *water R* until the filtrate is colourless and collect the residue on the filter. The residue, dried in an oven at 100-105 °C, weighs a maximum of 5 mg.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

Dilute 12 mL of solution S to 15 mL with *distilled water R*.

ASSAY

Dissolve 0.300 g in *water R* and dilute to 100.0 mL with the same solvent. To 20.0 mL of the solution add 20 mL of *water R*, 1 g of *potassium iodide R* and 10 mL of *dilute hydrochloric acid R*. Titrate the liberated iodine with *0.1 M sodium thiosulfate*, using 1 mL of *starch solution R* as indicator.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 3.160 mg of $KMnO_4$.

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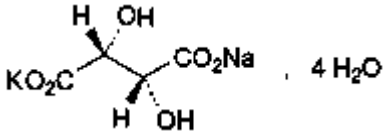
Potassium Sodium Tartrate Tetrahydrate

General Notices

(Ph. Eur. monograph 1986)



$C_4H_4KNaO_6,4H_2O$ 282.2 *6381-59-5*

Action and use

Excipient.

Ph Eur

DEFINITION

Potassium sodium (+)-(2*R*,3*R*)-2,3-dihydroxybutanedioate tetrahydrate.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless, transparent crystals.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. It gives reaction (b) of tartrates (2.3.1).

C. It gives reaction (b) of potassium (2.3.1).

D. It gives reaction (a) of sodium (2.3.1).

TESTS

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Solution S

Dissolve 5.000 g in *carbon dioxide-free water R*, prepared from *distilled water R*, and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 5 mL of solution S, add 0.1 mL of *phenolphthalein solution R*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*)

+ 28.0 to + 30.0 (anhydrous substance), determined on solution S.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 50 ppm.

Dissolve 1.0 g in *distilled water R* and dilute to 15 mL with the same solvent. Prepare the reference solution with a mixture of 5 mL of *sulfate standard solution (10 ppm SO_4) R* and 10 mL of *distilled water R*.

Ammonium (*2.4.1*)

Maximum 40 ppm, determined on 5 mL of solution S.

Barium and oxalates

To 5 mL of solution S, add 3 mL of *calcium sulfate solution R*. Allow to stand for 5 min. Any opalescence in the solution is not more intense than that in a mixture of 3 mL of *calcium sulfate solution R* and 5 mL of *distilled water R*.

Calcium (*2.4.3*)

Maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Water (*2.5.12*)

24.0 per cent to 26.5 per cent, determined on 50.0 mg. Use 50 mL of *anhydrous methanol R*. Titrate slowly.

ASSAY

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To 0.100 g of finely powdered substance add 40 mL of *anhydrous acetic acid R* and 20 mL of *acetic anhydride R*. Titrate slowly with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 10.51 mg of $C_4H_4KNaO_6$.

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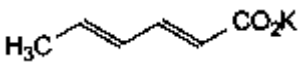
Potassium Sorbate

General Notices

(Ph. Eur. monograph 0618)



$C_6H_7KO_2$ 150.2 *590-00-1*

Action and use

Antimicrobial preservative.

Ph Eur

DEFINITION

Potassium (*E,E*)-hexa-2,4-dienoate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or granules.

Solubility

Very soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in water R and dilute to 250.0 mL with the same solvent. Dilute 2.0 mL of this solution to 200.0 mL with 0.1 M hydrochloric acid.

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Spectral range 230-350 nm.

Absorption maximum At 264 nm.

Specific absorbance at the absorption maximum 1650 to 1900.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *potassium sorbate CRS*.

C. Dissolve 1.0 g in 50 mL of *water R*, add 10 mL of *dilute hydrochloric acid R* and shake. Filter the crystalline precipitate, wash with *water R* and dry *in vacuo* over *sulfuric acid R* for 4 h. The residue obtained melts (2.2.14) at 132 °C to 136 °C.

D. Dissolve 0.2 g in 2 mL of *water R* and add 2 mL of *dilute acetic acid R*. Filter. The solution gives reaction (b) of potassium (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Acidity or alkalinity

To 20 mL of solution S add 0.1 mL of *phenolphthalein solution R*. Not more than 0.25 mL of *0.1 M sodium hydroxide* or *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Aldehydes

Maximum 0.15 per cent, expressed as C_2H_4O.

Dissolve 1.0 g in a mixture of 30 mL of *water R* and 50 mL of *2-propanol R*, adjust to pH 4 with *1 M hydrochloric acid* and dilute to 100 mL with *water R*. To 10 mL of the solution add 1 mL of *decolorised fuchsin solution R* and allow to stand for 30 min. Any colour in the solution is not more intense than that in a standard prepared at the same time by adding 1 mL of *decolorised fuchsin solution R* to a mixture of 1.5 mL of *acetaldehyde standard solution (100 ppm C_2H_4O) R*, 4 mL of *2-propanol R* and 4.5 mL of *water R*.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.120 g in 20 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* using 0.1 mL of *crystal violet solution R* as indicator until the colour changes from violet to bluish-green.

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1 mL of *0.1 M perchloric acid* is equivalent to 15.02 mg of $C_6H_7KO_2$.

STORAGE

Protected from light.

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Potassium Sulfate

General Notices

Potassium Sulphate

(Ph. Eur. monograph 1622)

K_2SO_4 174.3 *7778-80-5*

Ph Eur

DEFINITION

Content

98.5 per cent to 101.0 per cent of K_2SO_4 (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Soluble in water, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. It gives reaction (a) of sulfates (*2.3.1*).

B. It gives reaction (a) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in 90 mL of *carbon dioxide-free water R* prepared from *distilled water R*, heating gently. Allow to cool and dilute to 100 mL with *carbon dioxide-free water R* prepared from *distilled water R*.

Appearance of solution

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Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*)

Maximum 40 ppm.

Dilute 12.5 mL of solution S to 15 mL with *water R*.

Calcium (*2.4.3*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 10 ppm, determined on 10 mL of solution S.

Magnesium

Maximum 20 ppm.

To 5 mL of solution S add 5 mL of *water R*, 1 mL of *glycerol (85 per cent) R*, 0.15 mL of *titan yellow solution R*, 0.25 mL of *ammonium oxalate solution R* and 5 mL of *dilute sodium hydroxide solution R* and shake. Any pink colour in the test solution is not more intense than that in a standard prepared at the same time and in the same manner using a mixture of 1 mL of *magnesium standard solution (10 ppm Mg) R* and 9 mL of *water R*.

Sodium

Maximum 0.10 per cent.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Dissolve in *water R* 0.50 g of *sodium chloride R*, previously dried at 100-105 °C for 3 h, and dilute to 1000.0 mL with the same solvent (200 µg of Na per millilitre). Dilute as required.

Wavelength 589 nm.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 4 h.

ASSAY

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Pack 20 g of *strongly acidic ion-exchange resin R* into a glass column, at least 20 cm long and 20 mm in internal diameter, and cover it with *water R*. After 5 min, wash the resin with *water R* until the pH of the eluate is about 6 to 7 using a *pH indicator strip R*. Keep the resin covered with *water R*. Dissolve 0.600 g of the substance to be examined in 10 mL of *water R* in a beaker. Load the solution onto the column and pass through the resin at a flow rate of about 4 mL/min until the resin is just covered with the solution. Using about 200 mL of *water R*, rinse the beaker and pass the rinsings through the column at the same flow rate. Check that the pH of the last eluate is about 6 to 7 using a *pH indicator strip R*.

Titrate the eluate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 87.15 mg of K_2SO_4.

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Potato Starch[1]

General Notices

(Ph. Eur. monograph 0355)

Action and use

Excipient.

When Starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch or, in tropical countries where these are not available, Tapioca Starch may be supplied or used.

Ph Eur

DEFINITION

Potato starch is obtained from the tuber of *Solanum tuberosum* L.

♦ CHARACTERS

Appearance

Very fine, white or almost white powder which creaks when pressed between the fingers.

Solubility

Practically insoluble in cold water and in ethanol (96 per cent).

Potato starch does not contain starch granules of any other origin. It may contain a minute quantity, if any, of tissue fragments of the original plant.♦

IDENTIFICATION

A. Microscopic examination (*2.8.23*) using a 50 per cent *V/V* solution of *glycerol R*. It presents granules, either irregularly shaped, ovoid or pear-shaped, usually 30-100 µm in size but occasionally exceeding 100 µm, or rounded, 10-35 µm in size. There are occasional compound granules having 2-4 components (Figure 0355.-1). The ovoid and pear-shaped granules have an eccentric hilum and the rounded granules acentric or slightly eccentric hilum. All granules show clearly visible concentric striations. Between orthogonally orientated polarising plates or prisms, the granules show a distinct black cross intersecting at the hilum.

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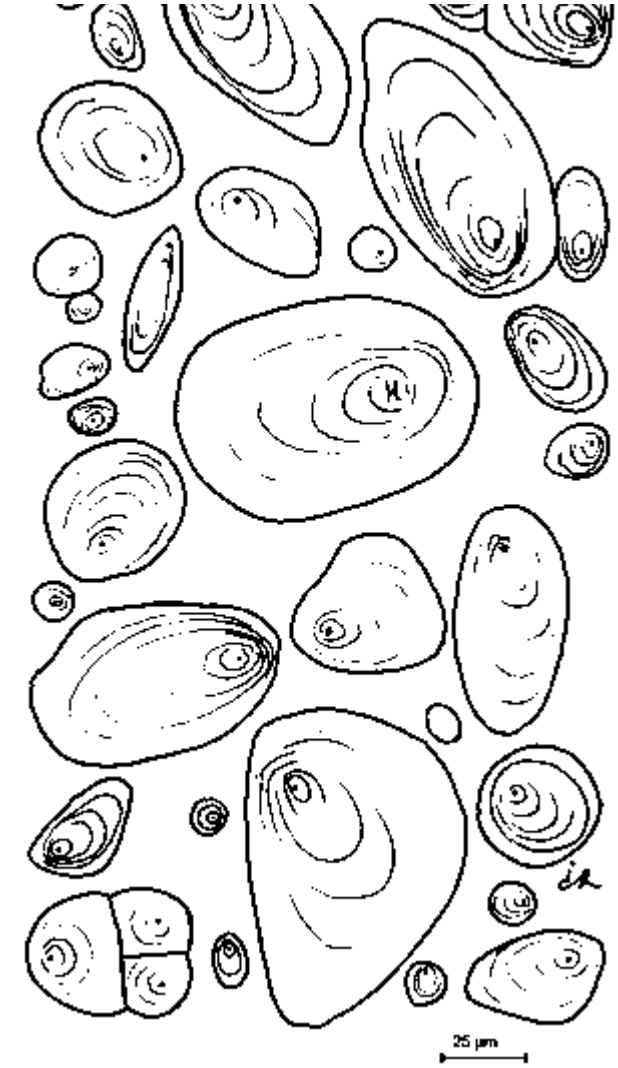

Figure 0355.-1. - *Illustration for identification test A of potato starch*

B. Suspend 1 g in 50 mL of *water R*, boil for 1 min and cool. A thick, opalescent mucilage is formed.

C. To 1 mL of the mucilage obtained in identification test B, add 0.05 mL of *iodine solution R1*. An orange-red to dark blue colour is produced which disappears on heating.

TESTS

pH (*2.2.3*)

5.0 to 8.0.

Shake 5.0 g with 25.0 mL of *carbon dioxide-free water R* for 60 s. Allow to stand for 15 min.

◊ Foreign matter

Examined under a microscope using a 50 per cent *V/V* solution of *glycerol R*, not more than traces of matter other than starch granules are present. No starch granules of any other origin are present.◊

Oxidising substances (*2.5.30*)

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Maximum 20 ppm, calculated as H_2O_2.

Sulfur dioxide (2.5.29)

Maximum 50 ppm.

Iron (2.4.9)

Maximum 10 ppm.

Shake 1.5 g with 15 mL of *dilute hydrochloric acid R*. Filter. The filtrate complies with the limit test for iron.

Loss on drying (2.2.32)

Maximum 20.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 90 min.

Sulfated ash (2.4.14)

Maximum 0.6 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

◊ Absence of *Salmonella* (2.6.13).◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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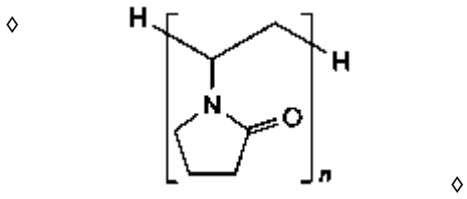
Povidone[1]

General Notices

(Ph. Eur. monograph 0685)



◊ $C_{6n}H_{9n+2}N_nO_n$◊ *9003-39-8*

Action and use

Disinfectant.

Preparations

Povidone-Iodine Eye Drops

Povidone-Iodine Mouthwash

Povidone-Iodine Solution

Ph Eur

DEFINITION

α-Hydro-ω-hydropoly[1-(2-oxopyrrolidin-1-yl)ethylene]. It consists of linear polymers of 1-ethenylpyrrolidin-2-one.

Content

11.5 per cent to 12.8 per cent of nitrogen (N; A_r 14.01) (anhydrous substance).

The different types of povidone are characterised by their viscosity in solution expressed as a nominal *K*-value. The nominal *K*-value is 10 to 120.

♦ CHARACTERS

Appearance

White or yellowish-white, hygroscopic powder or flakes.

Solubility

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Freely soluble in water, in ethanol (96 per cent) and in methanol, very slightly soluble in acetone.♦

IDENTIFICATION

First identification: A, D.

◊ *Second identification: B, C, D.*◊

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dry the substances beforehand at 105 °C for 6 h.

Comparison *povidone CRS*.

◊ B. To 1 mL of solution S1 (see Tests) add 0.2 mL of *dimethylaminobenzaldehyde solution R1* and 0.1 mL of *sulfuric acid R*. A pink colour is produced.

C. To 0.1 mL of solution S1 add 5 mL of *water R* and 0.2 mL of *0.05 M iodine*. A red colour is produced.◊

D. To 0.5 g add 10 mL of *water R* and shake. The substance dissolves.

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent. Add the substance to be examined to the water in small portions, stirring using a magnetic stirrer.

Solution S1

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent. Add the substance to be examined to the water in small portions, stirring using a magnetic stirrer.

♦ Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_6, BY_6 or R_6 (2.2.2, *Method II*).♦

pH (2.2.3)

3.0 to 5.0 for solution S, for povidone having a nominal *K*-value of not more than 30; 4.0 to 7.0 for solution S, for povidone having a nominal *K*-value of more than 30.

Viscosity, expressed as *K*-value

For povidone having a nominal value of 18 or less, use a 50.0 g/L solution. For povidone having a nominal value of more than 18 and not more than 95, use a 10.0 g/L solution. For povidone having a nominal value of more than 95, use a 1.0 g/L solution. Allow to stand for 1 h and determine the viscosity (2.2.9) of the solution at 25 °C, ◊ using a size no. 1 viscometer with a minimum flow time of 100 s◊ . Calculate the *K*-value using the following expression:

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$$\frac{1.5\log v_{rel} - 1}{0.15 + 0.003c} + \frac{\sqrt{300c\log v_{rel} + \left(c + 1.5c\log v_{rel}\right)^2}}{0.15c + 0.003c^2}$$

c = concentration of the substance to be examined (anhydrous substance), in grams per 100 mL;

v_{rel} = kinematic viscosity of the solution relative to that of *water R*.

The *K*-value of povidone having a nominal *K*-value of 15 or less is 85.0 per cent to 115.0 per cent of the nominal value.

The *K*-value of povidone having a nominal *K*-value of more than 15 is 90.0 per cent to 108.0 per cent of the nominal value.

Aldehydes

Maximum 500 ppm, expressed as acetaldehyde.

Test solution Dissolve a quantity of the substance to be examined equivalent to 1.0 g of anhydrous substance in *phosphate buffer solution pH 9.0 R* and dilute to 100.0 mL with the same solvent. Stopper the flask tightly and heat at 60 °C for 1 h. Allow to cool to room temperature.

Reference solution Dissolve 0.140 g of *acetaldehyde ammonia trimer trihydrate R* in *water R* and dilute to 200.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *phosphate buffer solution pH 9.0 R*.

Into 3 identical spectrophotometric cells with a path length of 1 cm, introduce separately 0.5 mL of the test solution, 0.5 mL of the reference solution and 0.5 mL of *water R* (blank). To each cell add 2.5 mL of *phosphate buffer solution pH 9.0 R* and 0.2 mL of *nicotinamide-adenine dinucleotide solution R*. Mix and stopper tightly. Allow to stand at 22 ± 2 °C for 2-3 min and measure the absorbance (*2.2.25*) of each solution at 340 nm, using *water R* as the compensation liquid. To each cell add 0.05 mL of *aldehyde dehydrogenase solution R*, mix and stopper tightly. Allow to stand at 22 ± 2 °C for 5 min. Measure the absorbance of each solution at 340 nm using *water R* as the compensation liquid.

Calculate the content of aldehydes using the following expression:

$$\frac{\left(A_{t2} - A_{t1}\right) - \left(A_{b2} - A_{b1}\right)}{\left(A_{s2} - A_{s1}\right) - \left(A_{b2} - A_{b1}\right)} \times \frac{100\,000 \times C}{m}$$

A_{t1} = absorbance of the test solution before the addition of aldehyde dehydrogenase;

A_{t2} = absorbance of the test solution after the addition of aldehyde dehydrogenase;

A_{s1} = absorbance of the reference solution before the addition of aldehyde dehydrogenase;

A_{s2} = absorbance of the reference solution after the addition of aldehyde dehydrogenase;

A_{b1} = absorbance of the blank before the addition of aldehyde dehydrogenase;

A_{b2} = absorbance of the blank after the addition of aldehyde dehydrogenase;

m = mass of the substance to be examined (anhydrous substance) in the test solution, in grams;

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C = concentration of acetaldehyde in the reference solution, calculated from the mass of *acetaldehyde ammonia trimer trihydrate R* with the factor 0.72, in milligrams per millilitre.

Peroxides

Maximum 400 ppm, expressed as H_2O_2.

Dissolve a quantity of the substance to be examined equivalent to 4.0 g of the anhydrous substance in *water R* and dilute to 100.0 mL with the same solvent (stock solution). To 25.0 mL of the stock solution add 2.0 mL of *titanium trichloride-sulfuric acid reagent R*. Allow to stand for 30 min. The absorbance (*2.2.25*) of the solution, measured at 405 nm using a mixture of 25.0 mL of the stock solution and 2.0 mL of a 13 per cent *V/V* solution of *sulfuric acid R* as the compensation liquid, is not greater than 0.35.

Formic acid

Liquid chromatography (*2.2.29*).

Test solution Dissolve a quantity of the substance to be examined equivalent to 2.0 g of the anhydrous substance in *water R* and dilute to 100.0 mL with the same solvent (stock solution). Transfer a suspension of *strongly acidic ion-exchange resin R* for column chromatography in *water R* to a column of about 0.8 cm in internal diameter to give a packing of about 20 mm in length and keep the strongly acidic ion-exchange resin layer constantly immersed in *water R*. Pour 5 mL of *water R* and adjust the flow rate to about 1 mL/min. When the level of the water comes down to near the top of the strongly acidic ion-exchange resin layer, introduce the stock solution into the column. Discard the first 2 mL of the eluate, then collect 1.5 mL of the solution and use this solution as the test solution.

Reference solution Dissolve 0.100 g of *anhydrous formic acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *strongly acidic ion-exchange resin R* for column chromatography (9 µm);

— *temperature*: 35 °C.

Mobile phase Dilute 1 mL of *perchloric acid R* to 700 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL.

Retention time Formic acid = about 8 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 2.0 per cent determined on 6 injections;

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— *number of theoretical plates*: minimum 1000;

— *symmetry factor*: 0.5 to 1.5.

Calculate the percentage content of formic acid using the following expression:

$$\frac{A_1}{A_2} \times \frac{M}{m}$$

A_1	=	area of the peak due to formic acid in the chromatogram obtained with the test solution;
A_2	=	area of the peak due to formic acid in the chromatogram obtained with the reference solution;
m	=	mass of the substance to be examined (anhydrous substance) in the test solution, in grams;
M	=	mass of *anhydrous formic acid R* in the reference solution, in grams.

Limit:

— *formic acid*: maximum 0.5 per cent.

Hydrazine

Thin-layer chromatography (2.2.27). *Use freshly prepared solutions.*

Test solution Dissolve a quantity of the substance to be examined equivalent to 2.5 g of the anhydrous substance in 25 mL of *water R*. Add 0.5 mL of a 50 g/L solution of *salicylaldehyde R* in *methanol R*, mix and heat in a water-bath at 60 °C for 15 min. Allow to cool, add 2.0 mL of *toluene R*, shake vigorously for 2 min and centrifuge. Use the upper layer.

Reference solution Dissolve 90 mg of *salicylaldehyde azine R* in *toluene R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *toluene R*.

Plate *TLC silanised silica gel F_{254} plate R*.

Mobile phase *water R*, *methanol R* (1:2 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 365 nm.

Retardation factor Salicylaldehyde azine = about 0.3.

Limit:

— *hydrazine*: any spot due to salicylaldehyde azine is not more intense than the spot in the chromatogram obtained with the reference solution (1 ppm).

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Impurity A

Liquid chromatography (2.2.29).

Test solution Dissolve a quantity of the substance to be examined equivalent to 0.250 g of the anhydrous substance in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *1-vinylpyrrolidin-2-one R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *1-vinylpyrrolidin-2-one R* (impurity A) and 0.5 g of *vinyl acetate R* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Precolumn:

— *size*: *l* = 0.010 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile for chromatography R*, *water for chromatography R* (10:90 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL; ◊ after each injection of the test solution, wait for about 2 min and wash the precolumn by passing the mobile phase through the column backwards for 30 min at the same flow rate as applied in the test.

Relative retention With reference to vinyl acetate (retention time = about 14 min): impurity A = about 0.6.◊

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity A and vinyl acetate in the chromatogram obtained with reference solution (b);

— *repeatability*: maximum relative standard deviation of 2.0 per cent determined on 6 injections of reference solution (a).

Calculate the content of impurity A in parts per million using the following expression:

$$\frac{A_1}{A_2} \times \frac{2.5}{m}$$

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A_1 = area of the peak due to impurity A in the chromatogram obtained with the test solution;

A_2 = area of the peak due to impurity A in the chromatogram obtained with reference solution (a);

m = mass of the substance to be examined (anhydrous substance) in the test solution, in grams.

Limit:

— *impurity A*: maximum 10 ppm.

Impurity B

Liquid chromatography (2.2.29).

Test solution Dissolve a quantity of the substance to be examined equivalent to 0.500 g of the anhydrous substance in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution Dissolve 0.150 g of *2-pyrrolidone R* (impurity B) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 100.0 mL with the mobile phase.

Precolumn:

— *size*: *l* = 0.010 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *methanol R2*, *water for chromatography R* (5:95 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 50 µL; ◊ after each injection of the test solution, wait for about 2 min and wash the precolumn by passing the mobile phase through the column backwards for about 30 min at the same flow rate as applied in the test.◊

Retention time Impurity B = about 7 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 2.0 per cent determined on 6 injections;

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— *number of theoretical plates*: minimum 5000.

Calculate the percentage content of impurity B using the following expression:

$$\frac{A_1}{A_2} \times \frac{0.3}{m}$$

A_1	=	area of the peak due to impurity B in the chromatogram obtained with the test solution;
A_2	=	area of the peak due to impurity B in the chromatogram obtained with the reference solution;
m	=	mass of the substance to be examined (anhydrous substance) in the test solution, in grams.

Limit:

— *impurity B*: maximum 3.0 per cent.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Place 0.100 g of the substance to be examined (*m* mg) in a combustion flask and add 5 g of a mixture of 1 g of *copper sulfate pentahydrate R*, 1 g of *titanium dioxide R* and 33 g of *dipotassium sulfate R*, and 3 glass beads. Wash any adhering particles from the neck into the flask with a small quantity of *water R*. Add 7 mL of *sulfuric acid R*, allowing it to run down the insides of the flask. Heat the flask gradually until the solution has a clear, yellowish-green colour, and the inside wall of the flask is free from any carbonised material, and then heat for a further 45 min. After cooling, add cautiously 20 mL of *water R*, and connect the flask to the distillation apparatus, which has been previously washed by passing steam through it. To the absorption flask add 30 mL of a 40 g/L solution of *boric acid R*, 3 drops of *bromocresol green-methyl red solution R* and sufficient water to immerse the lower end of the condenser tube. Add 30 mL of *strong sodium hydroxide solution R* through the funnel, rinse the funnel cautiously with 10 mL of *water R*, immediately close the clamp on the rubber tube, then start distillation with steam to obtain 80-100 mL of distillate. Remove the absorption flask from the lower end of the condenser tube, rinsing the end part with a small quantity of *water R*, and titrate the distillate with *0.025 M sulfuric acid* until the colour of the solution changes from green through pale greyish blue to pale greyish reddish-purple. Carry out a blank determination.

1 mL of *0.025 M sulfuric acid* is equivalent to 0.700 mg of N.

♦ STORAGE

In an airtight container.♦

LABELLING

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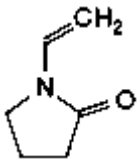
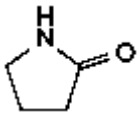
The label states the nominal *K*-value.

IMPURITIES



A. 1-ethenylpyrrolidin-2-one (1-vinylpyrrolidin-2-one),



B. pyrrolidin-2-one (2-pyrrolidone).

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for povidone used as solubiliser and stabiliser in liquid dosage forms.

Viscosity (2.2.9)

Determine the dynamic viscosity using a capillary viscometer on a 10 per cent solution (dried substance) at 25 °C. Typical values are shown in Table 0685.-1.

Molecular mass

(see Viscosity, expressed as *K*-value). Typical values are shown in Table 0685.-1.

The following characteristic may be relevant for povidone used as binder in tablets and granules.

Molecular mass

(see Viscosity, expressed as *K*-value). Typical values are shown in Table 0685.-1.

Table 0685.-1. – *Typical viscosity ranges and ranges for viscosity, expressed as K-value*

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	Viscosity range (mPa·s)	Molecular mass: viscosity, expressed as *K*-value
Povidone K 12	1.3-2.3	11-14
Povidone K 17	1.5-3.5	16-18
Povidone K 25	3.5-5.5	24-27
Povidone K 30	5.5-8.5	28-32
Povidone K 90	300-700	85-95

◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Povidone-Iodine Eye Drops

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Antiseptic.

DEFINITION

Povidone-Iodine Eye Drops are either a sterile solution of Iodinated Povidone in Purified Water or they are prepared by the interaction between Iodine and Povidone in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of available iodine, I

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear brown solution.

IDENTIFICATION

A. Dilute 1 mL to 10 mL with *water* and add 1 mL of the resulting solution to a mixture of 1 mL of *starch mucilage* and 9 mL of *water*. A deep blue colour is produced.

B. Transfer 20 mL to a small flask and cover the mouth of the flask with filter paper moistened with 0.05 mL of *starch mucilage*. No blue colour is produced on the paper within 60 seconds.

C. Dilute 4 mL to 10 mL with *water* and add, drop wise, 0.1M *sodium thiosulfate* until the colour of the iodine is just discharged. Reserve 5 mL of the resulting solution for test D. To 5 mL of the solution add 10 mL of 1M *hydrochloric acid* and 5 mL of a 7.0% w/v solution of *potassium dichromate*. A red precipitate is produced.

D. To 5 mL of the solution reserved in test C add 2 mL of *ammonium cobaltothiocyanate solution* previously acidified with 5M *hydrochloric acid*. A blue precipitate is produced.

TESTS

Acidity

pH, 3.5 to 6.5, Appendix V L.

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Iodide

Not more than 0.6% w/v, when determined by the following method. Dilute 10 mL of the preparation being examined to 100 mL with *water* and add *sodium metabisulfite* until the colour of iodine has disappeared. Add 25 mL of *0.1M silver nitrate VS*, 10 mL of *nitric acid* and 5 mL of *ferric ammonium sulfate solution R2*. Titrate with *0.1M ammonium thiocyanate VS*. Repeat the procedure without the preparation being examined. Each mL of *0.1M silver nitrate VS* is equivalent to 12.69 mg of total iodine. Calculate the percentage content of total iodine and subtract the percentage content of available iodine, determined in the Assay, to obtain the percentage content of iodide.

ASSAY

To 5 mL add 10 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 30 mL. Titrate immediately with 0.01M *sodium thiosulfate VS*, determining the end point potentiometrically. Each mL of 0.01M *sodium thiosulfate VS* is equivalent to 1.269 mg of I.

STORAGE

Povidone-Iodine Eye Drops should be protected from light.

LABELLING

The strength is stated as the percentage w/v of Iodinated Povidone.

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Povidone-Iodine Mouthwash

General Notices

Action and use

Disinfectant.

DEFINITION

Povidone-Iodine Mouthwash is either an aqueous solution of Iodinated Povidone or it is prepared by the interaction between Iodine and Povidone.

The mouthwash complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of available iodine, I

0.085 to 0.120% w/v.

CHARACTERISTICS

A yellowish-brown solution.

IDENTIFICATION

A. Dilute 1 mL to 2 mL with *water* and add 1 mL of the resulting solution to a mixture of 1 mL of *starch mucilage* and 9 mL of *water*. A deep blue colour is produced.

B. Transfer 10 mL to a small flask and cover the mouth of the flask with filter paper moistened with 0.05 mL of *starch mucilage*. No blue colour is produced on the paper within 60 seconds.

C. To 10 mL add drop wise 0.1M *sodium thiosulfate* until the colour of the iodine is just discharged. Reserve 5 mL of the resulting solution for test D. To 5 mL of the solution add 10 mL of 1M *hydrochloric acid* and 5 mL of a 7.0% w/v solution of *potassium dichromate*. A red precipitate is produced.

D. To 5 mL of the solution reserved in test C add 2 mL of *ammonium cobaltothiocyanate solution* previously acidified with 5M *hydrochloric acid*. A blue precipitate is produced.

TESTS

Acidity

pH, 3.0 to 6.5, Appendix V L.

Iodide

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Not more than 0.06% w/v when determined by the following method. To 50 mL of the mouthwash add *sodium metabisulfite* until the colour of iodine has disappeared. Add 25 mL of *0.1M silver nitrate VS*, 10 mL of *nitric acid* and 5 mL of *ferric ammonium sulfate solution R2*. Titrate with *0.1M ammonium thiocyanate VS*. Repeat the procedure without the solution being examined. Each mL of *0.1M silver nitrate VS* is equivalent to 12.69 mg of total iodine. Calculate the percentage content of total iodine and subtract the percentage content of available iodine determined in the Assay to obtain the percentage content of iodide.

ASSAY

To 100 mL add 10 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 150 mL and titrate with 0.1M *sodium thiosulfate VS* determining the end point potentiometrically. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 12.690 mg of I.

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Povidone-Iodine Solution

General Notices

Povidone-Iodine Cutaneous Solution

Action and use

Disinfectant.

DEFINITION

Povidone-Iodine Solution is either an aqueous solution of Iodinated Povidone or it is prepared by the interaction between Iodine and Povidone. It is a *cutaneous solution*.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of available iodine, I

0.85 to 1.20% w/v.

CHARACTERISTICS

A deep brown liquid.

IDENTIFICATION

A. Dilute 1 mL to 20 mL with *water* and add 1 mL of the resulting solution to a mixture of 1 mL of *starch mucilage* and 9 mL of *water*. A deep blue colour is produced.

B. Transfer 10 mL to a small flask and cover the mouth of the flask with filter paper moistened with 0.05 mL of *starch mucilage*. No blue colour is produced on the paper within 60 seconds.

C. Dilute 20 mL to 100 mL with *water*. To 10 mL add drop wise 0.1M *sodium thiosulfate* until the colour of the iodine is just discharged. Reserve 5 mL of the resulting solution for test D. To 5 mL of the solution add 10 mL of 1M *hydrochloric acid* and 5 mL of a 7.0% w/v solution of *potassium dichromate*. A red precipitate is produced.

D. To 5 mL of the solution reserved in test C add 2 mL of *ammonium cobaltothiocyanate solution* previously acidified with 5M *hydrochloric acid*. A blue precipitate is produced.

TESTS

Acidity

pH, 3.0 to 6.5, Appendix V L.

Iodide

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Not more than 0.6% w/v when determined by the following method. Dilute 5 mL of the solution being examined to 100 mL with *water* and add *sodium metabisulfite* until the colour of iodine has disappeared. Add 25 mL of *0.1M silver nitrate VS*, 10 mL of *nitric acid* and 5 mL of *ferric ammonium sulfate solution R2*. Titrate with *0.1M ammonium thiocyanate VS*. Repeat the procedure without the solution being examined. Each mL of *0.1M silver nitrate VS* is equivalent to 12.69 mg of total iodine. Calculate the percentage content of total iodine and subtract the percentage content of available iodine determined in the Assay to obtain the percentage content of iodide.

ASSAY

To 10 mL add 10 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 150 mL and titrate with 0.02M *sodium thiosulfate VS* determining the end point potentiometrically. Each mL of 0.02M *sodium thiosulfate VS* is equivalent to 2.538 mg of I.

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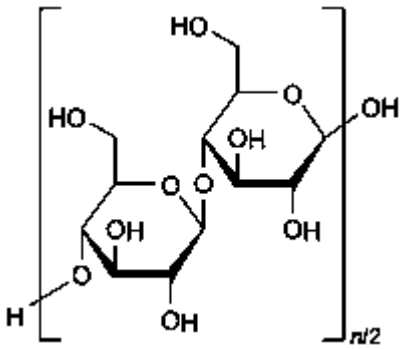
Powdered Cellulose[1]

General Notices

(Ph. Eur. monograph 0315)



$C_{6n}H_{10n+2}O_{5n+1}$

Cellulose *9004-34-6*

Action and use

Excipient.

Ph Eur

DEFINITION

Purified, mechanically disintegrated cellulose prepared by processing alpha-cellulose obtained as a pulp from fibrous plant material.

♦ CHARACTERS

Appearance

White or almost white, fine or granular powder.

Solubility

Practically insoluble in water, slightly soluble in a 50 g/L solution of sodium hydroxide, practically insoluble in acetone, in anhydrous ethanol, in toluene, in dilute acids and in most organic solvents.♦

IDENTIFICATION

A. Processing math: 100% on a watch-glass and disperse in 2 mL of *iodinated zinc chloride solution R*. The substance becomes violet-blue.

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B. The degree of polymerisation is greater than 440.

Transfer 0.250 g to a 125 mL conical flask. Add 25.0 mL of *water R* and 25.0 mL of *cupriethylenediamine hydroxide solution R*. Immediately purge the solution with *nitrogen R*, insert the stopper and shake until completely dissolved. Transfer an appropriate volume of the solution to a suitable capillary viscometer (2.2.9). Equilibrate the solution at 25 ± 0.1 °C for at least 5 min. Record the flow time (t_1) in seconds between the 2 marks on the viscometer. Calculate the kinematic viscosity (v_1) of the solution using the following expression:

$$t_1\left(k_1\right)$$

k_1 = viscometer constant.

Dilute a suitable volume of *cupriethylenediamine hydroxide solution R* with an equal volume of *water R* and measure the flow time (t_2) using a suitable capillary viscometer. Calculate the kinematic viscosity (v_2) of the solvent using the following expression:

$$t_2\left(k_2\right)$$

k_2 = viscometer constant.

Determine the relative viscosity (η_{rel}) of the substance to be examined using the following expression:

$$v_1 / v_2$$

Determine the intrinsic viscosity ($[\eta]_c$) by interpolation, using the intrinsic viscosity table (Table 0315.-1).

Calculate the degree of polymerisation (P) using the following expression:

$$\frac{95[\eta]_c}{m[(100-b)/100]}$$

m = mass of the substance to be examined, in grams;

b = loss on drying, in per cent.

TESTS

◊ Solubility

Dissolve 50 mg in 10 mL of *ammoniacal solution of copper tetrammine R*. It dissolves completely, leaving no residue.◊

pH (2.2.3)

5.0 to 7.5 for the supernatant.

Mix 10 g with 90 mL of *carbon dioxide-free water R* and allow to stand with occasional stirring for 1 h.

Ether-soluble substances

M Processing math: 100% (15.0 mg) for the difference between the mass of the residue and the mass obtained from a blank determination.

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Place 10.0 g in a chromatography column about 20 mm in internal diameter and pass 50 mL of *peroxide-free ether R* through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish, with the aid of a current of air in a fume cupboard. After all the ether has evaporated, dry the residue at 105 °C for 30 min, allow to cool in a desiccator and weigh. Carry out a blank determination.

Water-soluble substances

Maximum 1.5 per cent (15.0 mg) for the difference between the mass of the residue and the mass obtained from a blank determination.

Shake 6.0 g with 90 mL of *carbon dioxide-free water R* for 10 min. Filter with the aid of vacuum into a tared flask. Discard the first 10 mL of the filtrate and pass the filtrate through the same filter a second time, if necessary, to obtain a clear filtrate. Evaporate a 15.0 mL portion of the filtrate to dryness in a tared evaporating dish without charring. Dry at 105 °C for 1 h, allow to cool in a desiccator and weigh. Carry out a blank determination.

Loss on drying (*2.2.32*)

Maximum 6.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.3 per cent (dried substance), determined on 1.0 g.

♦ Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Pseudomonas aeruginosa* (*2.6.13*).

Absence of *Staphylococcus aureus* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).♦

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

Th Processing math: 100% *stics may be relevant for powdered cellulose used as diluent or disintegrant.*

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Loss on drying

(see Tests).

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

◊

Table 0315.-1. – *Intrinsic viscosity table*

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}										
	$[\eta]_c$									
η_{rel}	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
1.1	0.098	0.106	0.115	0.125	0.134	0.143	0.152	0.161	0.170	0.180
1.2	0.189	0.198	0.207	0.216	0.225	0.233	0.242	0.250	0.259	0.268
1.3	0.276	0.285	0.293	0.302	0.310	0.318	0.326	0.334	0.342	0.350
1.4	0.358	0.367	0.375	0.383	0.391	0.399	0.407	0.414	0.422	0.430
1.5	0.437	0.445	0.453	0.460	0.468	0.476	0.484	0.491	0.499	0.507
1.6	0.515	0.522	0.529	0.536	0.544	0.551	0.558	0.566	0.573	0.580
1.7	0.587	0.595	0.602	0.608	0.615	0.622	0.629	0.636	0.642	0.649
1.8	0.656	0.663	0.670	0.677	0.683	0.690	0.697	0.704	0.710	0.717
1.9	0.723	0.730	0.736	0.743	0.749	0.756	0.762	0.769	0.775	0.782
2.0	0.788	0.795	0.802	0.809	0.815	0.821	0.827	0.833	0.840	0.846
2.1	0.852	0.858	0.864	0.870	0.876	0.882	0.888	0.894	0.900	0.906
2.2	0.912	0.918	0.924	0.929	0.935	0.941	0.948	0.953	0.959	0.965
2.3	0.971	0.976	0.983	0.988	0.994	1.000	1.006	1.011	1.017	1.022
2.4	1.028	1.033	1.039	1.044	1.050	1.056	1.061	1.067	1.072	1.078
2.5	1.083	1.089	1.094	1.100	1.105	1.111	1.116	1.121	1.126	1.131
		1.142	1.147	1.153	1.158	1.163	1.169	1.174	1.179	1.184

Processing math: 100%

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
2.7	1.190	1.195	1.200	1.205	1.210	1.215	1.220	1.225	1.230	1.235
2.8	1.240	1.245	1.250	1.255	1.260	1.265	1.270	1.275	1.280	1.285
2.9	1.290	1.295	1.300	1.305	1.310	1.314	1.319	1.324	1.329	1.333
3.0	1.338	1.343	1.348	1.352	1.357	1.362	1.367	1.371	1.376	1.381
3.1	1.386	1.390	1.395	1.400	1.405	1.409	1.414	1.418	1.423	1.427
3.2	1.432	1.436	1.441	1.446	1.450	1.455	1.459	1.464	1.468	1.473
3.3	1.477	1.482	1.486	1.491	1.496	1.500	1.504	1.508	1.513	1.517
3.4	1.521	1.525	1.529	1.533	1.537	1.542	1.546	1.550	1.554	1.558
3.5	1.562	1.566	1.570	1.575	1.579	1.583	1.587	1.591	1.595	1.600
3.6	1.604	1.608	1.612	1.617	1.621	1.625	1.629	1.633	1.637	1.642
3.7	1.646	1.650	1.654	1.658	1.662	1.666	1.671	1.675	1.679	1.683
3.8	1.687	1.691	1.695	1.700	1.704	1.708	1.712	1.715	1.719	1.723
3.9	1.727	1.731	1.735	1.739	1.742	1.746	1.750	1.754	1.758	1.762
4.0	1.765	1.769	1.773	1.777	1.781	1.785	1.789	1.792	1.796	1.800
4.1	1.804	1.808	1.811	1.815	1.819	1.822	1.826	1.830	1.833	1.837
4.2	1.841	1.845	1.848	1.852	1.856	1.859	1.863	1.867	1.870	1.874
4.3	1.878	1.882	1.885	1.889	1.893	1.896	1.900	1.904	1.907	1.911
4.4	1.914	1.918	1.921	1.925	1.929	1.932	1.936	1.939	1.943	1.946
4.5	1.950	1.954	1.957	1.961	1.964	1.968	1.971	1.975	1.979	1.982
4.6	1.986	1.989	1.993	1.996	2.000	2.003	2.007	2.010	2.013	2.017
4.7	2.020	2.023	2.027	2.030	2.033	2.037	2.040	2.043	2.047	2.050
4.8	2.053	2.057	2.060	2.063	2.067	2.070	2.073	2.077	2.080	2.083
Processing math: 100%		2.090	2.093	2.097	2.100	2.103	2.107	2.110	2.113	2.116

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
5.0	2.119	2.122	2.125	2.129	2.132	2.135	2.139	2.142	2.145	2.148
5.1	2.151	2.154	2.158	2.160	2.164	2.167	2.170	2.173	2.176	2.180
5.2	2.183	2.186	2.190	2.192	2.195	2.197	2.200	2.203	2.206	2.209
5.3	2.212	2.215	2.218	2.221	2.224	2.227	2.230	2.233	2.236	2.240
5.4	2.243	2.246	2.249	2.252	2.255	2.258	2.261	2.264	2.267	2.270
5.5	2.273	2.276	2.279	2.282	2.285	2.288	2.291	2.294	2.297	2.300
5.6	2.303	2.306	2.309	2.312	2.315	2.318	2.320	2.324	2.326	2.329
5.7	2.332	2.335	2.338	2.341	2.344	2.347	2.350	2.353	2.355	2.358
5.8	2.361	2.364	2.367	2.370	2.373	2.376	2.379	2.382	2.384	2.387
5.9	2.390	2.393	2.396	2.400	2.403	2.405	2.408	2.411	2.414	2.417
6.0	2.419	2.422	2.425	2.428	2.431	2.433	2.436	2.439	2.442	2.444
6.1	2.447	2.450	2.453	2.456	2.458	2.461	2.464	2.467	2.470	2.472
6.2	2.475	2.478	2.481	2.483	2.486	2.489	2.492	2.494	2.497	2.500
6.3	2.503	2.505	2.508	2.511	2.513	2.516	2.518	2.521	2.524	2.526
6.4	2.529	2.532	2.534	2.537	2.540	2.542	2.545	2.547	2.550	2.553
6.5	2.555	2.558	2.561	2.563	2.566	2.568	2.571	2.574	2.576	2.579
6.6	2.581	2.584	2.587	2.590	2.592	2.595	2.597	2.600	2.603	2.605
6.7	2.608	2.610	2.613	2.615	2.618	2.620	2.623	2.625	2.627	2.630
6.8	2.633	2.635	2.637	2.640	2.643	2.645	2.648	2.650	2.653	2.655
6.9	2.658	2.660	2.663	2.665	2.668	2.670	2.673	2.675	2.678	2.680
7.0	2.683	2.685	2.687	2.690	2.693	2.695	2.698	2.700	2.702	2.705
Processing math: 100%		2.710	2.712	2.714	2.717	2.719	2.721	2.724	2.726	2.729

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
7.2	2.731	2.733	2.736	2.738	2.740	2.743	2.745	2.748	2.750	2.752
7.3	2.755	2.757	2.760	2.762	2.764	2.767	2.769	2.771	2.774	2.776
7.4	2.779	2.781	2.783	2.786	2.788	2.790	2.793	2.795	2.798	2.800
7.5	2.802	2.805	2.807	2.809	2.812	2.814	2.816	2.819	2.821	2.823
7.6	2.826	2.828	2.830	2.833	2.835	2.837	2.840	2.842	2.844	2.847
7.7	2.849	2.851	2.854	2.856	2.858	2.860	2.863	2.865	2.868	2.870
7.8	2.873	2.875	2.877	2.879	2.881	2.884	2.887	2.889	2.891	2.893
7.9	2.895	2.898	2.900	2.902	2.905	2.907	2.909	2.911	2.913	2.915
8.0	2.918	2.920	2.922	2.924	2.926	2.928	2.931	2.933	2.935	2.937
8.1	2.939	2.942	2.944	2.946	2.948	2.950	2.952	2.955	2.957	2.959
8.2	2.961	2.963	2.966	2.968	2.970	2.972	2.974	2.976	2.979	2.981
8.3	2.983	2.985	2.987	2.990	2.992	2.994	2.996	2.998	3.000	3.002
8.4	3.004	3.006	3.008	3.010	3.012	3.015	3.017	3.019	3.021	3.023
8.5	3.025	3.027	3.029	3.031	3.033	3.035	3.037	3.040	3.042	3.044
8.6	3.046	3.048	3.050	3.052	3.054	3.056	3.058	3.060	3.062	3.064
8.7	3.067	3.069	3.071	3.073	3.075	3.077	3.079	3.081	3.083	3.085
8.8	3.087	3.089	3.092	3.094	3.096	3.098	3.100	3.102	3.104	3.106
8.9	3.108	3.110	3.112	3.114	3.116	3.118	3.120	3.122	3.124	3.126
9.0	3.128	3.130	3.132	3.134	3.136	3.138	3.140	3.142	3.144	3.146
9.1	3.148	3.150	3.152	3.154	3.156	3.158	3.160	3.162	3.164	3.166
9.2	3.168	3.170	3.172	3.174	3.176	3.178	3.180	3.182	3.184	3.186
9.3	3.188	3.190	3.192	3.194	3.196	3.198	3.200	3.202	3.204	3.206
Processing math: 100%		3.210	3.212	3.214	3.215	3.217	3.219	3.221	3.223	3.225

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Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.00**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**
9.5	3.227	3.229	3.231	3.233	3.235	3.237	3.239	3.241	3.242	3.244
9.6	3.246	3.248	3.250	3.252	3.254	3.256	3.258	3.260	3.262	3.264
9.7	3.266	3.268	3.269	3.271	3.273	3.275	3.277	3.279	3.281	3.283
9.8	3.285	3.287	3.289	3.291	3.293	3.295	3.297	3.298	3.300	3.302
9.9	3.304	3.305	3.307	3.309	3.311	3.313	3.316	3.318	3.320	3.321

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	**0.0**	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
10	3.32	3.34	3.36	3.37	3.39	3.41	3.43	3.45	3.46	3.48
11	3.50	3.52	3.53	3.55	3.56	3.58	3.60	3.61	3.63	3.64
12	3.66	3.68	3.69	3.71	3.72	3.74	3.76	3.77	3.79	3.80
13	3.80	3.83	3.85	3.86	3.88	3.89	3.90	3.92	3.93	3.95
14	3.96	3.97	3.99	4.00	4.02	4.03	4.04	4.06	4.07	4.09
15	4.10	4.11	4.13	4.14	4.15	4.17	4.18	4.19	4.20	4.22
16	4.23	4.24	4.25	4.27	4.28	4.29	4.30	4.31	4.33	4.34
17	4.35	4.36	4.37	4.38	4.39	4.41	4.42	4.43	4.44	4.45
18	4.46	4.47	4.48	4.49	4.50	4.52	4.53	4.54	4.55	4.56
19	4.57	4.58	4.59	4.60	4.61	4.62	4.63	4.64	4.65	4.66

Ph Eur

[1] This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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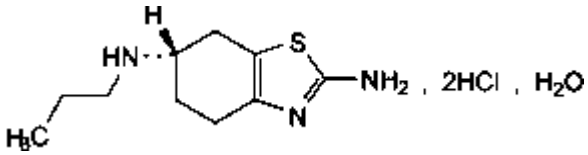
Pramipexole Dihydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 2416)



$C_{10}H_{19}Cl_2N_3S,H_2O$ 302.3 *191217-81-9*

Action and use

Dopamine receptor agonist; treatment of Parkinson's disease.

Preparations

Pramipexole Tablets

Pramipexole Prolonged-release Tablets

Ph Eur

DEFINITION

(6*S*)-6-*N*-Propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine dihydrochloride monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in methanol, sparingly soluble or slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

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Carry out either tests B, C, D or tests A, B, D.

A. Specific optical rotation (2.2.7): -69.5 to -67.0 (anhydrous substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *pramipexole dihydrochloride monohydrate CRS*.

C. Enantiomeric purity (see Tests).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 0.1 g in *water R* and dilute to 10 mL with the same solvent.

pH (2.2.3)

2.8 to 3.4.

Dissolve 0.4 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 5 g of *sodium octanesulfonate monohydrate R* and 9.1 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*. Adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Solvent mixture *acetonitrile R*, buffer solution (20:80 *V/V*).

Test solution Dissolve 75 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 7.5 mg of *pramipexole for system suitability CRS* (containing impurities A, B and C) in 5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

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— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: buffer solution;

— *mobile phase B*: acetonitrile R, buffer solution (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	60 → 20	40 → 80

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 264 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with pramipexole for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to pramipexole (retention time = about 6 min): impurity A = about 0.7; impurity B = about 1.5; impurity C = about 1.7.

System suitability Reference solution (b):

— resolution: minimum 6.0 between the peaks due to impurity A and pramipexole.

Limits:

— *impurities A, B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 6 mg of the substance to be examined in 5 mL of anhydrous ethanol R and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of pramipexole impurity D CRS in the mobile phase and dilute to 10 mL with the mobile phase. To 1 mL of this solution add 1 mL of the test solution and dilute to 20 mL with the mobile phase.

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Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R*.

Mobile phase *diethylamine R*, *anhydrous ethanol R*, *hexane R* (0.1:15:85 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 75 µL.

Run time 1.5 times the retention time of pramipexole.

Relative retention With reference to pramipexole (retention time = about 11 min): impurity D = about 0.5.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to impurity D and pramipexole in the chromatogram obtained with reference solution (a);

— *symmetry factor*: maximum 2.4 for the peak due to pramipexole in the chromatogram obtained with reference solution (b).

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent).

Water (2.5.12)

5.0 per cent to 7.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.120 g in 150 mL of *water R*. Add 10 mL of *dilute nitric acid R2* and titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 14.213 mg of $C_{10}H_{19}Cl_2N_3S$.

IMPURITIES

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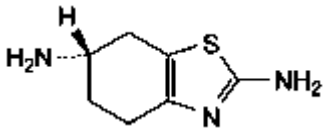
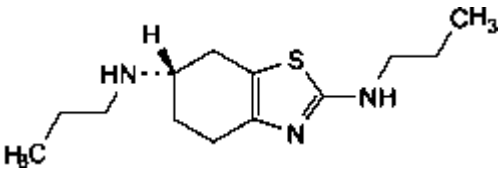
Specified impurities *A, B, C, D.*

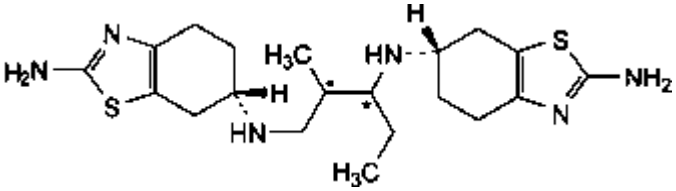
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E.*



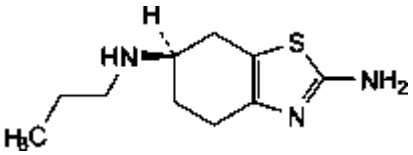
A. (6*S*)-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



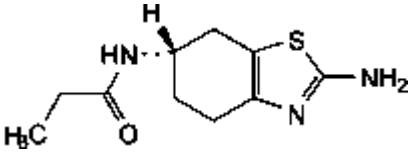
B. (6*S*)-*N*,*N*′-dipropyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



C. mixture of diastereoisomers of (6*S*)-6-*N*-[3-[[(6*S*)-2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl]amino]-1-ethyl-2-methylpropyl]-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



D. (6*R*)-6-*N*-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



E. *N*-[(6*S*)-2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl]propanamide.

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Pramipexole Prolonged-release Tablets

General Notices

Prolonged-release Pramipexole Tablets

Pramipexole Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Dopamine receptor agonist; treatment of Parkinson's disease.

DEFINITION

Pramipexole Prolonged-release Tablets contain Pramipexole Dihydrochloride Monohydrate.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of pramipexole. The dissolution profile reflects the *in vivo* performance, which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pramipexole, $C_{10}H_{17}N_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 1 mg of pramipexole in 10 mL of *methanol* and filter. Use the filtrate.

(2) 0.01% w/v of *pramipexole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *methanol*, 6 volumes of *ammonia*, 15 volumes of *toluene* and 80 volumes of *ethyl acetate*.

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CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, size and colour to that in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to pramipexole in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 40 volumes of methanol and 60 volumes of mobile phase A.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.26 mg of pramipexole with 10 mL of solution A. To 4 mL of this solution add sufficient solution A to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with solution A.
(3) 0.00375% w/v of *pramipexole for system suitability EPCRS* in solution A.
(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 264 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 5 g of *sodium octanesulfonate monohydrate* and 9.1 g of *potassium dihydrogen orthophosphate* in 900 mL of *water*. Adjust to pH 3.0 with *orthophosphoric acid* and dilute to 1000 mL with *water*.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of mobile phase A.

When the chromatograms are recorded under the prescribed conditions the retention times relative to pramipexole (retention time about 7.24 minutes) are: impurity A, about 0.7; impurity B, about 1.5 and impurity C, about 1.6.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	60	40	isocratic
1-16	60→20	40→80	linear gradient
16-20	20	80	isocratic
20-22	20→60	80→40	linear gradient
22-35	60	40	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pramipexole is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of pramipexole comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A, as described under Related substances.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.26 mg of pramipexole with 100mL solution A with the aid of ultrasound. Extract 10 mL, filter and dilute the filtrate, if necessary, to produce a solution containing the equivalent of 0.00013% w/v of pramipexole.

(2) 0.00013% w/v of *pramipexole BPCRS*.

(3) 0.0003% w/v of *pramipexole BPCRS* and 0.0003% w/v of *pramipexole impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

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(e) Use a detection wavelength of 264 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of mobile phase A, as described under Related substances.

When the chromatograms are recorded under the prescribed conditions the retention times for pramipexole and impurity A are about 4 minutes and 3 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pramipexole is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{17}N_3S$ in each tablet using the declared content of $C_{10}H_{17}N_3S$ in *pramipexole BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of pramipexole

Use the average of the individual results obtained in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w of pramipexole

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A, as described under Related substances.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.26 mg of pramipexole with 100 mL solution A with the aid if ultrasound. Extract 10 mL, filter and dilute the filtrate, if necessary, to produce a solution containing the equivalent of 0.00013% w/v of pramipexole.

(2) 0.00013% w/v of *pramipexole BPCRS*.

(3) 0.0003% w/v of *pramipexole BPCRS* and 0.0003% w/v of *pramipexole impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pramipexole is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{17}N_3S$ in the tablets using the declared content of $C_{10}H_{17}N_3S$ in *pramipexole BPCRS*.

IMPURITIES

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The impurities limited by the requirements of this monograph include impurities A, B and C listed under Pramipexole Dihydrochloride Monohydrate.

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Pramipexole Tablets

General Notices

Action and use

Dopamine receptor agonist; treatment of Parkinson's disease.

DEFINITION

Pramipexole Tablets contain Pramipexole Dihydrochloride Monohydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pramipexole, $C_{10}H_{17}N_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 1 mg of pramipexole in 10 mL of *methanol* for 60 minutes and filter.

(2) 0.01% w/v of *pramipexole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *methanol*, 6 volumes of 18M *ammonia*, 15 volumes of *toluene* and 80 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, size and colour to that in the chromatogram obtained with solution (2).

B. In Uniformity of content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to pramipexole in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the medium.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *0.1M hydrochloric acid* if necessary, expected to contain the equivalent of 0.000018% w/v of pramipexole.

(2) 0.000018% w/v of *pramipexole BPCRS*.

(3) 0.0003% w/v of *pramipexole BPCRS* and 0.0003% w/v of *pramipexole impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 264 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of mobile phase A (as described under Related substances).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pramipexole is at least 6.0.

DETERMINATION OF CONTENT

Calculate the total content of pramipexole in the medium using the chromatograms obtained and the declared content of $C_{10}H_{17}N_3S$ in *pramipexole BPCRS*.

LIMITS

The amount of pramipexole released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 20 volumes of *acetonitrile* and 80 volumes of mobile phase A.

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(1) Shake a quantity of powdered tablets containing the equivalent of 1.5 mg of pramipexole with 7 mL of solution A, add sufficient solution A to produce 10 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with solution A.

(3) 0.015% w/v of *pramipexole for system suitability EPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 264 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 5 g of *sodium octanesulfonate monohydrate* and 9.1 g of *potassium dihydrogen orthophosphate* in 900 mL of *water*. Adjust to pH 3.0 with *orthophosphoric acid* and dilute to 1000 mL with *water*.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of mobile phase A.

When the chromatograms are recorded under the prescribed conditions the retention times relative to pramipexole (retention time about 6.5 minutes) are: impurity A, about 0.7; impurity B, about 1.5 and impurity C, about 1.7.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	60	40	isocratic
1-16	60→20	40→80	linear gradient
16-20	20	80	isocratic
20-22	20→60	80→40	linear gradient
22-35	60	40	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pramipexole is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of pramipexole comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A, as described under Related substances.

(1) Mix with the aid of ultrasound one tablet with 7 mL of solution A, dilute to 10 mL with solution A and filter. Dilute the filtrate, if necessary, to produce a solution containing the equivalent of 0.00088% w/v of pramipexole.
(2) 0.00088% w/v of *pramipexole BPCRS*.
(3) 0.0003% w/v of *pramipexole BPCRS* and 0.0003% w/v of *pramipexole impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 20 µL.

When the chromatograms are recorded under the prescribed conditions, the retention times for pramipexole and impurity A are about 3 minutes and 2 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pramipexole is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{17}N_3S$ in each tablet using the declared content of $C_{10}H_{17}N_3S$ in *pramipexole BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of pramipexole

Use the average of the individual results obtained in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w of pramipexole

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A, as described under Related substances.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.88 mg of pramipexole with 70 mL of solution A, dilute to 100 mL with solution A and filter.
(2) 0.00088% w/v of *pramipexole BPCRS*.
(3) 0.0003% w/v of *pramipexole for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Dissolution may be used with an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pramipexole is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{17}N_3S$ in the tablets using the declared content of $C_{10}H_{17}N_3S$ in *pramipexole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Pramipexole Dihydrochloride Monohydrate.

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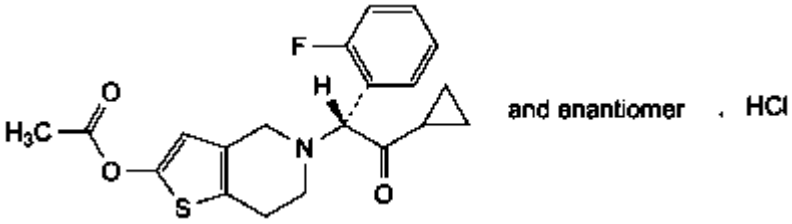
Prasugrel Hydrochloride

General Notices

(Ph. Eur. monograph 3040)



$C_{20}H_{21}ClFNO_3S$ 409.9 *389574-19-0*

Action and use

Inhibitor of ADP-mediated platelet aggregation.

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DEFINITION

5-[(1*RS*)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder.

Solubility

Slightly soluble in water, freely soluble in methanol, slightly soluble in acetonitrile, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *prasugrel hydrochloride CRS*.

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B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture water R, acetonitrile R (30:70 *V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dilute 2.0 mL of test solution (a) to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of prasugrel hydrochloride CRS in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 2.0 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2.5 mg of prasugrel for system suitability CRS (containing impurities B and E) in the solvent mixture and dilute to 2 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase Mix 35 volumes of acetonitrile R1 and 65 volumes of a 1.36 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 2.8 with phosphoric acid R.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 5 °C.

Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Run time 3.6 times the retention time of prasugrel.

Identification of impurities Use the chromatogram supplied with prasugrel for system suitability CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B and E.

Relative retention With reference to prasugrel (retention time = about 11 min): impurity B = about 1.1; impurity E = about 2.3.

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System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to prasugrel and impurity B.

Calculation of percentage contents:

— for each impurity, use the concentration of prasugrel hydrochloride in reference solution (b).

Limits:

— *impurity B*: maximum 0.3 per cent;

— *impurity E*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 0.5 per cent, determined on 0.100 g by direct sample introduction.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 260 nm.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{20}H_{21}ClFNO_3S$ taking into account the assigned content of *prasugrel hydrochloride CRS*.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *B, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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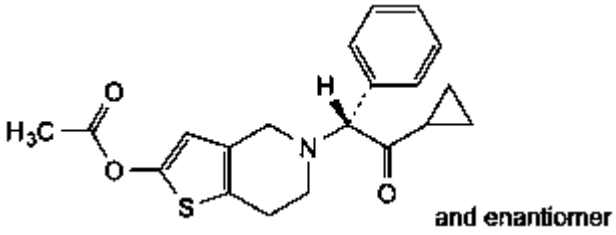
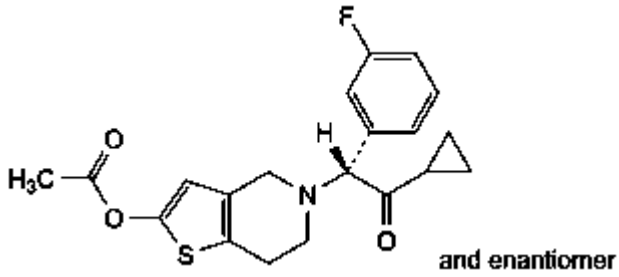
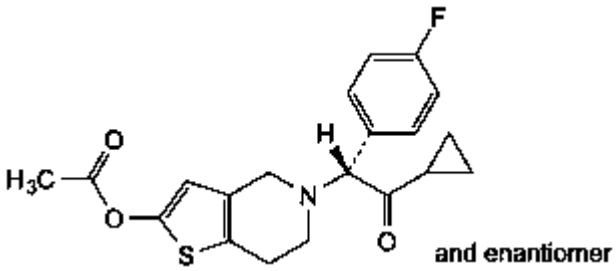
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D, F, G.



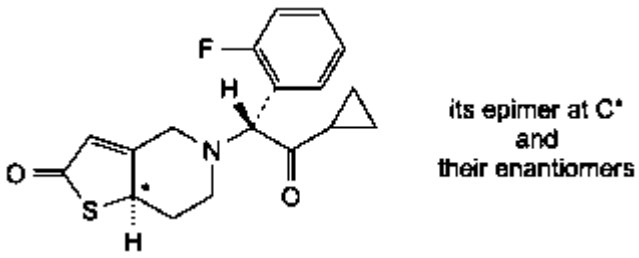
A. 5-[(1*RS*)-2-cyclopropyl-2-oxo-1-phenylethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate,



B. 5-[(1*RS*)-2-cyclopropyl-1-(3-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate,



C. 5-[(1*RS*)-2-cyclopropyl-1-(4-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate,



D. mixture of (7a*R*)-5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one and (7a*S*)-5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one,

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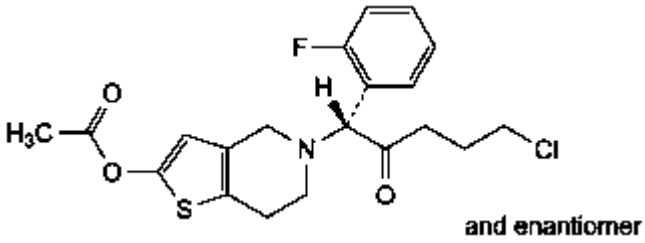
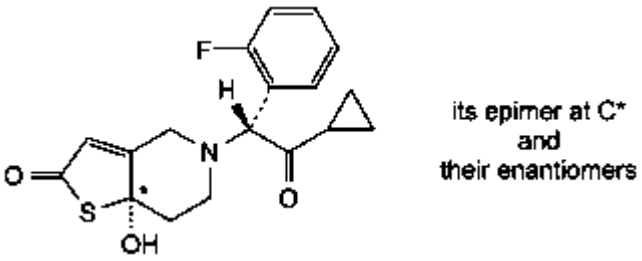
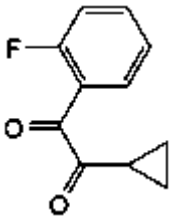


E. 5-[(1*RS*)-5-chloro-1-(2-fluorophenyl)-2-oxopentyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate,



F. mixture of (7a*R*)-5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-7a-hydroxy-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one and (7a*S*)-5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-7a-hydroxy-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one,



G. 1-cyclopropyl-2-(2-fluorophenyl)ethane-1,2-dione.

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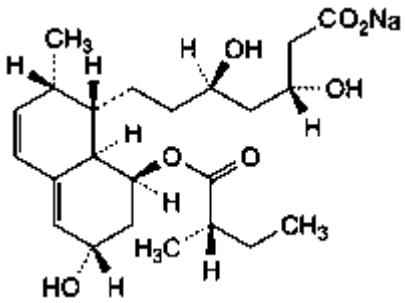
Pravastatin Sodium

General Notices

(Ph. Eur. monograph 2059)



$C_{23}H_{35}NaO_7$ 446.5 *81131-70-6*

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

Preparation

Pravastatin Tablets

Ph Eur

DEFINITION

Sodium (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoate.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white, hygroscopic powder or crystalline powder.

Solubility

Freely soluble in water and in methanol, soluble in anhydrous ethanol.

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IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of pravastatin sodium*.

C. 1 mL of solution S (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dilute 2.0 mL of solution S to 10.0 mL with *water R*.

pH (*2.2.3*)

7.2 to 9.0 for solution S.

Specific optical rotation (*2.2.7*)

+ 153 to + 159 (anhydrous substance).

Dilute 2.0 mL of solution S to 20.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *methanol R*, *water R* (45:55 *V/V*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *pravastatin impurity A CRS* in 1 mL of test solution (b).

Reference solution (b) Dilute 2.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 12.4 mg of *pravastatin 1,1,3,3-tetramethylbutylamine for assay CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

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Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase *glacial acetic acid R*, *triethylamine R*, *methanol R1*, *water for chromatography R* (1:1:450:550 *V/V/V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 238 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Run time 2.5 times the retention time of pravastatin.

Relative retention With reference to pravastatin (retention time = about 21 min): impurity F = about 0.1; impurity B = about 0.2; impurity E = about 0.3; impurity G = about 0.4; impurity A = about 0.6; impurity D = about 1.9; impurity C = about 2.1.

System suitability Reference solution (a):

— *resolution*: minimum 7.0 between the peaks due to impurity A and pravastatin.

Limits:

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities F, G*: for each impurity, not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Ethanol (*2.4.24, System A*)

Maximum 3.0 per cent.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.500 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

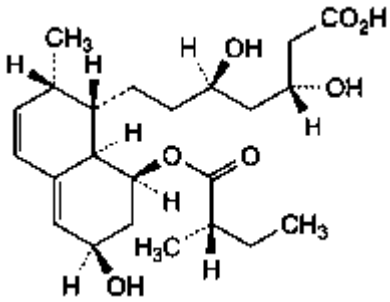
Calculate the percentage content of $C_{23}H_{35}NaO_7$ taking into account the assigned content of *pravastatin 1,1,3,3-tetramethylbutylamine for assay CRS* and a conversion factor of 0.806.

STORAGE

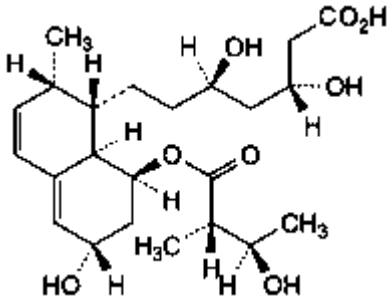
In an airtight container.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*



A. (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoic acid (6′-epipravastatin),



B. (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-8-[[(2*S*,3*R*)3-hydroxy-2-methylbutanoyl]oxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoic acid (3″-(*R*)-hydroxypravastatin),

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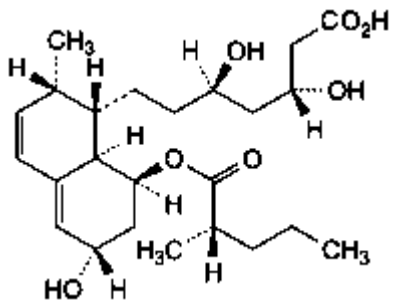
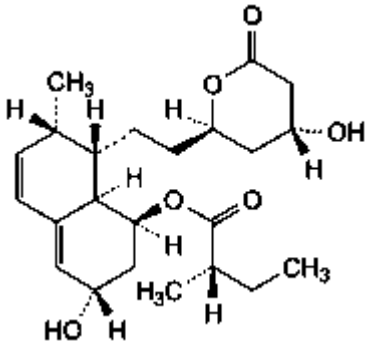
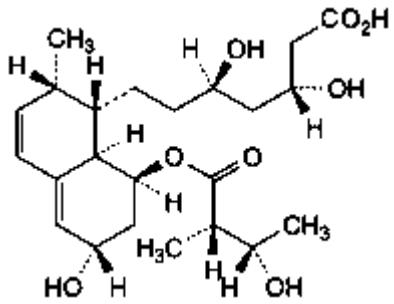


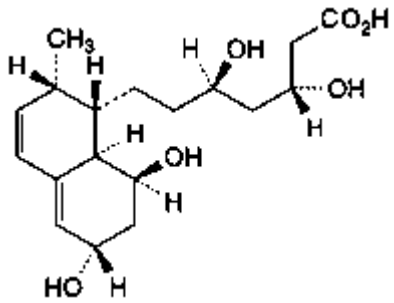
C. (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy2-methyl-8-[[(2*S*)-2-methylpentanoyl]oxy]-1,2,6,7,8,8ahexahydronaphthalen-1-yl]heptanoic acid,



D. (1*S*,3*S*,7*S*,8*S*,8a*R*)-3-hydroxy-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-7-methyl-1,2,3,7,8,8ahexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate (pravastatin lactone),



E. (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-8-[[(2*S*,3*S*)3-hydroxy-2-methylbutanoyl]oxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoic acid (3″-(*S*)-hydroxypravastatin),



F. (3*R*,5*R*)-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6,8-dihydroxy-2-methyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid,

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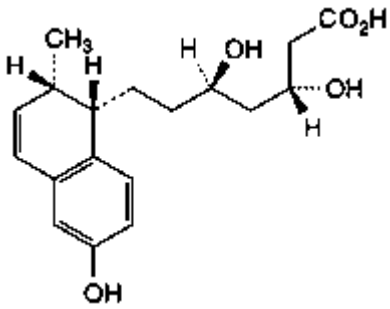

G. (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*)-6-hydroxy-2-methyl-1,2-dihydronaphthalen-1-yl]heptanoic acid.

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Pravastatin Tablets

General Notices

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

DEFINITION

Pravastatin Tablets contain Pravastatin Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pravastatin sodium, $C_{23}H_{35}NaO_7$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 10 mg of Pravastatin Sodium with 80 mL of *water* for 10 minutes, dilute to 100 mL with *water*, filter and dilute 1 mL to 10 mL with *water*. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 350 nm, exhibits a maximum only at 238 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Dissolve 4.10 g of *anhydrous sodium acetate* in 400 mL of *water*, adjust the pH to 5.6 with *glacial acetic acid* and add sufficient *water* to produce 500 mL (solution A). Mix 20 volumes of *methanol* with 80 volumes of solution A (solution B).

(1) Add 20 mL of solution A to a quantity of the powdered tablets containing 10 mg of Pravastatin Sodium, mix using a vortex mixer and then with the aid of ultrasound for 15 minutes. Centrifuge and dilute 1 volume of the clear supernatant liquid to 5 volumes with solution B.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution B.

(3) Dilute 1 volume of solution (2) to 5 volumes with solution B.

(4) Dilute 1 volume of solution (3) to 4 volumes with solution B

(5) Dissolve 2 mg of *pravastatin impurity A BPCRS* in the minimum volume of *methanol* and dilute to 20 mL with solution (1).

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5µm) (Ultrasphere ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 1 volume of *triethylamine*, 450 volumes of *methanol* and 550 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between the peaks corresponding to pravastatin impurity A and pravastatin is at least 7.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

not more than one *secondary peak* has an area greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

not more than one other *secondary peak* has an area greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Dissolve 4.10 g of *anhydrous sodium acetate* in 400 mL of *water*, adjust the pH to 5.6 with *glacial acetic acid* and add sufficient *water* to produce 500 mL (solution A). Mix 20 volumes of *methanol* with 80 volumes of solution A (solution B).

(1) Add 20 mL of solution A to a quantity of the powdered tablets containing 10 mg of Pravastatin Sodium, mix using a vortex mixer and then with the aid of ultrasound for 15 minutes. Centrifuge and dilute 1 volume of the clear supernatant liquid to 5 volumes with solution B.

(2) Dissolve 12.4 mg of *pravastatin 1,1,3,3,-tetramethylbutylamine BPCRS* in 20 mL of solution A and dilute 1 volume to 5 volumes with solution B.

(3) Dissolve 2 mg of *pravastatin impurity A BPCRS* in the minimum volume of *methanol* and dilute to 20 mL with solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to pravastatin impurity A and pravastatin is at least 7.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{35}NaO_7$ in the tablets using the declared content of $C_{23}H_{36}O_7$ in *pravastatin 1,1,3,3,-tetramethylbutylamine BPCRS*. Each mg of $C_{23}H_{36}O_7$ is equivalent to 1.052 mg of $C_{23}H_{35}NaO_7$.

STORAGE

Pravastatin Tablets should be protected from light and moisture.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Pravastatin Sodium.

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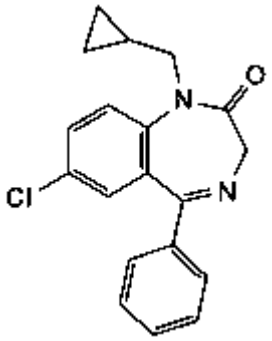
Prazepam

General Notices

(Ph. Eur. monograph 1466)



$C_{19}H_{17}ClN_2O$ 324.8 *2955-38-6*

Action and use

Anxiolytic.

Ph Eur

DEFINITION

7-Chloro-1-(cyclopropylmethyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol.

mp

About 145 °C.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *prazepam CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R1*, *water for chromatography R* (50:50 *V/V*).

Test solution Dissolve 50 mg of the substance to be examined in 25 mL of *acetonitrile R1* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (a) Dissolve 5 mg of *aminochlorobenzophenone R* (impurity C) in *acetonitrile R1* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (1.8 µm);

— *temperature*: 55 °C.

Mobile phase:

— *mobile phase A*: *methanol R1*, *water for chromatography R* (5:95 *V/V*);

— *mobile phase B*: *methanol R1*, *acetonitrile R1* (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	55	45
0.5 - 6.5	55 → 15	45 → 85
6.5 - 8.5	15	85

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 235 nm.

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Injection 2 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to prazepam (retention time = about 3 min): impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity C and prazepam.

Calculation of percentage contents:

— for each impurity, use the concentration of prazepam in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 32.48 mg of $C_{19}H_{17}ClN_2O$.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D.*

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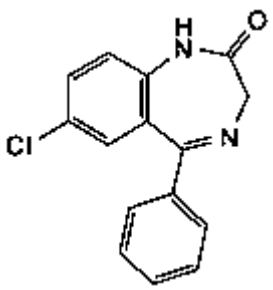
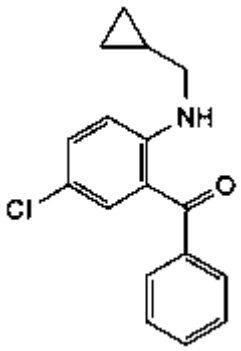
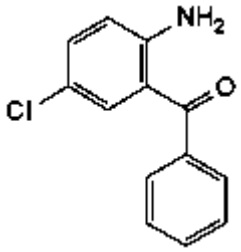


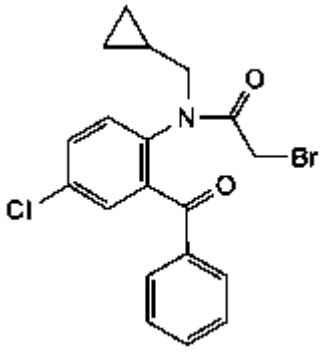
A. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (nordazepam),



B. [5-chloro-2-[(cyclopropylmethyl)amino]phenyl]phenylmethanone,



C. (2-amino-5-chlorophenyl)phenylmethanone (aminochlorobenzophenone),



D. *N*-(2-benzoyl-4-chlorophenyl)-2-bromo-*N*-(cyclopropylmethyl)acetamide.

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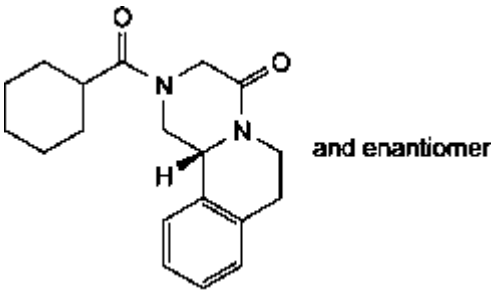
Praziquantel

General Notices

(Ph. Eur. monograph 0855)



$C_{19}H_{24}N_2O_2$ 312.4 *55268-74-1*

Action and use

Anthelminthic.

Ph Eur

DEFINITION

(11b*RS*)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *praziquantel CRS*.

If the spectra obtained show differences, dissolve 50 mg of the substance to be examined and 50 mg of the reference substance separately in 2 mL of *methanol R*. Evaporate and dry the residue at 60 °C at a pressure not exceeding 0.7 kPa. Record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 40.0 mg of *praziquantel CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *praziquantel for system suitability CRS* (containing impurities A and B) in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R1*, *water for chromatography R* (45:55 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solution (a) and reference solutions (b) and (c).

Run time 4 times the retention time of praziquantel.

Identification of impurities Use the chromatogram supplied with *praziquantel for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to praziquantel (retention time = about 10 min): impurity A = about 0.6; impurity B = about 2.2.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity A and praziquantel.

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Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.4;

— *impurities A, B*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 50 °C at a pressure not exceeding 0.7 kPa for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{19}H_{24}N_2O_2$ taking into account the assigned content of *praziquantel CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*

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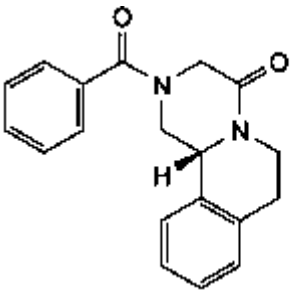
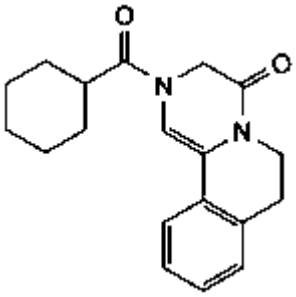
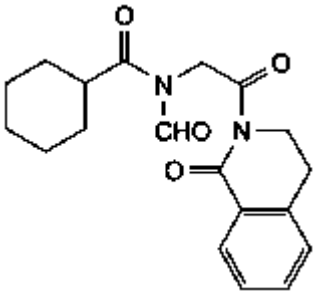

and enantiomer

A. (11b*RS*)-2-benzoyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one,



B. 2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one,



C. *N*-formyl-*N*-[2-oxo-2-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl]cyclohexanecarboxamide.

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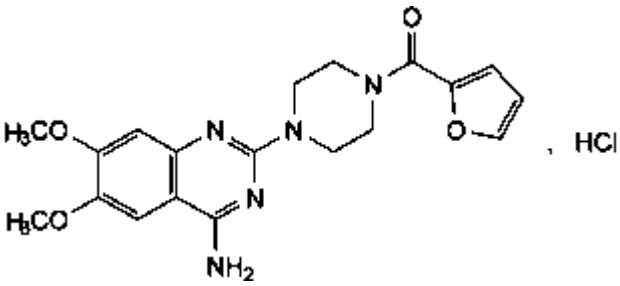
Prazosin Hydrochloride

General Notices

(Ph. Eur. monograph 0856)



$C_{19}H_{22}ClN_5O_4$ 419.9 *19237-84-4*

Action and use

Alpha1-adrenoceptor antagonist.

Preparation

Prazosin Tablets

Ph Eur

DEFINITION

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl](furan-2-yl)methanone hydrochloride.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent) and in methanol, practically insoluble in acetone.

IDENTIFICATION

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First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *prazosin hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 1 volume of *diethylamine R*, 10 volumes of *methanol R* and 10 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 10 mg of *prazosin hydrochloride CRS* in a mixture of 1 volume of *diethylamine R*, 10 volumes of *methanol R* and 10 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *diethylamine R*, *ethyl acetate R* (5:95 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve about 2 mg in 2 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1 mL of the test solution to 10 mL with the mobile phase. Use 1 mL of this solution to dissolve the contents of a vial of *prazosin impurity A CRS*.

Column:

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— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 50 volumes of *methanol R* and 50 volumes of a solution containing 3.5 g/L of *sodium pentanesulfonate R* and 3.6 g/L of *tetramethylammonium hydroxide R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 4 times the retention time of prazosin.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to prazosin (retention time = about 8 min): impurity A = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity A and prazosin.

Calculation of percentage contents:

— for each impurity, use the concentration of prazosin hydrochloride in reference solution (a).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Iron

Maximum 100 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution To 1.0 g add dropwise about 1.5 mL of *nitric acid R*. After fuming has subsided, evaporate on a water-bath and ignite by gradually raising the temperature from 150 °C to 1000 ± 50 °C, maintaining the final temperature for 1 h. Cool, dissolve the residue in 20 mL of *dilute hydrochloric acid R*, evaporate to about 5 mL and dilute to 25.0 mL with *dilute hydrochloric acid R*.

Reference solutions Prepare the reference solutions using *iron standard solution (8 ppm Fe) R*, diluted as necessary with *water R*.

Source Iron hollow-cathode lamp.

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Wavelength 248 nm.

Flame Air-acetylene.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g using a mixture of equal volumes of *methanol R* and *methylene chloride R* as solvent.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached.

Dissolve 0.350 g in a mixture of 20 mL of *anhydrous formic acid R* and 30 mL of *acetic anhydride R*. Titrate quickly with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 41.99 mg of $C_{19}H_{22}ClN_5O_4$.

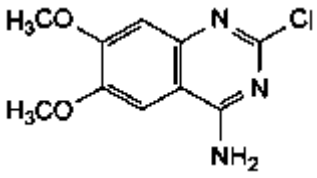
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*



A. 2-chloro-6,7-dimethoxyquinazolin-4-amine,

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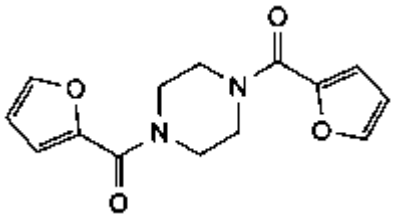
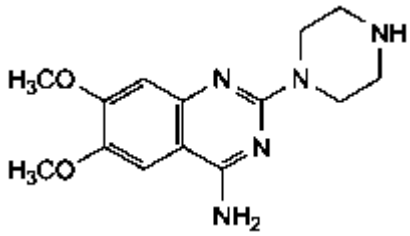
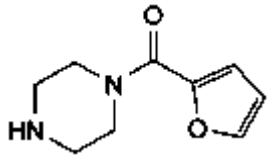


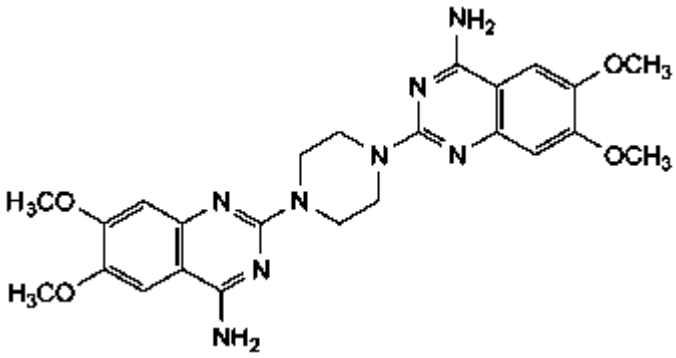
B. (piperazin-1,4-diyl)bis[(furan-2-yl)methanone],



C. 6,7-dimethoxy-2-(piperazin-1-yl)quinazolin-4-amine,



D. (furan-2-yl)(piperazin-1-yl)methanone,



E. 2,2′-(piperazin-1,4-diyl)bis(6,7-dimethoxyquinazolin-4-amine).

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Prazosin Tablets

General Notices

Action and use

Alpha$_1$-adrenoceptor antagonist.

DEFINITION

Prazosin Tablets contain Prazosin Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of prazosin, $C_{19}H_{21}N_5O_4$

90.0 to 110% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 10 mg of prazosin with a mixture of 10 mL of *dichloromethane* and 10 mL of 0.05M *potassium hydroxide*, filter the organic layer through absorbent cotton, evaporate to dryness and dry the residue at 60° at a pressure not exceeding 2 kPa for 2 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of prazosin (*RS 281*).

TESTS

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of prazosin comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 2 volumes of *glacial acetic acid*, 2 volumes of *water* and 96 volumes of *methanol*.

(1) Shake one tablet for 1 hour in a suitable volume of the solvent to produce a solution containing the equivalent of 0.002% w/v of prazosin, centrifuge and use the supernatant liquid.
(2) 0.0022% w/v of *prazosin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4 mm) packed with *silica gel for chromatography* (5 µm) (Zorbax Sil is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01% w/v of *diethylamine* in a mixture of 2 volumes of *glacial acetic acid*, 2 volumes of *water* and 96 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{21}N_5O_4$ in each tablet using the declared content of $C_{19}H_{21}N_5O_4$ in *prazosin hydrochloride BPCRS*.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 5 mg of prazosin with 2 mL of a mixture of 5 volumes of *diethylamine* and 95 volumes of *chloroform*, centrifuge and pass the supernatant liquid through a 0.5 µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with the same solvent.

(3) Dilute 2 volumes of solution (2) to 5 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}* (Analtech Uniplates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *diethylamine* and 95 volumes of *ethyl acetate*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) and not more than two such spots are more intense than the spot in the chromatogram obtained with solution (3).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 2 volumes of *glacial acetic acid*, 2 volumes of *water* and 96 volumes of *methanol*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 2 mg of prazosin with 100 mL of the solvent mixture for 30 minutes, centrifuge and use the supernatant liquid.

(2) 0.0022% w/v of *prazosin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

MOBILE PHASE

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0.01% w/v of *diethylamine* in a mixture of 2 volumes of *glacial acetic acid*, 2 volumes of *water* and 96 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{21}N_5O_4$ in the tablets using the declared content of $C_{19}H_{21}N_5O_4$ in *prazosin hydrochloride BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of prazosin.

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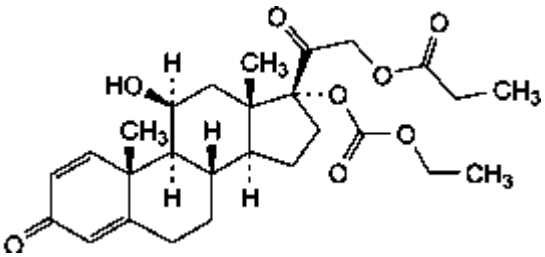
Prednicarbate

General Notices

(Ph. Eur. monograph 1467)



$C_{27}H_{36}O_8$ 488.6 *73771-04-7*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

11β-Hydroxy-3,20-dioxopregna-1,4-diene-17,21-diyl 17-(ethyl carbonate) 21-propanoate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent), sparingly soluble in propylene glycol.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

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Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *prednicarbate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol (96 per cent) R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *prednicarbate CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL; the volume may be adapted based on the type of plate used.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat the plate at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Specific optical rotation (2.2.7)

+ 60 to + 66 (dried substance).

Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 3 mg of *prednicarbate for system suitability A CRS* (containing impurities B, C, D, E and F) in the mobile phase and dilute to 5 mL with the mobile phase.

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Reference solution (b) Dissolve 3 mg of *prednicarbate for peak identification CRS* (containing impurity G) in the mobile phase and dilute to 5 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 30.0 mg of *prednicarbate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, *water for chromatography R* (50:60 *V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 243 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (c).

Run time 2.6 times the retention time of prednicarbate.

Identification of impurities Use the chromatogram supplied with *prednicarbate for system suitability A CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, C, D, E and F; use the chromatogram supplied with *prednicarbate for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to prednicarbate (retention time = about 20 min): impurity B = about 0.25; impurity C = about 0.35; impurity D = about 0.39; impurity E = about 0.6; impurity F = about 1.2; impurity G = about 2.4.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to prednicarbate and impurity F; minimum 1.5 between the peaks due to impurities C and D.

Calculation of percentage contents:

— for each impurity, use the concentration of prednicarbate in reference solution (c).

Limits:

— *impurity F*: maximum 0.8 per cent;

— *impurity C*: maximum 0.5 per cent;

— *impurity E*: maximum 0.3 per cent;

— *impurities B, D*: for each impurity, maximum 0.2 per cent;

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— *impurity G*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (d).

Calculate the percentage content of $C_{27}H_{36}O_8$ taking into account the assigned content of *prednicarbate CRS*.

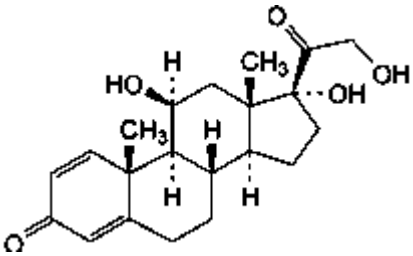
STORAGE

Protected from light.

IMPURITIES

Specified impurities *B, C, D, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



A. 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (prednisolone),

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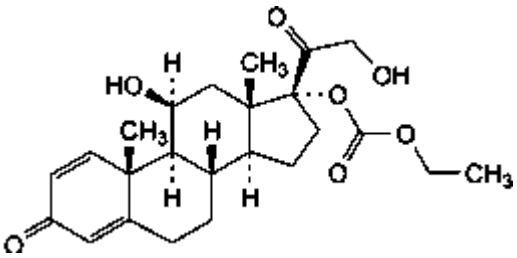
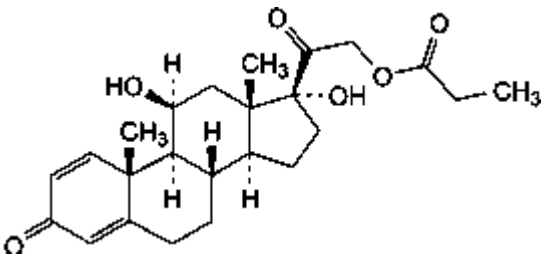
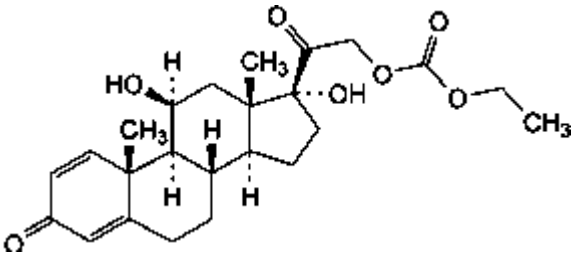


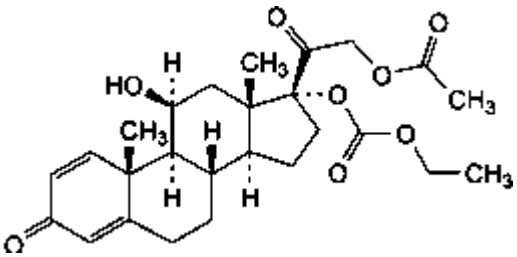
B. ethyl 11β,21-dihydroxy-3,20-dioxopregna-1,4-dien-17-yl carbonate (prednisolone 17-ethylcarbonate),



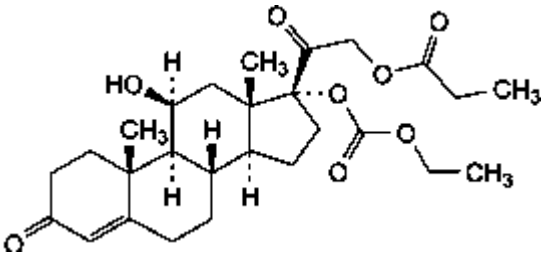
C. 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl propanoate (prednisolone 21-propanoate),



D. ethyl 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl carbonate (prednisolone 21-ethylcarbonate),



E. 11β-hydroxy-3,20-dioxopregna-1,4-diene-17,21-diyl 21-acetate 17-(ethyl carbonate) (prednisolone 21-acetate 17-ethylcarbonate),



F. 11β-hydroxy-3,20-dioxopregn-4-ene-17,21-diyl 17-(ethyl carbonate) 21-propanoate (1,2-dihydroprednicarbate),

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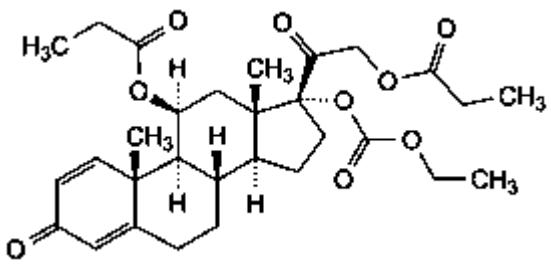

G. 3,20-dioxo-11β-pregna-1,4-diene-11,17,21-triyl 17-(ethyl carbonate) 11,21-dipropanoate (prednicarbate 11-propanoate).

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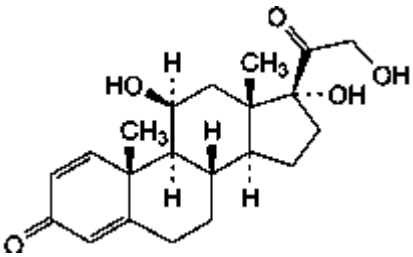
Prednisolone

General Notices

(Ph. Eur. monograph 0353)



$C_{21}H_{28}O_5$ 360.5 *50-24-8*

Action and use

Glucocorticoid.

Preparations

Prednisolone Tablets

Prednisolone Gastro-resistant Tablets

Ph Eur

DEFINITION

11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione.

Content

96.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline, hygroscopic powder.

Solubility

Very slightly soluble in water, soluble in ethanol (96 per cent) and in methanol, sparingly soluble in acetone, slightly soluble in methylene chloride.

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It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B.

Second identification: C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *prednisolone CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *prednisolone CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Specific optical rotation (2.2.7)

+ 113 to + 119 (dried substance).

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Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture *acetonitrile R*, *water R* (40:60 *V/V*).

Test solution (a) Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *prednisolone for system suitability CRS* (containing impurities A, B and C) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *prednisolone for peak identification CRS* (containing impurities F and J) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 25.0 mg of *prednisolone CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*, *methanol R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	60	40
14 - 20	60 → 20	40 → 80
20 - 25	20	80

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Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *prednisolone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C; use the chromatogram supplied with *prednisolone for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities F and J.

Relative retention With reference to prednisolone (retention time = about 12 min): impurity F = about 0.7; impurity B = about 0.9; impurity A = about 1.05; impurity J = about 1.5; impurity C = about 1.7.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to prednisolone.

Limits:

— *impurity A*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *impurity F*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurities B, C, J*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{21}H_{28}O_5$ taking into account the assigned content of *prednisolone CRS*.

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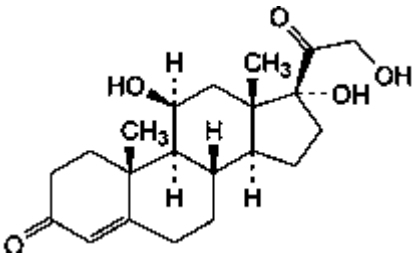
STORAGE

In an airtight container, protected from light.

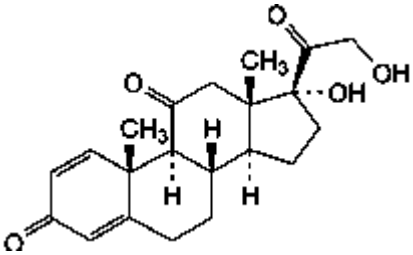
IMPURITIES

Specified impurities *A, B, C, F, J.*

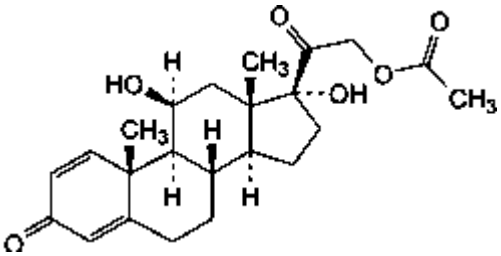
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, G, H, I.*



A. 11β,17,21-trihydroxypregn-4-ene-3,20-dione (hydrocortisone),



B. 17,21-dihydroxypregna-1,4-diene-3,11,20-trione (prednisone),



C. 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate (prednisolone acetate),

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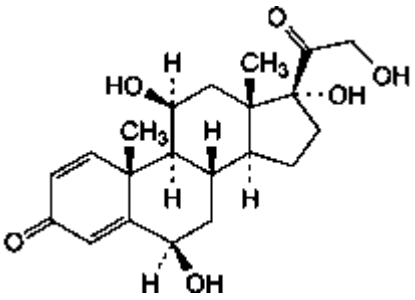
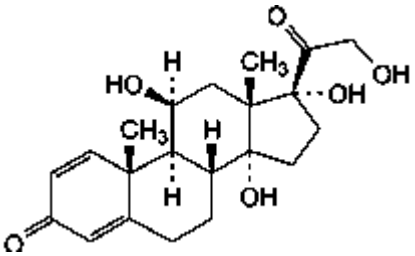
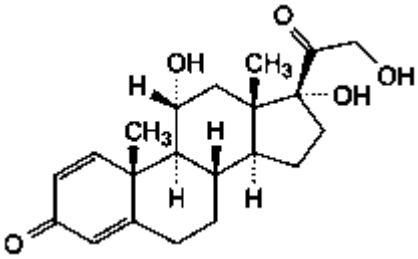


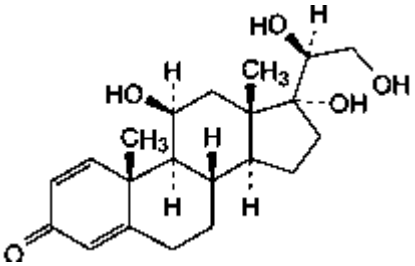
D. 6β,11β,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (6β-hydroxyprednisolone),



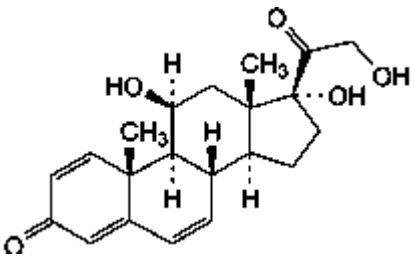
E. 11β,14α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (14α-hydroxyprednisolone),



F. 11α,17,21-trihydroxypregna-1,4-diene-3,20-dione (11-*epi*-prednisolone),



G. 11β,17,20β,21-tetrahydroxypregna-1,4-dien-3-one (20β-hydroxyprednisolone),



H. 11β,17,21-trihydroxypregna-1,4,6-triene-3,20-dione (Δ^6-prednisolone),

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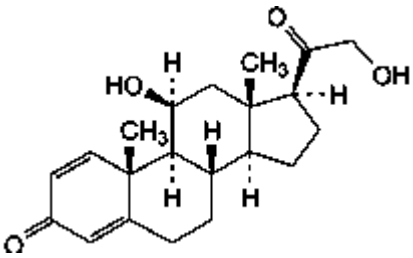
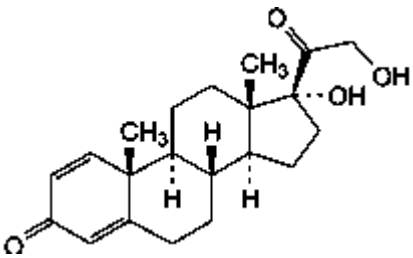


I. 11β,21-dihydroxypregna-1,4-diene-3,20-dione (17-deoxyprednisolone),



J. 17,21-dihydroxypregna-1,4-diene-3,20-dione (11-deoxyprednisolone).

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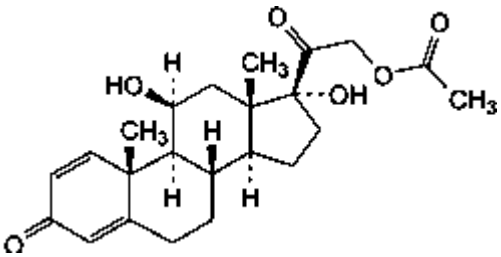
Prednisolone Acetate

General Notices

(Ph. Eur. monograph 0734)



$C_{23}H_{30}O_6$ 402.5 *52-21-1*

Action and use

Glucocorticoid.

Preparation

Prednisolone Acetate Injection

Ph Eur

DEFINITION

11β,17-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

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First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *prednisolone acetate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *prednisolone acetate CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, an intense red colour develops. When examined in ultraviolet light at 365 nm, a reddish-brown fluorescence is seen. Add the solution to 10 mL of *water R* and mix. The colour fades and there is an intense greenish-yellow fluorescence in ultraviolet light at 365 nm.

TESTS

Specific optical rotation (2.2.7)

+ 128 to + 137 (dried substance).

Dissolve 70.0 mg in *methanol R2* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

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Buffer solution pH 4 Mix 1 volume of *dilute hydrochloric acid R*, 5 volumes of a 68.1 g/L solution of *sodium acetate R*, 15 volumes of a 37.3 g/L solution of *potassium chloride R* and 79 volumes of *water R*.

Solvent mixture Mix equal volumes of *acetonitrile R* and buffer solution pH 4.

Test solution Dissolve 25.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2 mg of *prednisolone acetate CRS* and 2 mg of *hydrocortisone acetate CRS* (impurity A) in the solvent mixture and dilute to 100 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *prednisolone acetate for peak identification CRS* (containing impurities A, B and C) in the solvent mixture and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, *water for chromatography R* (35:65 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 2.5 times the retention time of prednisolone acetate.

Identification of impurities Use the chromatogram supplied with *prednisolone acetate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

Relative retention With reference to prednisolone acetate (retention time = about 17 min): impurity B = about 0.4; impurity A = about 1.1; impurity C = about 2.0.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to prednisolone acetate and impurity A.

Limits:

— *impurities A, B*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

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— *impurity C*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.100 g in ethanol (96 per cent) R and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with ethanol (96 per cent) R. Measure the absorbance (2.2.25) at the absorption maximum at 243 nm.

Calculate the content of $C_{23}H_{30}O_6$ taking the specific absorbance to be 370.

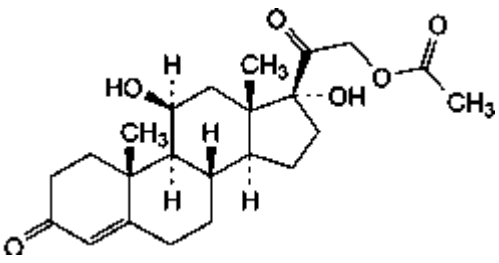
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B, C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, E.



A. 11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate (hydrocortisone acetate),

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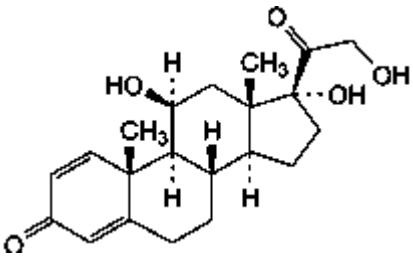
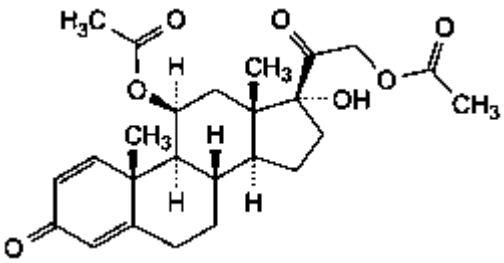
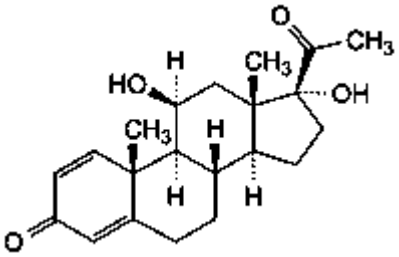


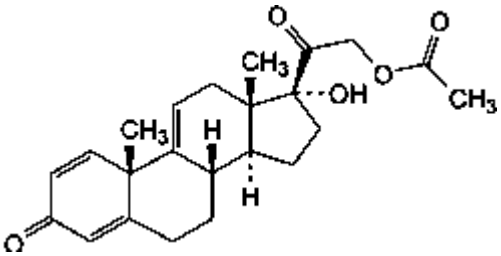
B. 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (prednisolone),



C. 17-hydroxy-3,20-dioxopregna-1,4-diene-11β,21-diyl diacetate (prednisolone 11,21-diacetate),



D. 11β,17-dihydroxypregna-1,4-diene-3,20-dione,



E. 17-hydroxy-3,20-dioxopregna-1,4,9(11)-trien-21-yl acetate.

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Prednisolone Acetate Injection

General Notices

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Acetate Injection is a suspension of Prednisolone Acetate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of prednisolone acetate, $C_{23}H_{30}O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane*.

(1) To a quantity of the injection containing 25 mg of Prednisolone Acetate add 20 mL of a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane*. Mix with the aid of ultrasound and dilute to 25 mL with the same solvent.

(2) 0.1% w/v of *prednisolone acetate BPCRS*.

(3) 0.1% w/v each of *prednisolone acetate BPCRS* and *prednisolone pivalate EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 105° for 10 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

Add a mixture of 1.2 volumes of *water* and 8 volumes of *methanol* to a mixture of 15 volumes of *ether* and 77 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 5.5 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solvent A Equal volumes of *acetonitrile* and a mixture containing 1 volume of *dilute hydrochloric acid*, 5 volumes of a 6.81% w/v solution of *sodium acetate*, 15 volumes of a 3.73% w/v solution of *potassium chloride* and 79 volumes of *water*.

(1) Mix with the aid of ultrasound a quantity of the injection containing 25 mg of Prednisolone Acetate with 7 mL of *methanol*, dilute to 10 mL with *water* and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A. Further dilute 1 volume of this solution to 5 volumes with solvent A.
(3) 0.01% w/v of *prednisolone acetate for peak identification EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Alltima C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 2.5 times the retention time of prednisolone acetate.

MOBILE PHASE

350 volumes of *acetonitrile* and 650 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to prednisolone acetate (retention time, about 17 minutes) are: impurity B, about 0.4; impurity A, about 1.1 and impurity C, about 2.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone acetate and prednisolone impurity A is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak due to prednisolone impurity A or prednisolone impurity B is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak due to prednisolone impurity C is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than ten times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solvent A Equal volumes of *acetonitrile* and a mixture containing 1 volume of *dilute hydrochloric acid*, 5 volumes of a 6.81% w/v solution of *sodium acetate*, 15 volumes of a 3.73% w/v solution of *potassium chloride* and 79 volumes of *water*.

(1) Mix with the aid of ultrasound a weighed quantity of the injection containing 25 mg of Prednisolone Acetate with 70 mL of *methanol*, dilute to 100 mL with *methanol* and filter.
(2) 0.025% w/v of *prednisolone acetate BPCRS* in *methanol*.
(3) 0.01% w/v of *prednisolone acetate for peak identification EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone acetate and prednisolone impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of Prednisolone Acetate, $C_{23}H_{30}O_6$, in the injection using the calculated content of $C_{23}H_{30}O_6$ in *prednisolone acetate BPCRS*.

STORAGE

Prednisolone Acetate Injection should be stored protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Prednisolone Acetate.

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Prednisolone Enema

General Notices

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Enema is a *rectal solution* containing Prednisolone Sodium Phophate in Purified Water. It contains suitable buffering and stabilising agents and a suitable antimicrobial preservative.

The enema complies with the requirements stated under Rectal Preparations and with the following requirements.

Content of prednisolone, $C_{21}H_{28}O_5$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak having the same retention time as the peak due to prednisolone sodium phosphate in the chromatogram obtained with solution (2).

B. Evaporate 5 mL to dryness on a water bath, cool and dissolve the residue in 0.5 mL of *sulfuric acid*. A dark red colour is produced.

TESTS

Acidity or alkalinity

pH, 5.5 to 7.5, Appendix V L.

Free prednisolone

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of equal volumes of *acetone* and *toluene* as the mobile phase. Apply separately to the plate 25 µL of each of the following solutions. For solution (1) dilute a volume of the enema containing the equivalent of 2.0 mg of prednisolone with sufficient *water* to produce 25 mL, add 2.5 g of *sodium chloride* and 1 mL of *hydrochloric acid*, extract with three 25-mL quantities of *chloroform* and wash each extract with the same 1 mL quantity of *0.1M hydrochloric acid* in a second separating funnel. Evaporate the combined chloroform extracts to about 5 mL using a rotary evaporator, transfer to a 15 mL stoppered tube and rinse the rotary evaporator flask with a few millilitres of *chloroform*, adding the rinsings to the tube. Evaporate in a gentle current of nitrogen and dissolve the residue in 1 mL of *chloroform*. Solution (2) contains 0.0134% w/v of *prednisolone BPCRS* in *chloroform*. After removal of the plate, allow it to dry and examine under *ultraviolet light (254 nm)*. Any spot in the chromatogram obtained with solution (1) corresponding to prednisolone is not more intense than the spot in the chromatogram obtained with solution (2).

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute, if necessary, a quantity of the enema containing the equivalent of 2 mg of prednisolone to 10 mL with *water*, add 10 mL of *water*, extract with three 20-mL quantities of *chloroform* and discard the lower layer. For solution (2) dissolve 55 mg of *prednisolone sodium phosphate BPCRS* in *water* and dilute to 200 mL (solution A); to 10 mL of solution A add 10 mL of a 0.035% w/v solution of *betamethasone sodium phosphate* in *water* (internal standard), extract with three 20-mL quantities of *chloroform* and discard the lower layer. Prepare solution (3) in the same manner as solution (1) but add 10 mL of a 0.035% w/v solution of *betamethasone sodium phosphate* in *water* in place of the 10 mL of water.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable) and maintained at 60°, (b) a mixture of 45 volumes of *methanol* and 55 volumes of *citro-phosphate buffer pH 5.0* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 247 nm.

Calculate the content of $C_{21}H_{28}O_5$ in solution A by measuring the *absorbance*, Appendix II B, of a solution obtained by diluting 1 volume of solution A to 10 volumes with *water* at the maximum at 247 nm and taking 419 as the value of A(1%, 1 cm) at the maximum at 247 nm. Calculate the content of $C_{21}H_{28}O_5$ in the enema using peak areas.

STORAGE

Prednisolone Enema should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent almount of prednisolone.

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Prednisolone Gastro-resistant Tablets

General Notices

Gastro-resistant Prednisolone Tablets

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Gastro-resistant Tablets contain Prednisolone. They are covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of prednisolone, $C_{21}H_{28}O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets with *dichloromethane*, filter and evaporate the filtrate to dryness. The residue complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase A*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak having the same retention time as the peak due to prednisolone in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

Use the apparatus described under Test A for the *disintegration test for tablets and capsules*, Appendix XII A1, introduce one tablet into each of six tubes and operate the apparatus without the discs for 60 minutes in 0.1M *hydrochloric acid*. Remove the tablets and use these tablets to carry out the dissolution test as described below.

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *mixed phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of 20 mL of the medium and filter through a membrane filter having a nominal pore size not greater than 0.45 µm, discarding the first 10 mL of filtrate.

(2) Prepare a 0.05% w/v solution of *prednisolone BPCRS* in a mixture of 42 volumes of *water* and 58 volumes of *methanol* and dilute with the dissolution medium to contain 0.00025% w/v of prednisolone.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

42 volumes of *water* and 58 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined using the peak due to prednisolone, is greater than 15,000 *theoretical plates* per metre.

DETERMINATION OF CONTENT

Calculate the total content of prednisolone, $C_{21}H_{28}O_5$, in the medium using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 10 mg of Prednisolone with 25 mL of *methanol* for 10 minutes and mix with the aid of ultrasound for 2 minutes. Filter the extract (Whatman GF/F is suitable), wash the filter with two 10-mL quantities of *methanol*, combine the filtrate and washings and evaporate to dryness using a rotary evaporator and a warm water bath; dissolve the residue in 10 mL of *tetrahydrofuran* and dilute to 20 mL with *water*.

(2) 0.002% w/v each of *prednisolone BPCRS* and *hydrocortisone BPCRS* in the mobile phase.

(3) Dilute 1 volume of solution (1) to 100 volumes with a 50% v/v solution of *tetrahydrofuran*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Alltima C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 45°.

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(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 4.5 times the retention time of the principal peak.

When the chromatograms are recorded in the prescribed conditions, the retention times are: prednisolone, about 14 minutes and hydrocortisone, about 15.5 minutes.

MOBILE PHASE

Mix 220 volumes of *tetrahydrofuran* with 700 volumes of *water*, allow to equilibrate and dilute to 1000 volumes with *water* and mix.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to prednisolone and hydrocortisone is at least 2.2. If necessary, adjust the concentration of *tetrahydrofuran* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the sum of the areas of any such peaks is not greater than four times the area of the principal peak in the chromatogram obtained with solution (3) (4%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%) and any peak with a retention time of 5 minutes or less.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 58 mL of *methanol* to a quantity of the powdered tablets containing 5 mg of Prednisolone, shake for 10 minutes, add sufficient *water* to produce 100 mL, mix and filter.

(2) Dissolve 5 mg of *prednisolone BPCRS* in 58 mL of *methanol* and dilute to 100 mL with *water*.

(3) Add 10 mL of a 0.075% w/v solution of *dexamethasone* in *methanol* and 48 mL of *methanol* to a quantity of the powdered tablets containing 5 mg of Prednisolone, shake for 10 minutes, add sufficient *water* to produce 100 mL, mix and filter.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to prednisolone and dexamethasone is at least 2.5;

the *column efficiency*, determined using the peak due to prednisolone, is greater than 15,000 *theoretical plates* per metre.

DETERMINATION OF CONTENT

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Calculate the content of $C_{21}H_{28}O_5$ in the tablets using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

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Prednisolone Pivalate

General Notices

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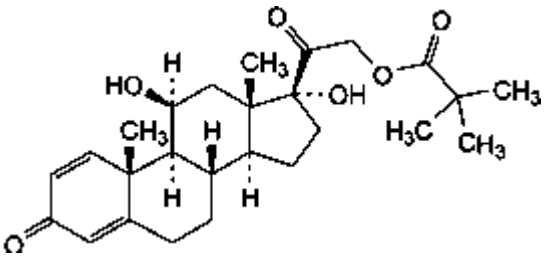

$C_{26}H_{36}O_6$ 444.6 *1107-99-9*

Action and use

Glucocorticoid.

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DEFINITION

11β,17-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), soluble in methylene chloride.

mp

About 229 °C, with decomposition.

IDENTIFICATION

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First identification: B, C.

Second identification: A, C, D.

A. Dissolve 10.0 mg in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Place 2.0 mL of this solution in a ground-glass-stoppered tube, add 10.0 mL of *phenylhydrazine-sulfuric acid solution R*, mix and heat in a water-bath at 60 °C for 20 min. Cool immediately. The absorbance (*2.2.25*) at the absorption maximum at 415 nm is 0.20 to 0.30.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *prednisolone pivalate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol (96 per cent) R*, evaporate to dryness on a water-bath and record new spectra using the residues.

C. Thin-layer chromatography (*2.2.27*).

Solvent mixture *methanol R*, *methylene chloride R* (1:9 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *prednisolone pivalate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *prednisolone acetate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture. Dilute 5 mL of this solution to 10 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *alcoholic solution of sulfuric acid R*, heat at 120 °C for 10 min or until the spots appear, and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

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— the chromatogram shows 2 clearly separated spots.

D. To 2 mL of *sulfuric acid R*, add about 2 mg and shake to dissolve. Within 5 min, an intense red colour develops. When examined in ultraviolet light at 365 nm, a reddish-brown fluorescence is seen. Add this solution to 10 mL of *water R* and mix. The colour fades and there is greenish-yellow fluorescence in ultraviolet light at 365 nm.

TESTS

Specific optical rotation (*2.2.7*)

+ 104 to + 112 (dried substance).

Dissolve 0.250 g in *dioxan R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 62.5 mg of the substance to be examined in 2 mL of a mixture of 1 volume of *water R* and 4 volumes of *tetrahydrofuran R* and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25 mg of *prednisolone acetate CRS*, 25 mg of *cortisone acetate CRS* and 25 mg of *prednisolone pivalate CRS* in 2 mL of a mixture of 1 volume of *water R* and 4 volumes of *tetrahydrofuran R* and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Carefully mix 19 mL of *butyl acetate R1* with 37 mL of *tetrahydrofuran R* and 213 mL of *ethylene glycol monomethyl ether R*, then add with 231 mL of *water R*; mix, allow to equilibrate for 1 h and filter through a 0.45 µm filter.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration With the mobile phase for about 30 min.

Injection 20 µL.

Run time 1.5 times the retention time of prednisolone pivalate.

Retention time Prednisolone acetate = about 3.5 min; cortisone acetate = about 4.5 min; prednisolone pivalate = about 13 min.

System suitability Reference solution (a):

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— *resolution*: minimum 2.5 between the peaks due to prednisolone acetate and cortisone acetate; if necessary, adjust the concentration of water in the mobile phase.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent), and not more than one such peak has an area greater than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *total*: not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent);

— *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 250.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 243 nm.

Calculate the content of $C_{26}H_{36}O_6$ taking the specific absorbance to be 337.

STORAGE

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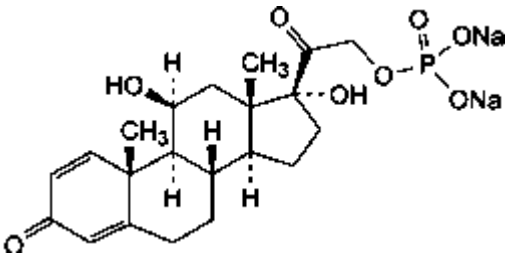
Prednisolone Sodium Phosphate

General Notices

(Ph. Eur. monograph 0735)



$C_{21}H_{27}Na_2O_8P$ 484.4 *125-02-0*

Action and use

Glucocorticoid.

Preparations

Prednisolone Enema

Prednisolone Gastro-resistant Tablets

Prednisolone Sodium Phosphate Ear Drops

Prednisolone Soluble Tablets

Prednisolone Sodium Phosphate Oral Solution

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DEFINITION

11β,17-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate.

Content

96.0 per cent to 103.0 per cent (anhydrous substance).

CHARACTERS

Appearance

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White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D, E.

A. Dissolve 10.0 mg in 5 mL of *water R* and dilute to 100.0 mL with *anhydrous ethanol R*. Place 2.0 mL of this solution in a ground-glass-stoppered tube, add 10.0 mL of *phenylhydrazine-sulfuric acid solution R*, mix and heat in a water-bath at 60 °C for 20 min. Cool immediately. The absorbance (*2.2.25*) at the absorption maximum at 415 nm is 0.10 to 0.20.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *prednisolone sodium phosphate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol (96 per cent) R*, evaporate to dryness on a water-bath and record new spectra using the residues.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *prednisolone sodium phosphate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *dexamethasone sodium phosphate CRS* in *methanol R* and dilute to 10 mL with the same solvent. Dilute 5 mL of this solution to 10 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *alcoholic solution of sulfuric acid R*, heat at 120 °C for 10 min or until the spots appear, and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

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Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 2 spots which may, however, not be completely separated.

D. To 2 mL of *sulfuric acid R* add about 2 mg and shake to dissolve. Within 5 min, an intense red colour develops. When examined in ultraviolet light at 365 nm, a reddish-brown fluorescence is seen. Add this solution to 10 mL of *water R* and mix. The colour fades and there is a greenish-yellow fluorescence in ultraviolet light at 365 nm.

E. To about 40 mg add 2 mL of *sulfuric acid R* and heat gently until white fumes are evolved. Add *nitric acid R* dropwise, continue the heating until the solution is almost colourless, and cool. Add 2 mL of *water R*, heat until white fumes are again evolved, cool, add 10 mL of *water R* and neutralise to *red litmus paper R* with *dilute ammonia R1*. The solution gives reaction (a) of sodium (*2.3.1*) and reaction (b) of phosphates (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

pH (*2.2.3*)

7.5 to 9.0 for solution S.

Specific optical rotation (*2.2.7*)

+ 94 to + 100 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 62.5 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25 mg of *prednisolone sodium phosphate CRS* and 25 mg of *prednisolone CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase.

Column:

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— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Into a 250 mL conical flask weigh 1.360 g of *potassium dihydrogen phosphate R* and 0.600 g of *hexylamine R*, mix, allow to stand for 10 min, then dissolve in 185 mL of *water R*; add 65 mL of *acetonitrile R*, mix, and filter through a 0.45 µm filter.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration With the mobile phase for about 30 min.

Injection 20 µL.

Run time 3 times the retention time of prednisolone sodium phosphate.

Retention time Prednisolone sodium phosphate = about 6.5 min; prednisolone = about 8.5 min.

System suitability Reference solution (a):

— *resolution*: minimum 4.5 between the peaks due to prednisolone sodium phosphate and prednisolone; if necessary, increase the concentration of *acetonitrile R* or *water R* in the mobile phase.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent), and not more than 1 such peak has an area greater than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3 per cent);

— *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Inorganic phosphate

Maximum 1 per cent.

Dissolve 50 mg in *water R* and dilute to 100 mL with the same solvent. To 10 mL of this solution add 5 mL of *molybdovanadic reagent R*, mix, and allow to stand for 5 min. Any yellow colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of *phosphate standard solution (5 ppm PO_4) R*.

Water (*2.5.12*)

Maximum 8.0 per cent, determined on 0.200 g.

ASSAY

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Dissolve 0.100 g in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 250.0 mL with *water R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 247 nm.

Calculate the content of $C_{21}H_{27}Na_2O_8P$ taking the specific absorbance to be 312.

STORAGE

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Prednisolone Sodium Phosphate Ear Drops

General Notices

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Sodium Phosphate Ear Drops are a solution of Prednisolone Sodium Phosphate in Purified Water.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of prednisolone sodium phosphate, $C_{21}H_{27}Na_2O_8P$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

For ear drops containing less than 0.1% w/v of Prednisolone Sodium Phosphate carry out test B only.

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the ear drops diluted, if necessary, with *water* to contain 0.1% w/v of Prednisolone Sodium Phosphate.

(2) 0.1% w/v of *prednisolone sodium phosphate BPCRS*.

(3) A mixture of equal volumes of solutions (1) and (2).

(4) A mixture of equal volumes of solution (2) and a 0.1% w/v solution of *betamethasone sodium phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 110° for 10 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

33 volumes of *water*, 47 volumes of *glacial acetic acid* and 120 volumes of *butan-1-ol*, prepared immediately before use.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two principal spots with almost identical Rf values.

CONFIRMATION

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The chromatograms obtained with solutions (1), (2) and (3) show single principal spots with similar Rf values.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to prednisolone sodium phosphate in the chromatogram obtained with solution (2).

C. To a volume containing 0.2 mg of Prednisolone Sodium Phosphate slowly add 1 mL of *sulfuric acid* and allow to stand for 2 minutes. A deep red colour is produced.

TESTS

Acidity or alkalinity

pH, 7.0 to 8.5, Appendix V L.

Free Prednisolone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.0004% w/v of *prednisolone BPCRS* in the mobile phase.

(2) Dilute the ear drops, if necessary, with the mobile phase to produce a solution containing 0.010% w/v of Prednisolone Sodium Phosphate.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 0.2 mL of each solution.

MOBILE PHASE

45 volumes of *methanol* and 55 volumes of *citro-phosphate buffer pH 5.0*.

LIMITS

In the chromatogram obtained with solution (2) the area of any peak corresponding to prednisolone is not greater than the area of the principal peak in the chromatogram obtained with solution (1) (4%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a quantity of the ear drops with *water*, if necessary, to contain 0.001% w/v of Prednisolone Sodium Phosphate.

(2) 0.0025% w/v of *prednisolone sodium phosphate BPCRS*.

(3) 0.001% w/v of *prednisolone sodium phosphate BPCRS*.

(4) 0.001% w/v of *each of* *prednisolone sodium phosphate BPCRS* and *betamethasone sodium phosphate BPCRS*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

45 volumes of *methanol* and 55 volumes of *citro-phosphate buffer pH 5.0*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to betamethasone sodium phosphate and prednisolone sodium phosphate is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{27}Na_2O_8P$ in solution (2) by measuring the *absorbance*, Appendix II B, of solution (2) at the maximum at 247 nm and taking 312 as the value of A(1%, 1 cm) at the maximum at 247 nm. Calculate the content of $C_{21}H_{27}Na_2O_8P$ in the ear drops using the calculated content of $C_{21}H_{27}Na_2O_8P$ in *prednisolone sodium phosphate BPCRS*.

STORAGE

Prednisolone Sodium Phosphate Ear Drops should be stored protected from light.

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Prednisolone Sodium Phosphate Eye Drops

General Notices

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Sodium Phosphate Eye Drops are a sterile solution of Prednisolone Sodium Phosphate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of prednisolone sodium phosphate, $C_{21}H_{27}Na_2O_8P$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

For eye drops containing less than 0.1% w/v of Prednisolone Sodium Phosphate carry out test B only.

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 33 volumes of *water*, 47 volumes of *glacial acetic acid* and 120 volumes of *butan-1-ol*, prepared immediately before use, as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) use the eye drops diluted, if necessary, with *water* to contain 0.1% w/v of Prednisolone Sodium Phosphate. Solution (2) contains 0.1% w/v of *prednisolone sodium phosphate BPCRS* in *water*. Solution (3) is a mixture of equal volumes of solutions (1) and (2). Solution (4) is a mixture of equal volumes of solution (2) and a 0.1% w/v solution of *betamethasone sodium phosphate BPCRS* in *water*. After removal of the plate, allow it to dry in air, heat at 110° for 10 minutes and examine under *ultraviolet light (254 nm)*. The chromatograms obtained with solutions (1), (2) and (3) show single principal spots with similar Rf values. The chromatogram obtained with solution (4) shows two principal spots with almost identical Rf values.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to prednisolone sodium phosphate in the chromatogram obtained with solution (2).

C. To a volume containing 0.2 mg of Prednisolone Sodium Phosphate slowly add 1 mL of *sulfuric acid* and allow to stand for 2 minutes. A deep red colour is produced.

TESTS

Acidity or alkalinity

pH, 7.0 to 8.5, Appendix V L.

Free prednisolone

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Carry out the method for *liquid chromatography*, Appendix III D. For eye drops containing 0.010% w/v or more of Prednisolone Sodium Phosphate use 50 µL of the following solutions. Solution (1) contains 0.00040% w/v of *prednisolone BPCRS* in the mobile phase. Prepare solution (2) in the following manner. Dilute the eye drops, if necessary, with the mobile phase to produce a solution containing 0.010% w/v of Prednisolone Sodium Phosphate.

For eye drops containing less than 0.010% w/v of Prednisolone Sodium Phosphate, use 0.2 mL of the following solutions. Solution (1) contains 0.00004% w/v of *prednisolone BPCRS* in the mobile phase. For solution (2) dilute the eye drops, if necessary, with the mobile phase to produce a solution containing 0.0010% w/v of Prednisolone Sodium Phosphate.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) a mixture of 45 volumes of *methanol* and 55 volumes of *citro-phosphate buffer pH 5.0* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 247 nm.

In the chromatogram obtained with solution (2) the area of any peak corresponding to prednisolone is not greater than the area of the principal peak in the chromatogram obtained with solution (1) (4%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using 50 µL of the following solutions. For solution (1) dilute a quantity of the eye drops, if necessary, to contain 0.001% w/v of Prednisolone Sodium Phosphate. For solution (2) dissolve 10 mg of *prednisolone sodium phosphate BPCRS* in sufficient *water* to produce 100 mL (solution A) and dilute 10 mL of the solution to 100 mL. For solution (3) add 10 mL of a 0.01% w/v solution of *betamethasone sodium phosphate BPCRS* in *water* to 10 mL of solution A and dilute to 100 mL with *water*.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) a mixture of 45 volumes of *methanol* and 55 volumes of *citro-phosphate buffer pH 5.0* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 247 nm.

The assay is not valid unless the *resolution factor* between the peaks due to betamethasone sodium phosphate and prednisolone sodium phosphate in the chromatogram obtained with solution (3) is at least 2.5.

Calculate the content of $C_{21}H_{27}Na_2O_8P$ in solution A by measuring the *absorbance*, Appendix II B, of a solution obtained by diluting 1 volume of solution A to 4 volumes with *water* at the maximum at 247 nm and taking 312 as the value of A(1%, 1 cm) at the maximum at 247 nm. Calculate the content of $C_{21}H_{27}Na_2O_8P$ in the eye drops using peak areas.

STORAGE

Prednisolone Sodium Phosphate Eye Drops should be stored protected from light.

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Prednisolone Sodium Phosphate Oral Solution

General Notices

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Sodium Phosphate Oral Solution is a solution of Prednisolone Sodium Phosphate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of prednisolone sodium phosphate, $C_{21}H_{27}Na_2O_8P$

95.0 to 105.0% of the stated amount.

The activity is due to both prednisolone and prednisolone sodium phosphate. For assay purposes the content of prednisolone is converted to prednisolone sodium phosphate.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to prednisolone sodium phosphate in the chromatogram obtained with solution (2).

B. Add a volume of the oral solution containing 2 mg of Prednisolone Sodium Phosphate to 2 mL of *sulfuric acid* and shake to dissolve. An intense red colour develops within 5 minutes.

TESTS

Alkalinity

pH, 7.4 to 8.0, Appendix V L.

Free prednisolone

In the Assay, the area of any peak due to prednisolone in the chromatogram obtained with solution (1) is not greater than the area of the corresponding peak in the chromatogram obtained with solution (5) (4%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Dilute a quantity of the oral solution containing 25 mg of Prednisolone Sodium Phosphate to 50 mL.

(2) Dilute 1 volume of solution (1) to 50 volumes.

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(3) 0.0002% w/v each of *prednisolone sodium phosphate BPCRS* and *prednisolone BPCRS*.

(4) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Luna C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 100 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of prednisolone sodium phosphate.

MOBILE PHASE

26 volumes of *acetonitrile* and 74 volumes of *water* containing 0.544% w/v of *potassium dihydrogen phosphate* and 0.240% w/v of *hexylamine*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone sodium phosphate and prednisolone is at least 4.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of not more than one *secondary peak* is greater than half the area of the principal peak in the chromatogram obtained with solution (2) (1%).

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak:

due to prednisolone;

with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a volume of the oral solution to produce a solution containing 0.025% w/v of Prednisolone Sodium Phosphate.

(2) 0.025% w/v of *prednisolone sodium phosphate BPCRS*.

(3) 0.0625% w/v of *prednisolone sodium phosphate BPCRS*.

(4) 0.025% w/v of each of *prednisolone BPCRS* *and* *prednisolone sodium phosphate BPCRS*.

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(5) 0.001% w/v of *prednisolone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with an injection volume of 20 µL.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to prednisolone and prednisolone sodium phosphate is at least 4.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_5$ (prednisolone) in the oral solution using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

Each mg of $C_{21}H_{28}O_5$ is equivalent to 1.344 mg of $C_{21}H_{27}Na_2O_8P$.

Calculate the content of $C_{21}H_{27}Na_2O_8P$ in the oral solution due to $C_{21}H_{27}Na_2O_8P$ (prednisolone sodium phosphate) using the area of the peak due to $C_{21}H_{27}Na_2O_8P$ (prednisolone sodium phosphate) and the calculated content of $C_{21}H_{27}Na_2O_8P$ in *prednisolone sodium phosphate BPCRS*.

Calculate the total content of $C_{21}H_{27}Na_2O_8P$ in the oral solution.

STORAGE

Prednisolone Sodium Phosphate Oral Solution should be stored protected from light.

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Prednisolone Tablets

General Notices

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Tablets contain Prednisolone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of prednisolone, $C_{21}H_{28}O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets with *acetone*, filter and evaporate the filtrate to dryness. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of prednisolone (*RS 282*).

B. Complies with the test for the Identification of steroids, Appendix III A, using *impregnating solvent I* and *mobile phase A*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, expected to contain 0.0001% w/v of Prednisolone.

(2) Dilute 1 volume of a 0.1% w/v solution of *prednisolone BPCRS* in *methanol* to 1000 volumes with *water*.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined using the peak due to prednisolone, is greater than 15,000 theoretical plates per metre.

DETERMINATION OF CONTENT

Calculate the total content of $C_{21}H_{28}O_5$ in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 10 mg of Prednisolone with 25 mL of *methanol* for 10 minutes and mix with the aid of ultrasound for 2 minutes; filter the extract (Whatman GF/F is suitable), wash the filter with two 10 mL quantities of *methanol*, combine the filtrate and washings and evaporate to dryness using a rotary evaporator and a warm water bath; dissolve the residue in 10 mL of *tetrahydrofuran* and dilute to 20 mL with *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with a 50% v/v solution of *tetrahydrofuran*.

(3) 0.002% w/v each of *prednisolone BPCRS* and *hydrocortisone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Alltima C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4.5 times the retention time of the principal peak.

In the chromatogram obtained with solution (3), the retention times are about 14 minutes and 15.5 minutes for prednisolone and hydrocortisone respectively.

MOBILE PHASE

Mix 220 volumes of *tetrahydrofuran* with 700 volumes of *water*, allow to equilibrate, dilute to 1000 volumes with *water* and mix.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone and hydrocortisone is at least 2.2. If necessary, adjust the concentration of *tetrahydrofuran* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%) and any peak with a retention time of 3 minutes or less.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Prednisolone comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 15 mL of the mobile phase to one tablet, mix with the aid of ultrasound for at least 10 minutes. Add sufficient of the mobile phase to produce a solution expected to contain 0.005% w/v of Prednisolone, centrifuge and use the supernatant liquid.
(2) 0.005% w/v of *prednisolone BPCRS* in a mixture of 58 volumes of *methanol* and 42 volumes of *water*.
(3) 0.0050% w/v of *prednisolone BPCRS* and 0.0075% w/v of *dexamethasone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

42 volumes of *water* and 58 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone and dexamethasone is greater than 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_5$ in each tablet using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 58 mL of *methanol* to a quantity of the powder containing 5 mg of Prednisolone, shake for 10 minutes, add sufficient *water* to produce 100 mL, mix and filter.
(2) 0.005% w/v of *prednisolone BPCRS* in a mixture of 58 volumes of *methanol* and 42 volumes of *water*.

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(3) 0.005% w/v of *prednisolone BPCRS* and 0.0075% w/v of *dexamethasone BPCRS* in a mixture of 58 volumes of *methanol* and 42 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone and dexamethasone is greater than 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_5$ in the tablets using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

STORAGE

Prednisolone Tablets should be protected from light.

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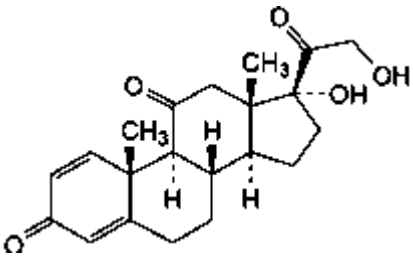
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Prednisone

General Notices

(Ph. Eur. monograph 0354)



$C_{21}H_{26}O_5$ 358.4 *53-03-2*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

17,21-Dihydroxypregna-1,4-diene-3,11,20-trione.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

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First identification: A, C.

Second identification: B, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *prednisone CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *prednisone CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

D. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a yellow colour develops with a blue fluorescence in ultraviolet light at 365 nm. Add this solution to 10 mL of *water R* and mix. The colour fades but the blue fluorescence in ultraviolet light does not disappear.

TESTS

Specific optical rotation (2.2.7)

+ 183 to + 191 (dried substance).

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Dissolve 0.125 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light. Prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *prednisone impurity B CRS* in the solvent mixture and dilute to 25 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with the solvent mixture.

Reference solution (b) Dissolve 4 mg of *prednisone for peak identification CRS* (containing impurities A, D and E) in the solvent mixture, add 1 mL of reference solution (a) and dilute to 5 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of *prednisone CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped ethylene-bridged polar-embedded octadecylsilyl silica gel for chromatography (hybrid material) R* (2.5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: 0.68 g/L solution of *potassium dihydrogen phosphate R*, adjusted to pH 2.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	83	17
2 - 25	83 → 80	17 → 20
25 - 28	80 → 65	20 → 35
28 - 33	65	35

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
33 - 43	65 → 20	35 → 80

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 244 nm.

Injection 5 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *prednisone for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, D and E; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to prednisone (retention time = about 18 min): impurity B = about 1.06; impurity A = about 1.12; impurity D = about 1.6; impurity E = about 1.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to prednisone.

Calculation of percentage contents:

— for each impurity, use the concentration of prednisone in reference solution (c).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity E*: maximum 0.2 per cent;

— *impurity D*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

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Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{21}H_{26}O_5$ taking into account the assigned content of *prednisone CRS*.

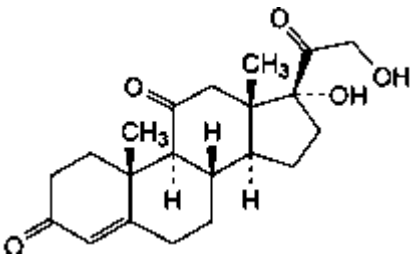
STORAGE

Protected from light.

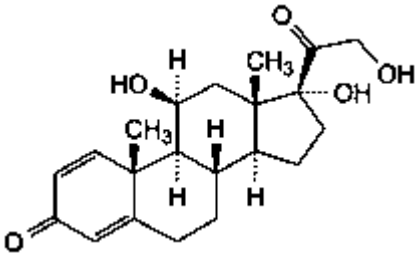
IMPURITIES

Specified impurities *A, D, E.*

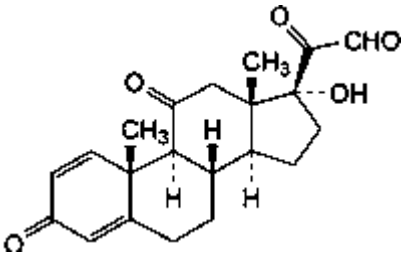
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, J, K, L.*



A. 17,21-dihydroxypregn-4-ene-3,11,20-trione (cortisone),



B. 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (prednisolone),



C. 17-hydroxy-3,11,20-trioxopregna-1,4-dien-21-al (prednisone-21-aldehyde),

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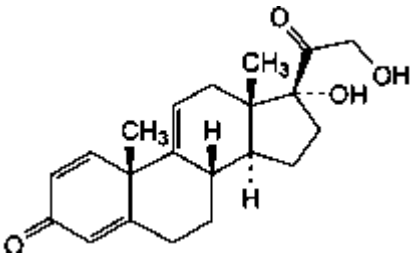
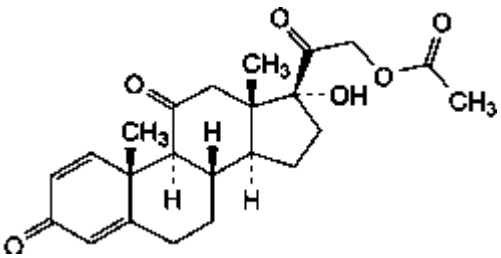
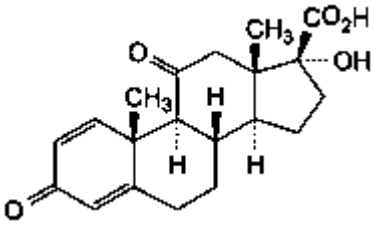


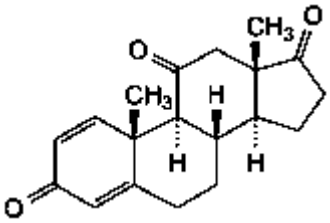
D. 17,21-dihydroxypregna-1,4,9(11)-triene-3,20-dione (deltacortinene),



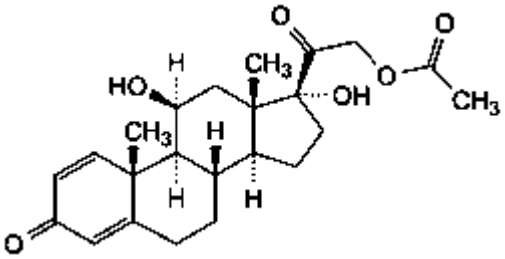
E. 17-hydroxy-3,11,20-trioxopregna-1,4-dien-21-yl acetate (prednisone acetate),



J. 17α-hydroxy-3,11-dioxoandrosta-1,4-diene-17β-carboxylic acid,



K. androsta-1,4-diene-3,11,17-trione,



L. 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate (prednisolone acetate).

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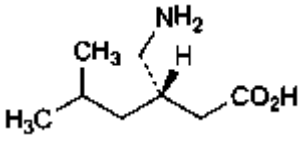
Pregabalin

General Notices

(Ph. Eur. monograph 2777)



$C_8H_{17}NO_2$ 159.2 *148553-50-8*

Action and use

Antiepileptic.

Preparations

Pregabalin Capsules

Pregabalin Oral Solution

Ph Eur

DEFINITION

(3*S*)-3-(Aminomethyl)-5-methylhexanoic acid.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, very slightly soluble in methanol, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *pregabalin CRS*.

B. Examine the chromatograms obtained in the test for enantiomeric purity.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Enantiomeric purity

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 20 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent. Derivatise the solution as described under Derivatisation.

Reference solution Dissolve 2 mg of *pregabalin impurity B CRS* in *water R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*. To 20 mg of *pregabalin CRS*, add 1.0 mL of this solution and dilute to 10.0 mL with *water R*. Derivatise this solution as described under Derivatisation.

Derivatisation Transfer 500 µL of the solution to a reaction vial. Add 500 µL of a 5 g/L solution of *1-fluoro-2,4-dinitrophenyl-5-L-alaninamide R* in *acetonitrile R*. Add 50 µL of an 84 g/L solution of *sodium hydrogen carbonate R*. Seal the vial, mix and derivatise by maintaining the vial at 40 °C for 1 h in a heating/stirring module. Stop the reaction by adding about 50 µL of a 103 g/L solution of *hydrochloric acid R*. Mix thoroughly. To 200 µL of the derivatised solution add 800 µL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, 1 per cent *V/V* solution of *triethylamine R* previously adjusted to pH 3.0 with *phosphoric acid R* (38:62 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 340 nm.

Injection 20 µL.

Run time 2.5 times the retention time of the pregabalin derivative.

Relative retention With reference to the pregabalin derivative (retention time = about 10 min): impurity B derivative = about 1.3.

System suitability Reference solution:

— *resolution*: minimum 4.4 between the peaks due to the pregabalin derivative and impurity B derivative.

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Limit:

— *impurity B*: maximum 0.15 per cent.

Related substances

A. Polar impurities eluting before pregabalin. Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 0.100 g of *pregabalin CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *mandelic acid R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.5 mL of the solution to 5.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R2*, 3.40 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 6.3 with *concentrated ammonia R* (15:85 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 1.3 times the retention time of pregabalin.

Relative retention With reference to pregabalin (retention time = about 10 min): impurity C = about 0.6.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity C and pregabalin.

Calculation of percentage contents:

— for each impurity, use the concentration of pregabalin in reference solution (b).

Limits:

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— *unspecified impurities eluting before pregabalin*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent.

B. Non-polar impurities eluting after pregabalin. Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.5 mg of *pregabalin impurity D CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase (solution A). Dissolve the contents of a vial of *pregabalin impurity A CRS* in the mobile phase, add 1.0 mL of solution A and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase 3.40 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 6.3 with *concentrated ammonia R*, *methanol R2* (45:55 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time 4 times the retention time of pregabalin.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and D.

Relative retention With reference to pregabalin (retention time = about 4 min): impurity A = about 2.4; impurity D = about 3.0.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to impurities A and D.

Calculation of percentage contents:

— for impurities A and D, use the concentration of each impurity in reference solution (b);

— for impurities other than A and D, use the concentration of pregabalin in reference solution (a).

Limits:

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— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities eluting after pregabalin*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent.

Limit:

— *total for tests A and B*: maximum 0.5 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 0.130 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in test A for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_8H_{17}NO_2$ taking into account the assigned content of *pregabalin CRS*.

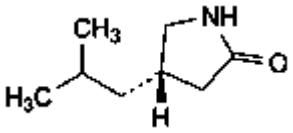
IMPURITIES

Test A for related substances: C.

Test B for related substances: A, D.

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D.*



A. (4*S*)-4-(2-methylpropyl)pyrrolidin-2-one,

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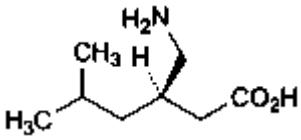
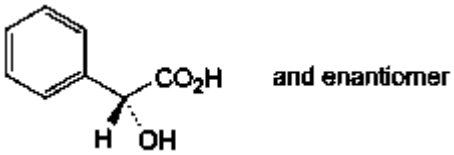
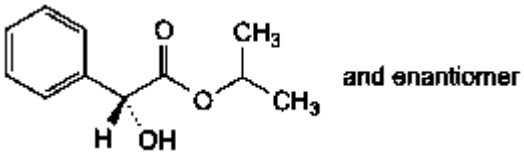


B. (3*R*)-3-(aminomethyl)-5-methylhexanoic acid (pregabalin enantiomer),



C. (2*RS*)-2-hydroxy-2-phenylacetic acid (mandelic acid),



D. 1-methylethyl (2*RS*)-2-hydroxy-2-phenylacetate.

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Pregabalin Capsules

General Notices

Action and use

Antiepileptic.

DEFINITION

Pregabalin Capsules contain Pregabalin.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of pregabalin, $C_8H_{17}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered capsule contents containing 0.1 g of Pregabalin with 20 mL of a mixture of equal volumes of *methanol* and *water*.

(2) 0.5% w/v of *pregabalin BPCRS* in a mixture of equal volumes of *methanol* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 4 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry under a stream of hot air. Spray with *ninhydrin solution R1*, heat at 90° for 2 minutes and examine the plate in daylight.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 50 volumes of *methanol* and 60 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

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TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.06M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes, withdraw a sample of the medium and filter (a 0.45-µm membrane filter is suitable). Use the filtered medium, diluted with 0.06M *hydrochloric acid* if necessary, to produce a solution expected to contain 0.0028% w/v of Pregabalin.

(2) 0.0028% w/v of *pregabalin BPCRS* in 0.06M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3V is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

10 volumes of *acetonitrile R1* and 90 volumes of 0.272% w/v *potassium dihydrogen orthophosphate*, previously adjusted to pH 5.9 with 1M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions the retention time of pregabalin is about 6 minutes.

DETERMINATION OF CONTENT

Calculate the total content of pregabalin, $C_8H_{17}NO_2$, in the medium using the declared content of $C_8H_{17}NO_2$ in *pregabalin BPCRS*.

LIMITS

The amount of pregabalin released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered capsule contents containing 0.3 g of Pregabalin, add 15 mL of *water* and mix with the aid of ultrasound with intermittent shaking. Dilute with sufficient *water* to produce 25 mL and filter through a 0.45-µm nylon filter.

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(2) Dilute 1 volume of solution (1) to 100 volumes with *water*. Further dilute 1 volume to 5 volumes with *water*.

(3) 0.0025% w/v of *pregabalin impurity A EPCRS* in *water*.

(4) 1.2% w/v of *pregabalin impurity standard BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3V is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of *acetonitrile R1* and 100 volumes of 0.272% w/v *potassium dihydrogen orthophosphate*, previously adjusted to pH 5.9 with 1M *sodium hydroxide*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	98	2	isocratic
3-31	98→75	2→25	linear gradient
31-43	75→45	25→55	linear gradient
43-48	45	55	isocratic
48-50	45→98	55→2	linear gradient
50-60	98	2	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retentions relative to pregabalin (retention time about 12 minutes) are: impurity C, about 0.6; impurity 1, about 1.4; impurity A, about 3.1 and impurity D, about 3.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to pregabalin and impurity 1 is at least 13.

LIMITS

Identify any peaks corresponding to impurities C, D and 1 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the peak areas by the following correction factors; impurity C, 0.01; impurity D, 0.01 and impurity 1, 0.3.

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

The total impurity content is not greater than 1.0%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water* (solution A).

(1) To a quantity of the powdered capsule contents containing 0.45 g of Pregabalin, add 100 mL of solution A and mix with the aid of ultrasound with intermittent shaking. Dilute to produce 250 mL and filter through a 0.45-µm membrane filter.
(2) 0.18% w/v of *pregabalin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-3V is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *acetonitrile R1* and 90 volumes of 0.272% w/v *potassium dihydrogen orthophosphate*, previously adjusted to pH 5.9 with 1M *sodium hydroxide*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-6	100→60	0→40	linear gradient
6-10	60	40	isocratic
10-11	60→100	40→0	linear gradient
11-17	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time of pregabalin is about 6 minutes.

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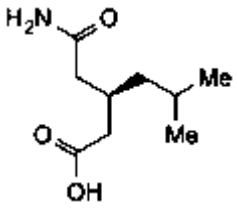
DETERMINATION OF CONTENT

Calculate the content of pregabalin, $C_8H_{17}NO_2$, in the capsules from the chromatograms obtained and using the declared content of $C_8H_{17}NO_2$ in *pregabalin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C and D listed under Pregabalin and:



1. *rac*-3-(carbamoylmethyl)-5-methylhexanoic acid (isobutylglutarmonoamide).

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Pregabalin Oral Solution

General Notices

Action and use

Antiepileptic.

DEFINITION

Pregabalin Oral Solution contains Pregabalin in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of pregabalin, $C_8H_{17}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the oral solution containing 0.1 g of Pregabalin to 20 mL with a mixture of equal volumes of *methanol* and *water*.

(2) 0.5% w/v of *pregabalin BPCRS* in a mixture of equal volumes of *methanol* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 4 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry under a stream of hot air. Spray with *ninhydrin solution R1*, heat at 90° for 2 minutes and examine the plate in daylight.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 50 volumes of *methanol* and 60 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

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Acidity

pH of a solution containing 2% w/v of pregabalin, 5.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 10 volumes of *acetonitrile R1*, 10 volumes of *methanol R1* and 80 volumes of 0.04M *diammonium hydrogen orthophosphate*, previously adjusted to pH 6.6 with *orthophosphoric acid*.

(1) Dilute a volume of the oral solution with solution A to produce a solution expected to contain 1.0% w/v of Pregabalin. Filter through a 0.2-µm regenerated cellulose filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and further dilute 1 volume to 5 volumes with solution A.
(3) 0.002% w/v of *pregabalin impurity A EPCRS* in *water*.
(4) 1.0% w/v of *pregabalin impurity standard BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 210 nm.
(f) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile R1*, 11 volumes of *methanol R1* and 84 volumes of 0.04M *diammonium hydrogen orthophosphate*, previously adjusted to pH 6.6 with *orthophosphoric acid*.

Mobile phase B *Acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-6	100	0	isocratic
6-45	100→76	0→24	linear gradient
45-50	76	24	isocratic
50-51	76→30	24→70	linear gradient
51-55	30	70	isocratic
55-59	30→100	70→0	linear gradient
59-68	100	0	re-equilibration

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When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to pregabalin (retention time about 9 minutes) are: impurity C, about 0.7; impurity 1, about 1.6 and impurity A, about 4.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to pregabalin and impurity 1 is at least 9.0.

LIMITS

Identify any peaks corresponding to impurities C and 1 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the peak areas by the following correction factors; impurity C, 0.01 and impurity 1, 0.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

The total impurity content is not greater than 1.0%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 10 volumes of *acetonitrile R1*, 10 volumes of *methanol R1* and 80 volumes of 0.04M *diammonium hydrogen orthophosphate*, previously adjusted to pH 6.6 with *orthophosphoric acid*.

(1) Dilute a weighed quantity of the oral solution with solution A to produce a solution expected to contain 0.20% w/v of Pregabalin. Filter through a 0.2-µm regenerated cellulose filter and use the filtrate.
(2) 0.2% w/v of *pregabalin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with the gradient elution and mobile phase described below.

MOBILE PHASE

Mobile phase A 4 volumes of *acetonitrile R1*, 11 volumes of *methanol R1* and 85 volumes of 0.04M *diammonium hydrogen orthophosphate*, previously adjusted to pH 6.6 with *orthophosphoric acid*.

Mobile phase B *Acetonitrile R1*.

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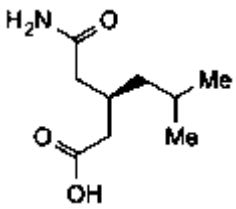
Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-12	100	0	isocratic
12-12.1	100→20	0→80	linear gradient
12.1-16	20	80	isocratic
16-17	20→100	80→0	linear gradient
17-25	100	0	re-equilibration

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_8H_{17}NO_2$, weight in volume, from the chromatograms obtained and using the declared content of $C_8H_{17}NO_2$ in *pregabalin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and C listed under Pregabalin and:



1. *rac*-3-(carbamoylmethyl)-5-methylhexanoic acid (isobutylglutarmonoamide).

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This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Pregelatinised Hydroxypropyl Starch

General Notices

(Ph. Eur. monograph 2645)

Ph Eur

DEFINITION

Pregelatinised hydroxypropyl starch is prepared from *Starch, hydroxypropyl (2165)* by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules, and subsequent drying.

Content

— *hydroxypropyl groups*: 0.5 per cent to 7.0 per cent.

PRODUCTION

The production of pregelatinised hydroxypropyl starch shall be in compliance with the requirements of the European legislation for food additives.

CHARACTERS

Appearance

White or slightly yellowish powder.

IDENTIFICATION

A. It swells in cold water.

B. Disperse 0.5 g in 2 mL of *water R*, without heating, and add 0.05 mL of *iodine solution R1*. A reddish-violet or greyish-blue colour is produced.

C. To 0.1 g add 12.5 mL of *dilute sulfuric acid R*. Heat in a water-bath until the sample is dissolved. Cool and dilute to 100 mL with *water R*. Introduce 1 mL of the solution into a 25 mL graduated test-tube with a ground-glass stopper and, with the tube immersed in cold water, add dropwise 8 mL of *sulfuric acid R*. Mix well and place the tube in a water-bath for exactly 3 min. Immediately transfer the tube to an ice-bath until the solution is chilled. Add 0.6 mL of *ninhydrin solution R2*, carefully allowing the reagent to run down the walls of the test-tube. Immediately shake well, and place the tube in a water-bath at 25 °C for 100 min. Dilute to 25 mL with *sulfuric acid R* and mix by inverting the tube several times. Do not shake. A violet colour develops within 5 min.

TESTS

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TESTS

pH (*2.2.3*)

4.5 to 8.0.

Progressively add 3.0 g to 100.0 mL of *carbon dioxide-free water R*, stirring continuously. Determine the pH when a homogeneous solution is obtained.

Impurity A

Gas chromatography (*2.2.28*).

Internal standard solution Mix 50.0 mg of *propane-1,3-diol R* with *anhydrous pyridine R* and dilute to 100.0 mL with the same solvent.

Test solution To 0.200 g of the substance to be examined add 1.0 mL of the internal standard solution and 9.0 mL of *anhydrous pyridine R*. Heat under a reflux condenser for 20 min. Allow to cool. Transfer 1.0 mL of this solution to a 2 mL vial with a screw cap fitted with a septum. Add 0.1 mL of *chlorotrimethylsilane R* and 0.2 mL of *hexamethyldisilazane R*. Close and mix. Allow to stand for 15 min.

Reference solution Mix 50.0 mg of *propane-1,3-diol R* and 50.0 mg of *propylene glycol CRS* (impurity A) with *anhydrous pyridine R* and dilute to 100.0 mL with the same solvent. Transfer 0.1 mL of the solution to a 2 mL vial with a screw cap fitted with a septum. Add 0.1 mL of *chlorotrimethylsilane R*, 0.2 mL of *hexamethyldisilazane R* and 0.9 mL of *anhydrous pyridine R*. Close and mix. Allow to stand for 15 min.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

NOTE: the column must be desorbed regularly. Conditions: temperature program of 70 °C to 300 °C at a rate of 7 °C/min. Maintain for 10 min at 300 °C.

Carrier gas *helium for chromatography R*.

Flow rate 3 mL/min.

Split ratio 1:30.

Temperature:

— *column*: 70 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL.

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Relative retention With reference to the trimethylsilyl derivative of propane-1,3-diol (retention time = about 8.5 min): trimethylsilyl derivative of propylene glycol = about 0.7.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to the trimethylsilyl derivative of propylene glycol and the trimethylsilyl derivative of propane-1,3-diol.

Calculation of percentage contents Use the internal standard method.

Limit:

— *impurity A*: maximum 0.1 per cent.

Oxidising substances (2.5.30)

Maximum 20 ppm, calculated as H_2O_2.

Use a mixture of equal volumes of *methanol R* and *water R* as solvent.

Sulfur dioxide (2.5.29)

Maximum 50 ppm.

Iron (2.4.9)

— For pregelatinised hydroxypropyl starch obtained from maize, potato, cassava or rice: maximum 20 ppm.

Dissolve the residue obtained in the test for sulfated ash in 20 mL of *dilute hydrochloric acid R* and filter. The filtrate complies with the test for iron.

— For pregelatinised hydroxypropyl starch obtained from pea: maximum 50 ppm.

Dissolve the residue obtained in the test for sulfated ash in 50 mL of *dilute hydrochloric acid R* and filter. The filtrate complies with the test for iron.

Loss on drying

(2.2.32) determined on 1.000 g by drying in an oven at 130 °C for 90 min:

— maximum 15.0 per cent for pregelatinised hydroxypropyl starch obtained from maize, cassava, rice or pea;

— maximum 20.0 per cent for pregelatinised hydroxypropyl starch obtained from potato.

Sulfated ash (2.4.14)

Maximum 0.6 per cent, determined on 1.0 g.

Microbial contamination

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TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

ASSAY

Nuclear magnetic resonance spectrometry (2.2.33).

Internal standard solution Disperse 50.0 mg of *3-trimethylsilyl-1-propanesulfonic acid sodium salt CRS* in about 5 g of *deuterium oxide R1*, weighed to the nearest 0.1 mg. Store in a sealed bottle.

Test solution Dry 5.000 g of the substance to be examined at 130 °C for 90 min. Weigh 12.0 mg of the dried substance in a 5 mm NMR tube. Add 0.1 mL of *deuterium chloride solution R* and 0.75 mL of *deuterium oxide R1*. Cap the tube, mix, and place it in a water-bath until a clear solution is obtained (3 min to maximum 1 h). When a clear solution is obtained, allow to cool to room temperature. Dry the exterior of the tube and weigh to the nearest 0.1 mg. Add 0.05 mL of the internal standard solution and weigh to the nearest 0.1 mg. Determine the mass of the internal standard solution introduced. Mix thoroughly.

Apparatus FT-NMR spectrometer operating at minimum 300 MHz.

Acquisition of ^1H NMR spectra The following parameters may be used:

— *sweep width*: 8 ppm (-1.0 to + 7 ppm);

— *irradiation frequency offset*: none;

— *time domain*: at least 64 K;

— *pulse width*: 90°;

— *pulse delay*: 10 s;

— *dummy scans*: 0;

— *number of scans*: 8.

Use the CH_3 signal of the internal standard for shift referencing. The shift of the singlet is set to 0 ppm.

Record the FID signal.

Call the integration sub-routine after phase corrections and baseline correction between -0.5 ppm and + 6 ppm.

Measure the peak areas of the doublet from the methyl groups of the hydroxypropyl function at + 1.2 ppm (A_2), and of the methyl groups at 0 ppm of the internal standard (A_1) without ^{13}C-satellites.

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Results Measure the signal coming from the 3 protons of the methyl group in the hydroxypropyl function; calculate the percentage content of hydroxypropyl groups using the following expression:

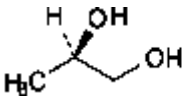
$$\frac{3A_2}{A_1} \times \frac{P}{100} \times \frac{W_1 \times m_1}{218} \times 59 \times \frac{100}{m}$$

3	=	numerical value representing the 3 methyl groups in the internal standard;
A_1	=	area of the methyl groups in the internal standard;
A_2	=	area of the methyl groups of hydroxypropyl;
P	=	percentage content of *3-trimethylsilyl-1-propanesulfonic acid sodium salt CRS*;
W_1	=	mass fraction of the internal standard in the internal standard solution, in milligrams per gram;
m_1	=	mass of the internal standard solution in the NMR tube, in grams;
218	=	molar mass of the internal standard, in grams per mole;
59	=	molar mass of the hydroxypropyl group, in grams per mole;
m	=	mass of the substance to be examined in the NMR tube, in milligrams.

LABELLING

The label states the botanical source of the starch and the type of modification.

IMPURITIES



and enantiomer

A. (2*RS*)-propane-1,2-diol (propylene glycol).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for pregelatinised hydroxypropyl starch used as film former in oral solid dosage forms.

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Hydroxypropyl groups content

(see Assay).

Appearance of a film

Dissolve 15 g in 50 mL of *water R* and spread on glass plate. A clear film is formed.

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Pregelatinised Starch

General Notices

Pregelatinised Maize Starch

(Ph. Eur. monograph 1267)

When Pregelatinised Starch is prepared *Zea mays*, the title Pregelatinised Maize Starch may be used.

Ph Eur

DEFINITION

Pregelatinised starch is prepared from *Maize starch (0344)*, *Potato starch (0355)* or *Rice starch (0349)* by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules, and subsequent drying. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics.

CHARACTERS

Appearance

White or yellowish-white powder.

It swells in cold water.

IDENTIFICATION

A. Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R* it presents irregular, translucent, white or yellowish-white flakes or pieces with an uneven surface. Under polarised light (between crossed nicol prisms), starch granules with a distinct black cross intersecting at the hilum may be seen.

B. Disperse 0.5 g in 2 mL of *water R* without heating and add 0.05 mL of *iodine solution R1*. A reddish-violet or blue colour is produced.

TESTS

pH (*2.2.3*)

4.5 to 7.0.

Progressively add 3.0 g to 100.0 mL of *carbon dioxide-free water R*, stirring continuously. Determine the pH when a homogeneous solution is obtained.

Oxidising substances (*2.5.30*)

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It complies with the test for oxidising substances. Use a mixture of equal volumes of *methanol R* and *water R* as solvent.

Sulfur dioxide (2.5.29)

Maximum 50 ppm.

Iron (2.4.9)

Maximum 20 ppm.

Dissolve the residue obtained in the test for sulfated ash in 20 mL of *dilute hydrochloric acid R*. Filter. The filtrate complies with the test.

Foreign matter

Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R*, not more than traces of matter other than starch granules are present.

Loss on drying (2.2.32)

Maximum 15.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 90 min.

Sulfated ash (2.4.14)

Maximum 0.6 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

LABELLING

The label states the type of starch used as starting material.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the

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purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for pregelatinised starch used as filler, binder or disintegrant in tablets and in hard capsules.

Cold-water-soluble matter

Transfer 100 mL of *water R* at 25 ± 1 °C into a beaker and add 1.000-3.000 g of the substance to be examined while stirring. Continue to stir for 10 min. Transfer 35 mL of the dispersion to a centrifuge tube and centrifuge at 3000 *g* for 15 min. Transfer 25 mL of the supernatant to a crucible that has previously been dried in an oven at 120 ± 2 °C for 4 h and weighed to the nearest 0.1 mg. Evaporate to dryness on a water-bath, then place the crucible in an oven at 120 ± 2 °C for 4 h. Allow to cool in a desiccator. Weigh the crucible to the nearest 0.1 mg again.

Determine the percentage of cold-water-soluble matter using the following expression:

$$\frac{(B-A)\times\frac{100}{25}\times 100}{S\times\frac{100-C}{100}}$$

A	=	initial crucible mass, in grams;
B	=	final crucible mass, in grams;
C	=	loss on drying, in per cent;
S	=	sample mass, in grams.

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

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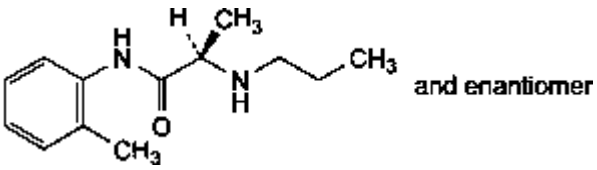
Prilocaine

General Notices

(Ph. Eur. monograph 1362)



and enantiomer

$C_{13}H_{20}N_2O$ 220.3 *721-50-6*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

(2*RS*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, very soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Preparation Prepare a film between 2 plates of *sodium chloride R* by heating at 40-45 °C until the substance has melted.

Comparison *prilocaine CRS*.

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TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 2.50 g in 15 mL of *dilute hydrochloric acid R* and dilute to 50.0 mL with *water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.5 mg of the substance to be examined and 3 mg of *prilocaine impurity E CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 33.5 mg of *prilocaine impurity B CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 15 mg of *prilocaine for peak identification CRS* (containing impurity G) in the mobile phase and dilute to 5.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 26 volumes of *acetonitrile for chromatography R* and 74 volumes of a solution prepared as follows: dissolve 0.180 g of *sodium dihydrogen phosphate monohydrate R* and 2.89 g of *disodium hydrogen phosphate dihydrate R* in 1000 mL of *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time Twice the retention time of prilocaine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

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Relative retention With reference to prilocaine (retention time = about 25 min): impurity B = about 0.3; impurity G = about 0.8; impurity E = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to prilocaine and impurity E.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (100 ppm);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 22.03 mg of $C_{13}H_{20}N_2O$.

IMPURITIES

Specified impurities *B, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, F.*

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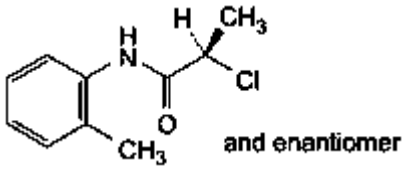
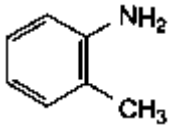
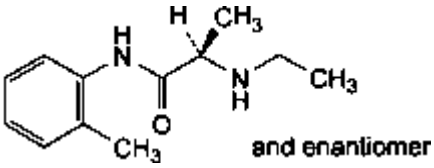


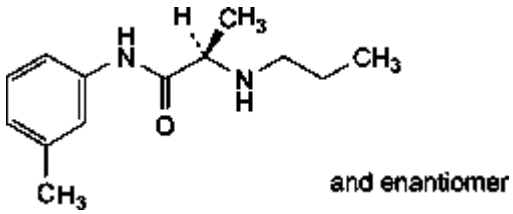
A. (2*RS*)-2-chloro-*N*-(2-methylphenyl)propanamide,



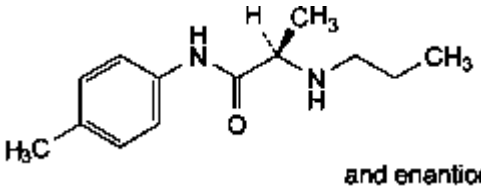
B. 2-methylbenzenamine (*o*-toluidine),



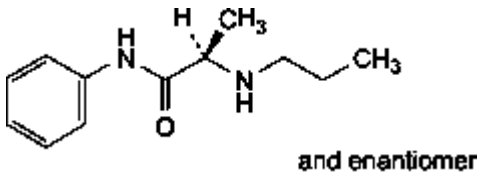
C. (2*RS*)-2-(ethylamino)-*N*-(2-methylphenyl)propanamide,



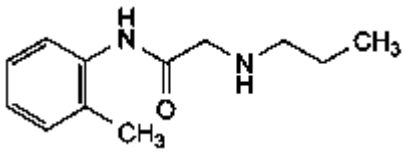
D. (2*RS*)-*N*-(3-methylphenyl)-2-(propylamino)propanamide,



E. (2*RS*)-*N*-(4-methylphenyl)-2-(propylamino)propanamide,



F. (2*RS*)-*N*-phenyl-2-(propylamino)propanamide,



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G. *N*-(2-methylphenyl)-2-(propylamino)acetamide.

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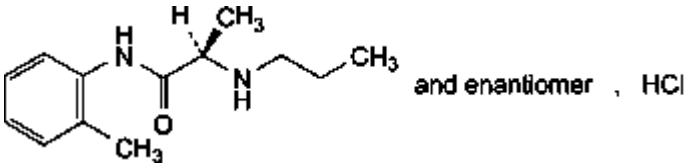
Prilocaine Hydrochloride

General Notices

(Ph. Eur. monograph 1363)



$C_{13}H_{21}ClN_2O$ 256.8 *1786-81-8*

Action and use

Local anaesthetic.

Preparation

Prilocaine Injection

Ph Eur

DEFINITION

(2*RS*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water and in ethanol (96 per cent), very slightly soluble in acetone.

IDENTIFICATION

First identification: B, D.

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Second identification: A, C, D.

A. Melting point (2.2.14): 168 °C to 171 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *prilocaine hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20.0 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 20.0 mg of *prilocaine hydrochloride CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 20.0 mg of *lidocaine hydrochloride CRS* and 20.0 mg of *prilocaine hydrochloride CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *1,1-dimethylethyl methyl ether R* (1:5:100 *V/V/V*).

Application 10 µL.

Development Over a path of 12 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

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Dilute 4 mL of solution S to 10 mL with *carbon dioxide-free water R*. Add 0.1 mL of *bromocresol green solution R* and 0.40 mL of *0.01 M sodium hydroxide*; the solution is blue. Add 0.80 mL of *0.01 M hydrochloric acid*; the solution is yellow.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 30 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 3 mg of the substance to be examined and 3 mg of *prilocaine impurity E CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 30.0 mg of *prilocaine impurity B CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 15 mg of *prilocaine for peak identification CRS* (containing impurity G) in the mobile phase and dilute to 5.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 26 volumes of *acetonitrile for chromatography R* and 74 volumes of a solution prepared as follows: dissolve 0.180 g of *sodium dihydrogen phosphate monohydrate R* and 2.89 g of *disodium hydrogen phosphate dihydrate R* in 1000 mL of *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time Twice the retention time of prilocaine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

Relative retention With reference to prilocaine (retention time = about 25 min): impurity B = about 0.3; impurity G = about 0.8; impurity E = about 1.2.

System suitability Reference solution (a):

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— *resolution*: minimum 3.0 between the peaks due to prilocaine and impurity E.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (100 ppm);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

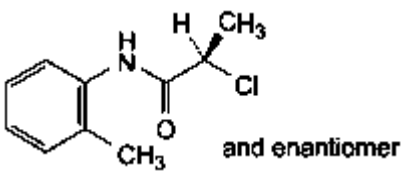
Dissolve 0.200 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 25.68 mg of $C_{13}H_{21}ClN_2O$.

IMPURITIES

Specified impurities *B, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, F.*



A. (2*RS*)-2-chloro-*N*-(2-methylphenyl)propanamide,

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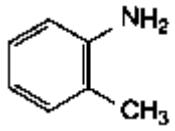
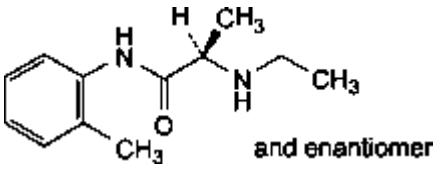
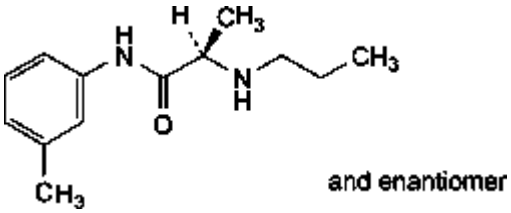


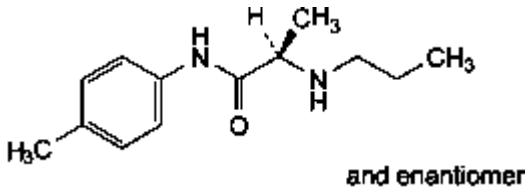
B. 2-methylbenzenamine (*o*-toluidine),



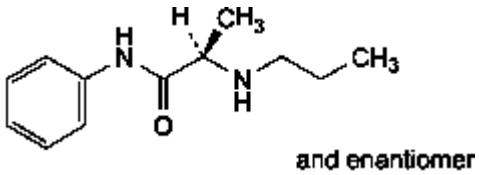
C. (2*RS*)-2-(ethylamino)-*N*-(2-methylphenyl)propanamide,



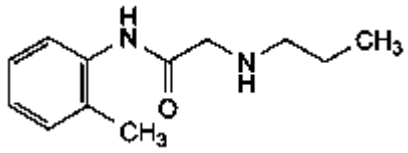
D. (2*RS*)-*N*-(3-methylphenyl)-2-(propylamino)propanamide,



E. (2*RS*)-*N*-(4-methylphenyl)-2-(propylamino)propanamide,



F. (2*RS*)-*N*-phenyl-2-(propylamino)propanamide,



G. *N*-(2-methylphenyl)-2-(propylamino)acetamide.

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Prilocaine Injection

General Notices

Action and use

Local anaesthetic.

DEFINITION

Prilocaine Injection is a sterile solution of Prilocaine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of prilocaine hydrochloride, $C_{13}H_{20}N_2O,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. To a volume containing 0.1 g of Prilocaine Hydrochloride add 2M *sodium hydroxide* until the solution is about pH 11. Add 20 mL of *ethyl acetate*, shake, allow the layers to separate, dry the organic layer over *anhydrous calcium chloride* at a pressure of 2 kPa, filter and evaporate the filtrate to dryness under reduced pressure. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of prilocaine (*RS 284*).

B. In the Assay, the principal peak in the chromatogram obtained with solution (3) has the same retention time as the peak due to prilocaine in the chromatogram obtained with solution (1).

TESTS

Acidity

pH, 5.0 to 7.0, Appendix V L.

Aromatic amines

To 1 mL of the injection, diluted if necessary to contain 0.05% w/v of Prilocaine Hydrochloride, add 1 mL of a 1% w/v solution of *4-dimethylaminobenzaldehyde* in *methanol* and 2 mL of *glacial acetic acid*. Shake and allow to stand for 10 minutes. Measure the *absorbance* of the solution at 430 nm, Appendix II B, using *water* in the reference cell. The absorbance is not more intense than that

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produced in a solution prepared at the same time and in the same manner but using 1 mL of a solution in *water* containing 5 µg per mL of o-*toluidine hydrochloride* (0.75%, calculated as *o*-toluidine).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.01% w/v of *prilocaine hydrochloride BPCRS* in the mobile phase. For solution (2) dilute the injection with the mobile phase to produce a solution containing 0.01% w/v of Prilocaine Hydrochloride.

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable), (b) a mixture of 30 volumes of 0.05M *mixed phosphate buffer pH 8* and 70 volumes of *methanol* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 240 nm.

Calculate the content of $C_{13}H_{20}N_2O$,HCl in the injection using the declared content of $C_{13}H_{20}N_2O$,HCl in *prilocaine hydrochloride BPCRS*.

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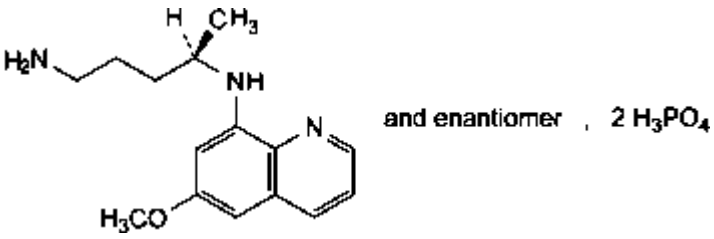
Primaquine Phosphate

General Notices

(Primaquine Diphosphate, Ph. Eur. monograph 0635)



$C_{15}H_{27}N_3O_9P_2$ 455.3 *63-45-6*

Action and use

Antiprotozoal (malaria).

Ph Eur

DEFINITION

(4*RS*)-N^4-(6-Methoxyquinolin-8-yl)pentane-1,4-diamine bis(dihydrogen phosphate).

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Orange, crystalline powder.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

mp

About 200 °C, with decomposition.

IDENTIFICATION

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First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution (a) Dissolve 15 mg in a 1.03 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with a 1.03 g/L solution of *hydrochloric acid R*.

Spectral range 310-450 nm for test solution (a); 215-310 nm for test solution (b).

Absorption maxima At 332 nm and 415 nm for test solution (a); at 225 nm, 265 nm and 282 nm for test solution (b).

Specific absorbance at the absorption maxima:

— at 332 nm: 45 to 52 for test solution (a);

— at 415 nm: 27 to 35 for test solution (a);

— at 225 nm: 495 to 515 for test solution (b);

— at 265 nm: 335 to 350 for test solution (b);

— at 282 nm: 330 to 345 for test solution (b).

B. Infrared absorption spectrophotometry (2.2.24).
Examine the substances in discs prepared as follows: dissolve separately 0.1 g of the substance to be examined and 0.1 g of the reference substance in 5 mL of *water R*, add 2 mL of *dilute ammonia R2* and 5 mL of *methylene chloride R*, then shake. Dry the methylene chloride layer over 0.5 g of *anhydrous sodium sulfate R*. Prepare a blank disc using about 0.3 g of *potassium bromide R*. Apply dropwise to the disc 0.1 mL of the methylene chloride layer, allowing the methylene chloride to evaporate between applications. Dry the disc at 50 °C for 2 min.

Comparison *primaquine diphosphate CRS*.

C. Thin-layer chromatography (2.2.27). *Carry out all operations as rapidly as possible, protected from light. Prepare the solutions immediately before use.*

Test solution Dissolve 0.20 g of the substance to be examined in 5 mL of *water R* and dilute to 10 mL with *methanol R*. Dilute 1 mL of this solution to 10 mL with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution Dissolve 20 mg of *primaquine diphosphate CRS* in 5 mL of *water R* and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel GF_{254} plate R*.

Pretreatment Wash the plate with the mobile phase and allow to dry in air.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (1:40:60 *V/V/V*).

Application 5 µL.

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Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 50 mg in 5 mL of *water R*. Add 2 mL of *dilute sodium hydroxide solution R* and shake with 2 quantities, each of 5 mL, of *methylene chloride R*. The aqueous layer, acidified by addition of *nitric acid R*, gives reaction (b) of phosphates (*2.3.1*).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution *Use a freshly prepared solution.* Dissolve 25.0 mg of the substance to be examined in mobile phase A, using sonication if necessary, and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *primaquine for system suitability CRS* (containing impurity A) in mobile phase A and dilute to 10 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography with embedded polar groups R* (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *tetrahydrofuran R*, *acetonitrile R*, *water for chromatography R* (0.1/1/9/90 *V/V/V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 40	100 → 50	0 → 50

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Flow rate 1.2 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 25 µL.

Relative retention With reference to primaquine (retention time = about 13 min): impurity A = about 0.86.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity A and primaquine.

Calculation of percentage contents:

— for each impurity, use the concentration of primaquine diphosphate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.200 g in 40 mL of *anhydrous acetic acid R*, heating gently. Allow to cool and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 22.77 mg of $C_{15}H_{27}N_3O_9P_2$.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D.*

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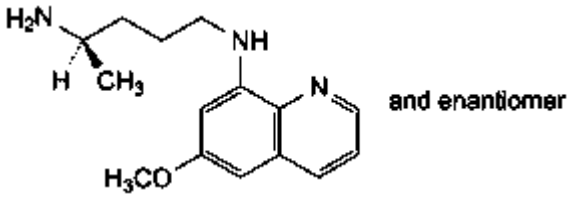
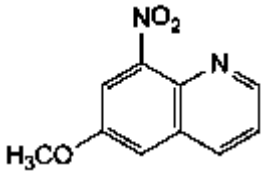
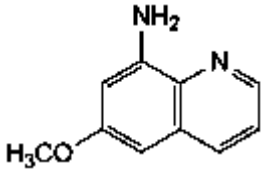


and enantiomer

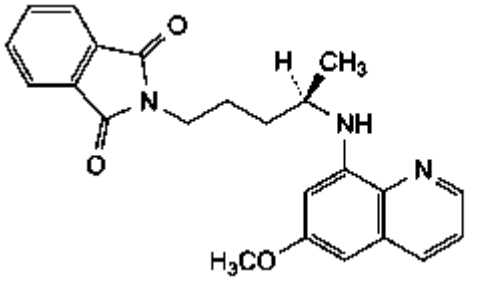
A. (4*RS*)-N^1-(6-methoxyquinolin-8-yl)pentane-1,4-diamine (quinocide),



B. 6-methoxy-8-nitroquinoline,



C. 6-methoxyquinolin-8-amine,



and enantiomer

D. 2-[(4*RS*)-4-[(6-methoxyquinolin-8-yl)amino]pentyl]-1*H*-isoindole-1,3(2*H*)-dione.

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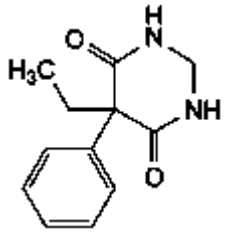
Primidone

General Notices

(Ph. Eur. monograph 0584)



$C_{12}H_{14}N_2O_2$ 218.3 *125-33-7*

Action and use

Antiepileptic.

Preparations

Primidone Oral Suspension

Primidone Tablets

Ph Eur

DEFINITION

5-Ethyl-5-phenyl-1,3-diazinane-4,6-dione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in alkaline solutions.

IDENTIFICATION

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison primidone CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in methanol R and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with methanol R. Dilute 1.0 mL of this solution to 10.0 mL with methanol R.

Reference solution (b) Dissolve 5 mg of primidone for system suitability CRS (containing impurities B and C) in methanol R and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped monolithic octadecylsilyl silica gel for chromatography R (2 µm).

Mobile phase:

— *mobile phase A*: 1.36 g/L solution of potassium dihydrogen phosphate R;

— *mobile phase B*: methanol R2;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	75	25
1 - 6	75 → 40	25 → 60
6 - 8	40	60

Flow rate 3.2 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with primidone for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to primidone (retention time = about 2.2 min): impurity B = about 1.4; impurity C = about 1.6.

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System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurities B and C.

Calculation of percentage contents:

— for each impurity, use the concentration of primidone in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

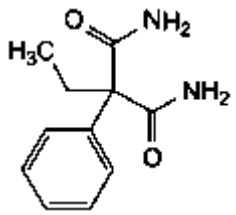
ASSAY

Dissolve 60.0 mg with heating in 70 mL of *ethanol (96 per cent) R*, cool and dilute to 100.0 mL with the same solvent. Prepare a reference solution in the same manner using 60.0 mg of *primidone CRS*. Measure the absorbance (2.2.25) of the 2 solutions at the absorption maximum at 257 nm.

Calculate the content of $C_{12}H_{14}N_2O_2$ from the absorbances measured and the concentrations of the solutions.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F.



A. 2-ethyl-2-phenylpropanediamide (ethylphenylmalonamide),

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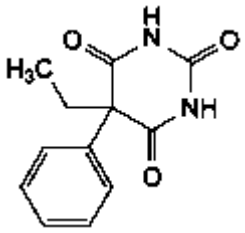
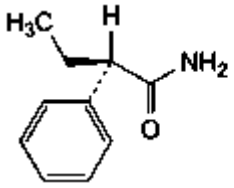
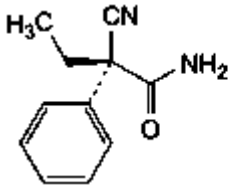


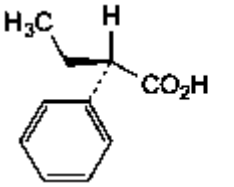
B. 5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione (phenobarbital),



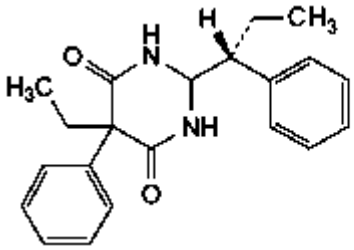
C. (2*RS*)-2-phenylbutanamide,



D. (2*RS*)-2-cyano-2-phenylbutanamide,



E. (2*RS*)-2-phenylbutanoic acid,



F. 5-ethyl-5-phenyl-2-[(1*RS*)-1-phenylpropyl]-1,3-diazinane-4,6-dione.

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Primidone Oral Suspension

General Notices

Primidone Oral Suspensions from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Antiepileptic.

DEFINITION

Primidone Oral Suspension is a suspension of Primidone in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of primidone, $C_{12}H_{14}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to primidone in the chromatogram obtained with solution (3).

B. To a quantity containing 0.5 g of Primidone add 100 mL of *methanol*, boil gently for 10 minutes, stirring constantly, centrifuge, evaporate the clear supernatant liquid almost to dryness on a water bath, add 40 mL of *water* at about 60°, stir for 3 minutes, filter under reduced pressure, wash the residue with three 5 mL quantities of hot *water* and dry at 100° to 105° for 30 minutes. Dissolve 0.1 g of the residue in 5 mL of *chromotropic acid-sulfuric acid solution* and heat in a water bath for 30 minutes. A pinkish blue colour is produced.

ASSAY

Carry out the method for *gas chromatography*, Appendix III B. Dissolve 0.24 g of N-*phenylcarbazole* (internal standard) in sufficient *methanol* to produce 100 mL (solution A).

(1) Add 100 mL of *methanol* to a weighed quantity of the oral suspension containing 0.3 g of Primidone and heat on a water bath for 5 minutes, shaking occasionally, cool, allow any undissolved material to settle and use the supernatant liquid.

(2) Prepare in the same manner as solution (1) but add 50 mL of solution A and 50 mL of *methanol* in place of 100 mL of *methanol*.

(3) Add 25 mL of solution A to 0.15 g of *primidone BPCRS* and add sufficient methanol to produce 50 mL, warming to dissolve if necessary.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 200 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable).

(b) Use isothermal conditions maintained at 260°.

(c) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_{12}H_{14}N_2O_2$ using the declared content of $C_{12}H_{14}N_2O_2$ in *primidone BPCRS*. Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{12}H_{14}N_2O_2$, weight in volume.

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Primidone Tablets

General Notices

Primidone Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Antiepileptic.

DEFINITION

Primidone Tablets contain Primidone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of primidone, $C_{12}H_{14}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of Primidone with 50 mL of hot *ethanol* (*96%*), filter and evaporate the filtrate to dryness. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of primidone (*RS 286*).

B. Dissolve 0.1 g in 5 mL of *chromotropic acid-sulfuric acid solution* and heat in a water bath for 30 minutes. A pinkish blue colour is produced.

2-Ethyl-2-phenylmalondiamide

Dissolve 25 mg of *octadecan-1-ol* (internal standard) in sufficient *pyridine* to produce 50 mL (solution A). Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) add 2 mL of solution A and 1 mL of *N,O-bis(trimethylsilyl)acetamide* to 2 mL of a 0.050% w/v solution of *2-ethyl-2-phenylmalondiamide* in *pyridine*. For solution (2) mix of a quantity of the powdered tablets containing 0.1 g of Primidone with 2 mL of *pyridine*, add 2 mL of solution A and 1 mL of *N,O-bis-(trimethylsilyl)acetamide*, allow to stand at 100° for 5 minutes, cool and dilute to 10 mL with *pyridine*. Prepare solution (3) in the same manner as solution (2) but use 4 mL of *pyridine* and omit the addition of solution A.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable) and maintained at 170°.

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In the chromatogram obtained with solution (2) the ratio of the area of any peak derived from 2-ethyl-2-phenylmalondiamide to the area of the peak derived from the internal standard is not greater than the corresponding ratio in the chromatogram obtained with solution (1).

ASSAY

Weigh and powder 20 tablets. Dissolve 0.24 g of *N-phenylcarbazole* (internal standard) in sufficient *methanol* to produce 100 mL (solution A). Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) add 25 mL of solution A to 0.15 g of *primidone BPCRS* and dilute to 50 mL with *methanol*, warming to dissolve if necessary. For solution (2) add 100 mL of *methanol* to a quantity of the powdered tablets containing 0.3 g of Primidone, heat on a water bath for 5 minutes, shaking occasionally, cool, allow any undissolved material to settle and use the clear supernatant liquid. Prepare solution (3) in the same manner as solution (2) but add 50 mL of solution A and 50 mL of *methanol* in place of 100 mL of *methanol*.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable) and maintained at 260°.

Calculate the content of $C_{12}H_{14}N_2O_2$ using the declared content of $C_{12}H_{14}N_2O_2$ in *primidone BPCRS*.

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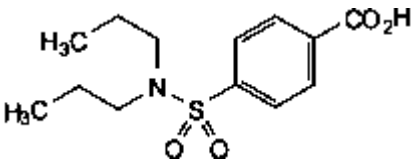
Probenecid

General Notices

(Ph. Eur. monograph 0243)



$C_{13}H_{19}NO_4S$ 285.4 *57-66-9*

Action and use

Uricosuric drug.

Preparation

Probenecid Tablets

Ph Eur

DEFINITION

4-(Dipropylsulfamoyl)benzoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or small crystals.

Solubility

Practically insoluble in water, soluble in acetone, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: A, C.

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Second identification: A, B, D.

A. Melting point (2.2.14): 197 °C to 202 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20 mg in a mixture of 1 volume of *0.1 M hydrochloric acid* and 9 volumes of *ethanol (96 per cent) R* and dilute to 100.0 mL with the same mixture of solvents. Dilute 5.0 mL of the solution to 100.0 mL with a mixture of 1 volume of *0.1 M hydrochloric acid* and 9 volumes of *ethanol (96 per cent) R*.

Spectral range 220-350 nm.

Absorption maxima At 223 nm and 248 nm.

Specific absorbance at the absorption maximum at 248 nm 310 to 350.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *probenecid CRS*.

D. Dissolve 0.2 g in the smallest necessary quantity of *dilute ammonia R2* (about 0.6 mL). Add 3 mL of *silver nitrate solution R2*. A white precipitate is formed which dissolves in an excess of ammonia.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 1.0 g in *1 M sodium hydroxide* and dilute to 10 mL with the same solvent.

Acidity

To 2.0 g add 100 mL of *water R* and heat on a water-bath for 30 min. Make up to the original volume with *water R*, allow to cool to room temperature and filter. To 50 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. Not more than 0.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (2.2.29).

Solution A Mix 1 volume of *glacial acetic acid R* and 100 volumes of *acetonitrile R*.

Solution B Mix 1 volume of *glacial acetic acid R* and 100 volumes of a 6.9 g/L solution of *sodium dihydrogen phosphate monohydrate R* in *water for chromatography R* and adjust to pH 3.0 with *dilute phosphoric acid R*.

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *potassium 4-sulfobenzoate R* (impurity A) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Solution A, solution B (50:50 *V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time 4 times the retention time of probenecid.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to probenecid (retention time = about 7 min): impurity A = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and probenecid.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.4;

— for each impurity, use the concentration of probenecid in reference solution (a).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

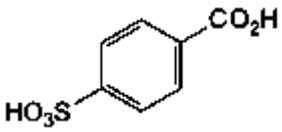
Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R*, shaking and heating slightly if necessary. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.54 mg of $C_{13}H_{19}NO_4S$.

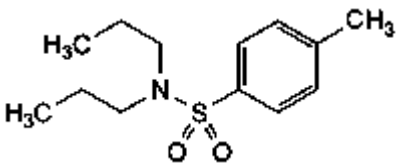
IMPURITIES

Specified impurities *A.*

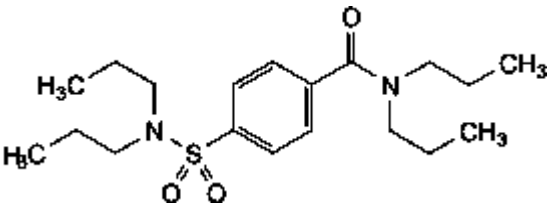
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D.*



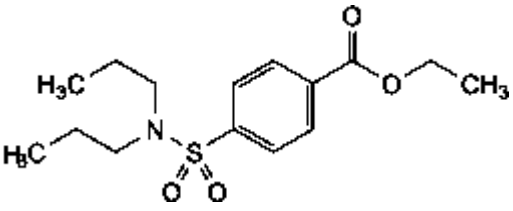
A. 4-sulfobenzoic acid,



B. 4-methyl-*N*,*N*-dipropylbenzenesulfonamide,



C. 4-(dipropylsulfamoyl)-*N*,*N*-dipropylbenzamide,



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D. ethyl 4-(dipropylsulfamoyl)benzoate.

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Probenecid Tablets

General Notices

Action and use

Uricosuric drug.

DEFINITION

Probenecid Tablets contain Probenecid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of probenecid, $C_{13}H_{19}NO_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Triturate a quantity of the powdered tablets containing 0.5 g of Probenecid with *ethanol* (*96%*), filter, concentrate the filtrate by evaporation on a water bath, cool, filter and recrystallise the residue from *ethanol* (*50%*). The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of probenecid (*RS 287*).

B. The *light absorption* of the final solution obtained in the Assay, Appendix II B, exhibits maxima at 225 nm and 248 nm.

C. *Melting point* of the residue obtained in test A, about 199°, Appendix V A.

TESTS

Disintegration

Maximum time, 30 minutes, Appendix XII A1.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *glacial acetic acid*, 15 volumes of *chloroform*, 20 volumes of *di-isopropyl ether* and 55 volumes of *toluene* as the mobile phase. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 0.2 g of Probenecid with 20 mL of *acetone*, filter and use the filtrate. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *acetone*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

Dissolution

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Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Rotate the paddle at 50 revolutions per minute and use as the medium 900 mL of a phosphate buffer prepared in the following manner. Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 250 mL of *water*, add 190 mL of 0.2M *sodium hydroxide* and 400 mL of *water*, adjust the pH to 7.5 with 0.2M *sodium hydroxide* and add sufficient *water* to produce 1000 mL. Withdraw a sample of 10 mL of the medium, filter and dilute 4 mL of the filtrate to 100 mL with 0.1M *sodium hydroxide*. Measure the *absorbance* of this solution, Appendix II B, at 244 nm using in the reference cell a solution prepared by diluting 4 mL of the phosphate buffer to 100 mL with 0.1M *sodium hydroxide*. Calculate the total content of $C_{13}H_{19}NO_4S$ in the medium taking 359 as the value of A(1%, 1 cm) at the maximum at 244 nm.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.2 g of Probenecid add 200 mL of *ethanol* (*96%*) and 5 mL of 1M *hydrochloric acid*, heat on a water bath at 70° for 30 minutes, shaking occasionally, cool, add sufficient *ethanol* (*96%*) to produce 250 mL and filter. To 5 mL of the filtrate add 5 mL of 0.1M *hydrochloric acid*, dilute to 250 mL with *ethanol* (*96%*) and measure the *absorbance* of the resulting solution at the maximum at 248 nm, Appendix II B. Calculate the content of $C_{13}H_{19}NO_4S$ taking 332 as the value of A(1%, 1 cm) at the maximum at 248 nm.

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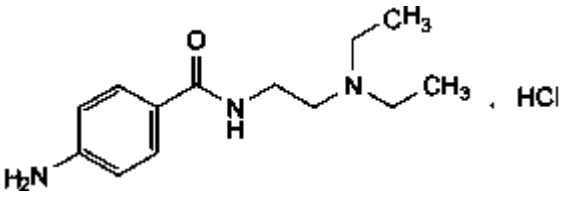
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Procainamide Hydrochloride

General Notices

(Ph. Eur. monograph 0567)



$C_{13}H_{22}ClN_3O$ 271.8 *614-39-1*

Action and use

Class I antiarrhythmic.

Preparations

Procainamide Injection

Procainamide Tablets

Ph Eur

DEFINITION

Procainamide hydrochloride contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 4-amino-*N*-[2-(diethylamino)ethyl]benzamide hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or very slightly yellow, crystalline powder, hygroscopic, very soluble in water, freely soluble in ethanol (96 per cent), slightly soluble in acetone.

IDENTIFICATION

First identification: C, D.

Second identification: A, B, D, E.

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A. Melting point (2.2.14): 166 °C to 170 °C.

B. Dissolve 10.0 mg in *0.1 M sodium hydroxide* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *0.1 M sodium hydroxide*. Examined between 220 nm and 350 nm (2.2.25), the solution shows an absorption maximum at 273 nm. The specific absorbance at the maximum is 580 to 610.

C. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *procainamide hydrochloride CRS*.

D. Dilute 1 mL of solution S to 5 mL with *water R*. The solution gives reaction (a) of chlorides (2.3.1).

E. Dilute 1 mL of solution S (see Tests) to 2 mL with *water R*. 1 mL of this solution gives the reaction of primary aromatic amines (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_6 (2.2.2, *Method II*).

pH (2.2.3)

The pH of solution S is 5.6 to 6.3.

Related substances

Examine by thin-layer chromatography (2.2.27), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 0.10 g of the substance to be examined in *alcohol R* and dilute to 10 mL with the same solvent.

Reference solution Dilute 1 mL of the test solution to 200 mL with *alcohol R*.

Apply to the plate 5 µL of each solution. Develop over a path of 12 cm using a mixture of 15 volumes of *glacial acetic acid R*, 30 volumes of *water R* and 60 volumes of *butanol R*. Place the plate in a stream of cold air until the plate appears dry. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Loss on drying (2.2.32)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.2500 g in 50 mL of *dilute hydrochloric acid R*. Carry out the determination of primary aromatic amino-nitrogen (2.5.8).

1 mL of *0.1 M sodium nitrite* is equivalent to 27.18 mg of $C_{13}H_{22}ClN_3O$.

STORAGE

Store in an airtight container, protected from light.

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Procainamide Injection

General Notices

Action and use

Class I antiarrhythmic.

DEFINITION

Procainamide Injection is a sterile solution of Procainamide Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of procainamide hydrochloride, $C_{13}H_{21}N_3O,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Dilute a volume containing 0.25 g of Procainamide Hydrochloride to 25 mL with *water*, make alkaline with 5M *sodium hydroxide* and extract with two 10 mL quantities of *chloroform*. Filter the combined extracts through *anhydrous sodium sulfate*, evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 5 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of procainamide (*RS 288*).

B. Dilute with *water* to produce a solution containing 0.0005% w/v of Procainamide Hydrochloride. The *absorbance* at 280 nm is about 0.30, Appendix II B.

C. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 4.0 to 5.5, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dilute a volume of the injection containing 0.10 g of Procainamide Hydrochloride to 5 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes.

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CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of a 20% v/v solution of 13.5M *ammonia* in *methanol* to each point of application and 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *alcoholic dimethylaminobenzaldehyde solution*.

MOBILE PHASE

0.7 volumes of 13.5M *ammonia*, 30 volumes of *methanol* and 70 volumes of *chloroform*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

To a volume containing 0.5 g of Procainamide Hydrochloride add 45 mL of *6M hydrochloric acid* and boil for 1 minute. Cool and titrate with 0.1M *sodium nitrite VS*, using 1 mL of *ferrocyphen solution* as indicator, until a violet colour is produced that is stable for not less than 3 minutes. Repeat the operation without the injection. The difference between the titrations represents the amount of sodium nitrite required. Each mL of 0.1M *sodium nitrite VS* is equivalent to 27.18 mg of $C_{13}H_{21}N_3O,HCl$.

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Procainamide Tablets

General Notices

Action and use

Class I antiarrhythmic.

DEFINITION

Procainamide Tablets contain Procainamide Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of procainamide hydrochloride, $C_{13}H_{21}N_3O,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.25 g of Procainamide Hydrochloride with 25 mL of *water*, make alkaline with 5M *sodium hydroxide* and extract with two 5 mL quantities of *chloroform*. Filter the combined extracts through *anhydrous sodium sulfate*, evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 5 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of procainamide (*RS 288*).

B. Triturate a quantity of the powdered tablets containing 2 g of Procainamide Hydrochloride with 20 mL of *water* and filter. Reserve 10 mL of the filtrate for test C. To the remainder add 10 mL of 5M *sodium hydroxide* and extract with 10 mL of *chloroform*. Add 10 mL of *toluene* to the extract, dry over *anhydrous sodium sulfate* and filter. Mix the filtrate with 5 mL of dry *pyridine*, add 1 mL of *benzoyl chloride* drop wise, heat on a water bath for 30 minutes and pour into 100 mL of 2.5M *sodium hydroxide*. Extract with 10 mL of *ether*, wash the extract with 20 mL of *water*, dilute with 30 mL of *ether* and allow to crystallise. The *melting point* of the crystals, after recrystallisation from *ethanol* (*45%*), is about 186°, Appendix V A.

C. 10 mL of the filtrate reserved in test B yields the reactions characteristic of *chlorides*, Appendix VI.

Related substances

Comply with the test described under Procainamide Injection using the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.4 g of Procainamide Hydrochloride with 20 mL of *methanol* (*90%*) for 15 minutes and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *methanol*.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.5 g of Procainamide Hydrochloride in a stoppered flask add 100 mL of *6M hydrochloric acid*, shake for 15 minutes and titrate with 0.1M *sodium nitrite VS*, using *ferrocyphen solution* as indicator, until a violet

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colour is produced that is stable for not less than 3 minutes. Repeat the operation without the powdered tablets. The difference between the titrations represents the amount of sodium nitrite required. Each mL of 0.1M *sodium nitrite VS* is equivalent to 27.18 mg of $C_{13}H_{21}N_3O,HCl$.

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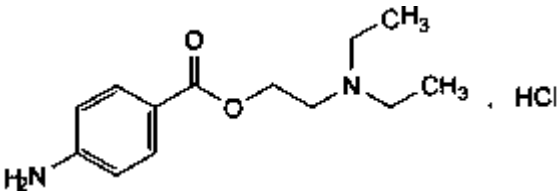
Procaine Hydrochloride

General Notices

(Ph. Eur. monograph 0050)



$C_{13}H_{21}ClN_2O_2$ 272.8 *51-05-8*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

Procaine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 2-(diethylamino)ethyl 4-aminobenzoate hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E, F.

A. Melting point (2.2.14): 154 °C to 158 °C.

B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *procaine hydrochloride CRS*.

C. To about 5 mg add 0.5 mL of *fuming nitric acid R*. Evaporate to dryness on a water-bath, allow to cool and dissolve the residue in 5 mL of *acetone R*. Add 1 mL of *0.1 M alcoholic potassium hydroxide*. Only a brownish-red colour develops.

D. To 0.2 mL of solution S (see Tests) add 2 mL of *water R* and 0.5 mL of *dilute sulfuric acid R* and shake. Add 1 mL of a 1 g/L solution of *potassium permanganate R*. The colour is immediately discharged.

E. It gives reaction (a) of chlorides (2.3.1).

F. Dilute 1 mL of solution S to 100 mL with *water R*. 2 mL of this solution gives the reaction of primary aromatic amines (2.3.1).

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TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

Dilute 4 mL of solution S to 10 mL with *carbon dioxide-free water R*. The pH of the solution is 5.0 to 6.5.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *4-aminobenzoic acid R* in *water R* and dilute to 100 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *water R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 10 cm using a mixture of 4 volumes of *glacial acetic acid R*, 16 volumes of *hexane R* and 80 volumes of *dibutyl ether R*. Dry the plate at 100 °C to 105 °C for 10 min and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.05 per cent). The principal spot in the chromatogram obtained with the test solution remains on the point of application.

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.00 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *dilute hydrochloric acid R*. Carry out the determination of primary aromatic amino nitrogen (*2.5.8*).

1 mL of *0.1 M sodium nitrite* is equivalent to 27.28 mg of $C_{13}H_{21}ClN_2O_2$.

STORAGE

Store protected from light.

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Prochlorperazine Buccal Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Prochlorperazine Buccal Tablets contain Prochlorperazine Maleate in a suitable basis.

The tablets comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of prochlorperazine maleate, $C_{20}H_{24}ClN_3S,2C_4H_4O_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 24 mg of Prochlorperazine Maleate add 10 mL of *water* and 1 mL of 1M *sodium hydroxide*, shake, extract with 25 mL of *dichloromethane* and evaporate to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of prochlorperazine (*RS 390*).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 10 volumes of *acetone*, 10 volumes of *diethylamine*, and 80 volumes of *cyclohexane* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 60 mg of Prochlorperazine Maleate with 5 mL of 0.18M *methanolic ammonia*, shake for 15 minutes, centrifuge and use the supernatant liquid. Solution (2) contains 0.006% w/v of *prochlorperazine maleate BPCRS* in 0.18M *methanolic ammonia*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%). Disregard any spot remaining on the line of application.

ASSAY

Weigh and finely powder 20 tablets. To a quantity of the powdered tablets containing 10 mg of Prochlorperazine Maleate add 50 mL of 1M *methanesulfonic acid*, shake for 5 minutes and disperse with the aid of ultrasound for 2 minutes. Add sufficient 1M *methanesulfonic acid* to produce 100 mL, mix, centrifuge the mixture and dilute 10 mL of the supernatant liquid to 100 mL with *water*. Measure the *absorbance* of the resulting solution at 254 nm, Appendix II B, using 0.1M *methanesulfonic acid* in the reference cell. Measure the *absorbance* of a solution

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prepared by diluting 1 volume of a 0.01% w/v solution of *prochlorperazine maleate BPCRS* in 1M *methanesulfonic acid* to 10 volumes with *water* using 0.1M *methanesulfonic acid* in the reference cell. Calculate the content of $C_{20}H_{24}ClN_3S,2C_4H_4O_4$ from the absorbances obtained and from the declared content of $C_{20}H_{24}ClN_3S,2C_4H_4O_4$ in *prochlorperazine maleate BPCRS*.

STORAGE

Prochlorperazine Buccal Tablets should be protected from light.

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Prochlorperazine Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Prochlorperazine Injection is a sterile solution of Prochlorperazine Mesilate in Water for Injections free from dissolved air.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of prochlorperazine mesilate, $C_{20}H_{24}ClN_3S,2CH_4SO_3$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. To a volume containing 0.1 g of Prochlorperazine Mesilate add 20 mL of *water* and 2 mL of 10M *sodium hydroxide*. Shake and extract the mixture with 25 mL of *ether*. Wash the ether layer with two 5 mL quantities of *water*, dry with *anhydrous sodium sulfate* and evaporate to dryness. Dissolve the residue in 1 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of prochlorperazine (*RS 289*).

B. To a volume containing 5 mg of Prochlorperazine Mesilate add carefully 2 mL of *sulfuric acid* and allow to stand for 5 minutes. A red colour is produced.

C. To a volume containing 0.2 g of Prochlorperazine Mesilate add 1.5 mL of 5M *sodium hydroxide* and extract with 10 mL of *ether*. Wash the ether layer with two 5 mL quantities of *water*, evaporate the ether layer to dryness, dissolve the residue in 10 mL of *methanol* and add a solution of 0.3 g of *picric acid* in a mixture of 5 mL of *methanol* and 5 mL of *water*. The *melting point* of the precipitate, after washing with 15 mL of *methanol*, is about 255°, with decomposition, Appendix V A.

TESTS

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Acidity

pH, 5.5 to 6.5, Appendix V L.

Related substances

Carry out the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and the following solutions. For solution (1) use the injection being examined. For solution (2) dilute 1 volume of solution (1) to 40 volumes with *methanol* containing 0.5% v/v of 13.5M *ammonia* immediately before use. For solution (3) dilute 1 volume of solution (1) to 200 volumes with the methanol–ammonia mixture immediately before use. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the principal spot in the chromatogram obtained with solution (2) (2.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Carry out the following procedure protected from light. To a quantity containing 12.5 mg of Prochlorperazine Mesilate add sufficient *absolute ethanol* containing 0.01% v/v of 13.5M *ammonia* to produce 100 mL. Dilute 5 mL of the solution to 100 mL with the ammoniacal ethanol and measure the *absorbance* of the resulting solution at the maximum at 258 nm, Appendix II B. Calculate the content of $C_{20}H_{24}ClN_3S,2CH_4SO_3$ taking 635 as the value of A(1%, 1 cm) at the maximum at 258 nm.

STORAGE

Prochlorperazine Injection should be protected from light.

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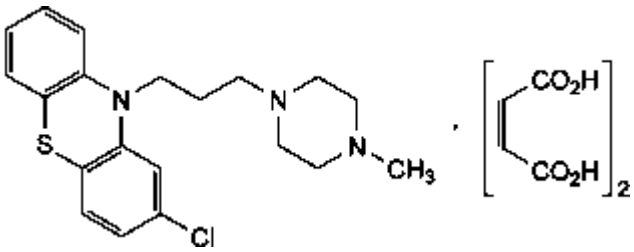
Prochlorperazine Maleate

General Notices

(Ph. Eur. monograph 0244)



$C_{28}H_{32}ClN_3O_8S$ 606 *84-02-6*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparations

Prochlorperazine Tablets

Prochlorperazine Buccal Tablets

Ph Eur

DEFINITION

2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine bis[hydrogen (2*Z*)-but-2-enedioate].

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or pale-yellow, crystalline powder.

Solubility

Very slightly soluble in water and in ethanol (96 per cent).

IDENTIFICATION

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IDENTIFICATION

First identification: A, B.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *prochlorperazine maleate CRS*.

B. Identification of phenothiazines by thin-layer chromatography (2.3.3) with the following modifications.

Test solution Dissolve 20 mg of the substance to be examined in a mixture of equal volumes of *methanol R* and *methylene chloride R*, and dilute to 20 mL with the same mixture of solvents.

Reference solution Dissolve 20 mg of *prochlorperazine maleate CRS* in a mixture of equal volumes of *methanol R* and *methylene chloride R*, and dilute to 20 mL with the same mixture of solvents.

Application 4 µL.

TESTS

pH (2.2.3)

3.0 to 4.0 for a freshly prepared saturated solution in *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Buffer solution Dissolve 0.96 g of *ammonium carbonate R* in about 800 mL of *water for chromatography R*. Adjust to pH 10.0 with *concentrated ammonia R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *prochlorperazine for system suitability CRS* (containing impurities B and D) in the mobile phase and dilute to 25 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped propyl-2-phenylsilyl amorphous organosilica polymer R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase *tetrahydrofuran R*, *methanol R*, buffer solution (15:33:52 *V/V/V*).

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Flow rate 0.4 mL/min.

Detection Spectrophotometer at 252 nm.

Injection 10 µL.

Run time 1.5 times the retention time of prochlorperazine.

Identification of impurities Use the chromatogram supplied with *prochlorperazine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and D.

Relative retention With reference to prochlorperazine (retention time = about 24 min): maleic acid = about 0.06; impurity B = about 0.56; impurity D = about 1.11.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to prochlorperazine.

Calculation of percentage contents:

— for each impurity, use the concentration of prochlorperazine maleate in reference solution (a).

Limits:

— *impurity B*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to maleic acid.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g of the powdered substance to be examined in 50 mL of *anhydrous acetic acid R*, warming on a water-bath. Allow to cool to room temperature. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid*, is equivalent to 30.31 mg of $C_{28}H_{32}ClN_3O_8S$.

STORAGE

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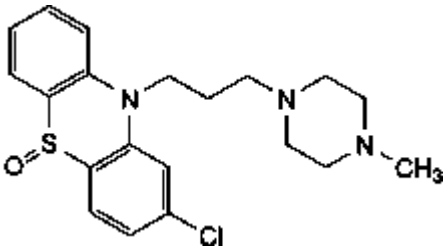
Protected from light.

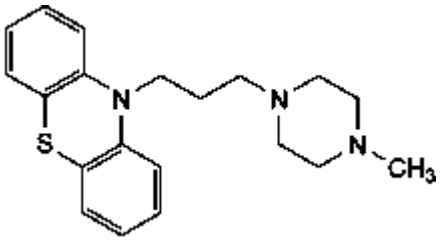
IMPURITIES

Specified impurities B.

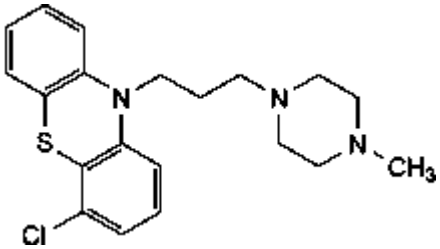
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D.



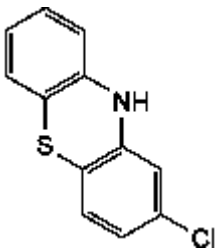
A. 2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-5λ^4-phenothiazin-5(10*H*)-one,



B. 10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine,



C. 4-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine,



D. 2-chloro-10*H*-phenothiazine.

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Prochlorperazine Oral Solution

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Prochlorperazine Oral Solution contains Prochlorperazine Mesilate in a suitable aqueous vehicle.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of prochlorperazine mesilate, $C_{20}H_{24}ClN_3S,2CH_4SO_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a volume of the oral solution containing 50 mg of Prochlorperazine Mesilate add 50 mL of *water* and 2 mL of 10M *sodium hydroxide*, add *sodium chloride* and extract with two 50 mL quantities of *ether*. Wash the combined ether extracts with two 5 mL quantities of *water*, filter through *anhydrous sodium sulfate* and evaporate to dryness. Dissolve the residue in 10 mL of *methanol* and add a solution prepared by dissolving 0.1 g of *picric acid* in a mixture of 5 mL of *methanol* and 5 mL of *water*, wash the resulting precipitate with 15 mL of *methanol* and dry at 100° for 40 minutes. The *melting point* of the dried precipitate is about 255°, with decomposition, Appendix V A.

B. In the test for Prochlorperazine sulfoxide, the principal spot in the chromatogram obtained with solution (2) is similar in position, size and intensity to that in the chromatogram obtained with solution (3).

Prochlorperazine sulfoxide

Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using a precoated silica gel F_{254} plate activated by drying at 105° for 1 hour and a mixture of 5 volumes of *diethylamine*, 45 volumes of *acetone* and 50 volumes of *hexane* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) mix a quantity of the oral solution containing 10 mg of Prochlorperazine Mesilate with 35 mL of *water* and 5 mL of a 20% w/v solution of *sodium hydroxide*, extract with four 40 mL quantities of *chloroform*, shaking for 2 minutes each time, and filter each extract through *anhydrous sodium sulfate* washing the sodium sulfate with 5 mL of *chloroform*. Evaporate the combined chloroform extracts and washings to dryness at 30° under reduced pressure using

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a current of *nitrogen* to remove the last of the solvent and dissolve the residue in 1 mL of a mixture of equal volumes of *chloroform* and *methanol*. For solution (2) dilute 1 volume of solution (1) to 10 volumes with a mixture of equal volumes of *chloroform* and *methanol*. Solution (3) contains 0.1% w/v of *prochlorperazine mesilate BPCRS* in a mixture of equal volumes of *chloroform* and *methanol*. Solution (4) contains 0.03% w/v of *prochlorperazine sulfoxide BPCRS* in a mixture of equal volumes of *chloroform* and *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any spot corresponding to prochlorperazine sulfoxide in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4) (3%).

ASSAY

Carry out the following procedure protected from light. To a weighed quantity containing 10 mg of Prochlorperazine Mesilate add 25 mL of *water* and 5 mL of a 10% w/v solution of *sodium hydroxide*. Extract the mixture with three 50 mL quantities of *chloroform*, shaking vigorously for 1 minute, allowing to separate and shaking vigorously for two further 1-minute intervals each time. Evaporate the combined extracts to dryness at about 30° under reduced pressure and dissolve the residue in sufficient *0.1M hydrochloric acid* to produce 25 mL (solution A). Dilute 10 mL of solution A to 50 mL with *water* (solution B). To a further 10 mL of solution A add 5 mL of *peroxyacetic acid solution*, allow to stand for 10 minutes and add sufficient *water* to produce 50 mL (solution C). Measure the *absorbance* of solution C at the maximum at 343 nm, Appendix II B, using solution B in the reference cell. Repeat the procedure using a 0.04% w/v solution of *prochlorperazine mesilate BPCRS* in *0.1M hydrochloric acid* in place of solution A and beginning at the words ‘Dilute 10 mL of...’. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{20}H_{24}ClN_3S,2CH_4SO_3$, weight in volume, using the declared content of $C_{20}H_{24}ClN_3S,2CH_4SO_3$ in *prochlorperazine mesilate BPCRS*.

STORAGE

Prochlorperazine Oral Solution should be protected from light.

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Prochlorperazine Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Prochlorperazine Tablets contain Prochlorperazine Maleate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of prochlorperazine maleate, $C_{20}H_{24}ClN_3S,2C_4H_4O_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 50 mg of Prochlorperazine Maleate add 20 mL of *water* and 2 mL of 1M *sodium hydroxide*, shake and extract with 50 mL of *dichloromethane* and evaporate the dichloromethane layer to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of prochlorperazine (*RS 390*).

B. To a quantity of the powdered tablets containing 5 mg of Prochlorperazine Maleate add 5 mL of *sulfuric acid* and allow to stand for 5 minutes. A red colour is produced.

C. To a quantity of the powdered tablets containing 0.2 g of Prochlorperazine Maleate add 2 mL of *water* and 1 mL of 5M *sodium hydroxide*, mix and extract with three 10 mL quantities of *ether*. Dry the combined extracts with *anhydrous sodium sulfate*, filter, evaporate to dryness, dissolve the residue in 10 mL of *methanol* and add a solution of 0.15 g of *picric acid* in 10 mL of *methanol*. The *melting point* of the precipitate, after washing with a small quantity of *methanol*, is about 255°, with decomposition, Appendix V A.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light using a silica gel GF_{254} precoated plate (Merck plates are suitable) and a mixture of 10 volumes of *acetone*, 10 volumes of *diethylamine* and 80 volumes of *cyclohexane* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 60 mg of Prochlorperazine Maleate with 5 mL of 0.18M *methanolic ammonia*, shake for 15 minutes, centrifuge and use the supernatant liquid. Solution (2) contains 0.006% w/v of *prochlorperazine maleate BPCRS* in 0.18M *methanolic ammonia*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%). Disregard any spot remaining on the line of application.

ASSAY

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Weigh and finely powder 20 tablets. To a quantity of the powdered tablets containing 10 mg of Prochlorperazine Maleate add 50 mL of 1M *methanesulfonic acid*, shake for 5 minutes and disperse with the aid of ultrasound for 2 minutes. Add sufficient 1M *methanesulfonic acid* to produce 100 mL, mix, centrifuge the mixture and dilute 10 mL of the supernatant liquid to 100 mL with *water*. Measure the *absorbance* of the resulting solution at 254 nm, Appendix II B, using 0.1M *methanesulfonic acid* in the reference cell. Measure the *absorbance* of a solution prepared by diluting 1 volume of a 0.01% w/v solution of *prochlorperazine maleate BPCRS* in 1M *methanesulfonic acid* to 10 volumes with *water* using 0.1M *methanesulfonic acid* in the reference cell. Calculate the content of $C_{20}H_{24}ClN_3S,2C_4H_4O_4$ from the absorbances obtained and from the declared content of $C_{20}H_{24}ClN_3S,2C_4H_4O_4$ in *prochlorperazine maleate BPCRS*.

STORAGE

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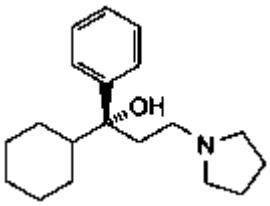
Procyclidine Hydrochloride

General Notices



$C_{19}H_{29}NO,HCl$ 323.9 *1508-76-5*

Action and use

Anticholinergic.

Preparations

Procyclidine Injection

Procyclidine Tablets

DEFINITION

Procyclidine Hydrochloride is (*RS*)-1-cyclohexyl-1-phenyl-3-pyrrolidin-1-ylpropan-1ol hydrochloride. It contains not less than 99.0% and not more than 101.0% of $C_{19}H_{29}NO,HCl$, calculated with reference to the dried substance.

CHARACTERISTICS

A white, crystalline powder.

Sparingly soluble in *water*; soluble in *ethanol (96%)*; practically insoluble in *acetone* and in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of procyclidine hydrochloride *(RS 292)*.

B. Dissolve 0.25 g in 10 mL of *water*, make alkaline with 5M *ammonia* and extract with three 10-mL quantities of *ether*. Dry the combined extracts over *anhydrous sodium sulfate*, filter, evaporate the ether and scratch the residue with a glass rod to induce solidification. The *melting point* of the residue is about 85°, Appendix V A.

C. Yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

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Acidity

pH of a 1% w/v solution, 4.5 to 6.5, Appendix V L.

Related substances

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *chloroform*.

(1) 2.0% w/v of the substance being examined.

(2) 0.0040% w/v of *1-phenyl-3-pyrrolidinopropan-1-one hydrochloride BPCRS*.

(3) 0.010% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it at 105° for 15 minutes and examine under *ultraviolet light (254 nm)*. Spray the plate with *dilute potassium iodobismuthate solution* and examine.

MOBILE PHASE

1 volume of 13.5M *ammonia* and 100 volumes of *ether*.

LIMITS

When examined under UV light:

any spot corresponding to 1-phenyl-3-pyrrolidinopropan-1-one in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%).

When examined after spraying:

any other *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

B. Carry out the method for *gas chromatography*, Appendix III B. Use a solution containing 0.06% w/v of *triphenylethylene* in *ether* as the internal standard.

(1) Add 5 mL of 1.25M *sodium hydroxide* to 20 mL of a 0.50% w/v solution of the substance being examined and mix. Extract with two 20-mL quantities of *ether*, add to the combined extracts 5 mL of the internal standard, shake with *anhydrous sodium sulfate* and filter; evaporate the filtrate and dissolve the residue in 1 mL of *ether*.

(2) Prepare in the same manner as solution (1) but omitting the addition of the internal standard solution.

(3) Prepare in the same manner as solution (1) but using 20 mL of a 0.015% w/v solution of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica column (15 m × 0.32 mm) bonded with a 0.25 µm film of *polyethylene glycol 20,000* (DB-Wax is suitable).

(b) Use *nitrogen* as the carrier gas at 0.8 mL per minute.

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(c) Use isothermal conditions maintained at 210°.

(d) Use an inlet temperature of 250°.

(e) Use a flame ionisation detector at a temperature of 250°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:5.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated peaks.

LIMITS

The ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard in the chromatogram obtained with solution (1) is not more than the ratio of the area of the principal peak to the area of the internal standard peak in the chromatogram obtained with solution (3) (3%).

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.7 g and *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 32.39 mg of $C_{19}H_{29}NO,HCl$.

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Procyclidine Injection

General Notices

Action and use

Anticholinergic.

DEFINITION

Procyclidine Injection is a sterile solution of Procyclidine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of procyclidine hydrochloride, $C_{19}H_{29}NO,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Extract a volume of the injection containing 30 mg of Procyclidine Hydrochloride with three 5 mL quantities of *dichloromethane*, dry the combined extracts with *anhydrous sodium sulfate*, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of procyclidine hydrochloride (*RS 292*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the injection, if necessary, with *water* to give a solution containing 0.50% w/v of Procyclidine Hydrochloride.

(2) 0.50% w/v of *procyclidine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.8, Appendix V L.

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Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the injection, if necessary, with *water* to give a solution containing 0.50% w/v of Procyclidine Hydrochloride.

(2) 0.0010% w/v of *1-phenyl-3-pyrrolidinopropan-1-one hydrochloride BPCRS* in *chloroform*.

(3) Dilute 1 volume of solution (1) to 200 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 105° for 15 minutes and examine under *ultraviolet light (254 nm)* (first examination). Spray the plate with *dilute potassium iodobismuthate solution* (second examination).

MOBILE PHASE

1 volume of 13.5M *ammonia* and 100 volumes of *ether*.

LIMITS

In the first examination:

any spot corresponding to 1-phenyl-3-pyrrolidinopropan-1-one in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%).

In the second examination:

any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

Disregard any spot due to excipient on the line of application.

ASSAY

Record *second-derivative ultraviolet absorption spectra*, Appendix II B, of the following solutions in the range 220 to 280 nm. For solution (1) dilute a volume of the injection containing 25 mg of Procyclidine Hydrochloride to 100 mL with *0.1M hydrochloric acid*. Solution (2) contains 0.025% w/v of *procyclidine hydrochloride BPCRS* in *0.1M hydrochloric acid*.

For each solution measure the amplitude from the largest trough at about 257 nm to the largest peak at about 254 nm. Calculate the content of $C_{19}H_{29}NO,HCl$ using the declared content of $C_{19}H_{29}NO,HCl$ in *procyclidine hydrochloride BPCRS*.

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Procyclidine Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Procyclidine Tablets contain Procyclidine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of procyclidine hydrochloride, $C_{19}H_{29}NO,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the powdered tablets containing 25 mg of Procyclidine Hydrochloride in 10 mL of *water*, shake with 20 mL of *ether* and discard the ether layer. Make the aqueous layer alkaline with 2M *sodium hydroxide* and extract with two 20-mL quantities of *ether*. Wash the combined ether extracts with two 10-mL quantities of *water*, dry by shaking with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. If necessary, induce crystallisation by scratching with a glass rod. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of procyclidine (*RS 291*).

B. The powdered tablets yield the reactions characteristic of *chlorides*, Appendix VI.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *chloroform*.

(1) Shake a quantity of the powdered tablets containing 25 mg of Procyclidine Hydrochloride with 5 mL of *chloroform* and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.001% w/v of *1-phenyl-3-pyrrolidinopropan-1-one hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 105° for 15 minutes and examine under *ultraviolet light (254 nm)* (first examination). Spray the plate with *dilute potassium iodobismuthate solution* (second examination).

MOBILE PHASE

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1 volume of 13.5M *ammonia* and 100 volumes of *ether*.

LIMITS

In the first examination:

any spot corresponding to 1-phenyl-3-pyrrolidinopropan-1-one in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

In the second examination:

any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

Disregard any spot due to excipients on the line of application.

ASSAY

Weigh and finely powder 20 tablets. Record *second-derivative ultraviolet absorption spectra* of the following solutions, Appendix II B, in the range 220 to 280 nm. For solution (1) add 80 mL of *0.1M hydrochloric acid* to a quantity of the powdered tablets containing 25 mg of Procyclidine Hydrochloride, mix with the aid of ultrasound for 15 minutes, cool, dilute to 100 mL with *0.1M hydrochloric acid* and filter through a glass fibre paper having a maximum pore size of 0.7 µm (Whatman GF/F paper is suitable) discarding the first 10 mL of filtrate. Solution (2) contains 0.025% w/v of *procyclidine hydrochloride BPCRS* in *0.1M hydrochloric acid*.

For each solution measure the amplitude from the largest trough at about 257 nm to the largest peak at about 254 nm. Calculate the content of $C_{19}H_{29}NO,HCl$ using the declared content of $C_{19}H_{29}NO,HCl$ in *procyclidine hydrochloride BPCRS*.

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Products of Fermentation

General Notices

(Ph. Eur. monograph 1468)

Ph Eur

This monograph applies to indirect gene products obtained by fermentation. It is not applicable to:

- *— monographs in the Pharmacopoeia concerning vaccines for human or veterinary use;*
- *— products derived from continuous cell lines of human or animal origin;*
- *— direct gene products that result from the transcription and translation from nucleic acid to protein, whether or not subject to post-translational modification;*
- *— products obtained by semi-synthesis from a product of fermentation and those obtained by biocatalytic transformation;*
- *— whole broth concentrates or raw fermentation products.*

This monograph provides general requirements for the development and manufacture of products of fermentation. These requirements are not necessarily comprehensive in a given case and requirements complementary or additional to those prescribed in this monograph may be imposed in an individual monograph or by the competent authority.

DEFINITION

For the purposes of this monograph, products of fermentation are active or inactive pharmaceutical substances produced by controlled fermentation as indirect gene products. They are primary or secondary metabolites of micro-organisms such as bacteria, yeasts, fungi and micro-algae, whether or not modified by traditional procedures or recombinant DNA (rDNA) technology. Such metabolites include vitamins, amino acids, antibiotics, alkaloids and polysaccharides.

They may be obtained by batch or continuous fermentation processes followed by procedures such as extraction, concentration, purification and isolation.

PRODUCTION

Production is based on a process that has been validated and shown to be suitable. The extent of validation depends on the critical nature of the respective process step.

CHARACTERISATION OF THE PRODUCER MICRO-ORGANISM

The history of the micro-organism used for production is documented. The micro-organism is adequately characterised. This may include determination of the phenotype of the micro-organism, macroscopic and microscopic methods and biochemical tests and, if appropriate,

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determination of the genotype of the micro-organism and molecular genetic tests.

PROCESSES USING A SEED-LOT SYSTEM

The *master cell bank* is a homogeneous suspension or lyophilisate of the original cells distributed into individual containers for storage. The viability and productivity of the cells under the selected storage conditions and their suitability for initiating a satisfactory production process after storage must be demonstrated.

Propagation of the master cell bank may take place through a seed-lot system that uses a working cell bank.

The *working cell bank* is a homogeneous suspension or lyophilisate of the cell material derived from the master cell bank, distributed in equal volumes into individual containers for storage (for example, in liquid nitrogen).

Production may take place by batch or continuous culture and may be terminated under defined conditions.

All containers in a cell bank are stored under identical conditions. Once removed from storage, the individual ampoules, vials or culture straws are not returned to the cell bank.

PROCESSES USING STAGED GROWTH IN CULTURES

The contents of a container of the working cell bank are used, if necessary after resuspension, to prepare an inoculum in a suitable medium. After a suitable period of growth, the cultures are used to initiate the fermentation process, if necessary following preculture in a prefermentor. The conditions to be used at each stage of the process are defined and must be met with each production run.

CHANGE CONTROL

If the production process is altered in a way that causes a significant change in the impurity profile of the product, the critical steps associated with this change in impurity profile are revalidated.

If a significant change has taken place in the micro-organism used for production that causes a significant change in the impurity profile of the product, the critical steps of the production process associated with this change, particularly the procedure for purification and isolation, are revalidated.

Revalidation includes demonstration that new impurities present in the product as a result of the change are adequately controlled by the test procedures. If necessary, additional or alternative tests must be introduced with appropriate limits. If the change in the process or in the micro-organism results in an increase in the level of an impurity already present, the acceptability of such an increase is addressed.

When a master cell bank is replaced, the critical steps of the production process must be revalidated to the extent necessary to demonstrate that no adverse change has occurred in the quality and safety of the product. Particular attention must be given to possible changes in the impurity profile of the product if a modified or new micro-organism is introduced into the process.

RAW MATERIALS

The raw materials employed in the fermentation and/or down-stream processing are of suitable quality for the intended purpose. They are tested to ensure that they comply with written specifications. Special attention must be paid to the levels of free histidine in fish peptones as

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the presence of free histidine may lead to histamine formation in certain conditions.

Levels of bioburden in media or in the inlet air for aeration are reduced to an adequately low level to ensure that if microbial contamination occurs, it does not adversely affect the quality, purity and safety of the product. Addition of components such as nutrients, precursors, and substrates during fermentation takes place aseptically.

IN-PROCESS CONTROLS

In-process controls are in place to ensure the consistency of the conditions during fermentation and down-stream processing and of the quality of the isolated product. Particular attention must be paid to ensure that any microbial contamination that adversely affects the quality, purity and safety of the product is detected by the controls applied.

Production conditions may be monitored, as appropriate, by suitable procedures for example to control and check:

— temperature,

— pH,

— rate of aeration,

— rate of agitation,

— pressure,

and to monitor the concentration of the required product.

DOWN-STREAM PROCESSING

At the end of fermentation, the producer micro-organism is inactivated or removed. Further processing is designed to reduce residues originating from the culture medium to an acceptable level and to ensure that the desired product is recovered with consistent quality.

Various purification processes may be used, for example, charcoal treatment, ultrafiltration and solvent extraction. It must be demonstrated that the process or processes chosen reduce to a minimum or remove:

— residues from the producer micro-organism, culture media, substrates and precursors;

— unwanted transformation products of substrates and precursors;

— histamine and other biogenic amines from fish and fishery products used in raw materials.

If necessary, suitable tests are performed either as in-process controls or on the isolated product of fermentation.

IDENTIFICATION, TESTS AND ASSAY

The requirements with which the product must comply throughout its shelf life, as well as specific test methods, are stated in the individual monographs.

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Products of Recombinant DNA Technology

General Notices

(Ph. Eur. monograph 0784)

Ph Eur

This monograph provides general requirements for the manufacture and control of finished products derived from recombinant DNA (rDNA) technology, and includes requirements for the active substance in these products. Active substances produced by rDNA technology are expected to meet the requirements given in the corresponding section of the present monograph. These requirements are not necessarily comprehensive in a given case and complementary or additional requirements may be prescribed in an individual monograph or imposed by the competent authority.

The monograph is also applicable to vaccine antigens produced by rDNA technology, with more detailed requirements provided in the general monograph Vaccines for human use (0153) and in individual vaccine monographs.

Certain aspects of the monograph may apply to products produced in transgenic animals and plants.

The monograph is not applicable to recombinant organisms that are intended to be used directly in man and animals, for example as live recombinant vectors or vaccines.

DEFINITION

Products of rDNA technology are produced by genetic modification in which DNA coding for the required product is introduced, usually by means of a plasmid or a viral vector, into suitable micro-organisms such as bacteria and yeast, or a suitable cell line of mammalian (including human), insect or plant origin. The DNA introduced can then be expressed as a protein.

The desired product is then recovered by extraction and purification. The cell or micro-organism used to harbour the vector is referred to as the host cell, and the stable association of the two used in the manufacturing process is referred to as the host-vector system.

Products of rDNA technology can also undergo intentional modifications such as pegylation or conjugation.

PRODUCTION

GENERAL PROVISIONS

Production of rDNA products is based on a validated seed-lot system using a host-vector combination that has been shown suitable.

The seed-lot system typically uses a master cell bank and a working cell bank. The host cell, the vector, the host-vector system, the master cell bank and the working cell bank, as well as their establishment, maintenance and cultivation are to be described in detail.

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Where products of rDNA technology are manufactured using materials of human or animal origin, the requirements of general chapter 5.1.7. *Viral safety* apply.

The production process is validated for the following aspects:

— process consistency, including cell-culture/fermentation, purification and any subsequent intentional modification of the active substance where applicable;

— removal or inactivation of extraneous agents;

— removal of product- and process-related impurities (e.g. unwanted variants, host-cell proteins and DNA, antibiotics, cell-culture components);

— removal of pyrogenic substances where applicable.

A batch shown to be stable and representative of batches tested clinically is used as a reference preparation for identification, tests and assay. The reference preparation is appropriately characterised.

EXPRESSION VECTOR AND HOST CELL

The starting materials to be used for the production of the rDNA product, including the expression vector, the host-cell and the pool of transformed or transfected cells from which the initial clone will be derived, are documented.

Information on the source and history of the host cell and of the expression vector is recorded. The gene coding for the protein of interest as well as other functional sequences of the vector should be characterised (e.g. nucleotide sequence of the gene of interest and its flanking regions, restriction map).

The suitability of the host-vector system, particularly with regard to microbiological purity, is demonstrated by:

— phenotypic and genotypic characterisation of the host cell;

— characterisation of the expression vector within the host cell (e.g. integration, copy number, nucleotide sequence);

— documentation on the raw materials, the transformation/transfection of the host cell by the expression vector and the strategy for deriving the clone used to establish the cell bank system.

CELL BANKS

The master cell bank (MCB) is a homogeneous suspension of the original cells already transformed or transfected by the expression vector containing the desired gene, distributed as equal volumes in a single operation into individual containers for storage (e.g. in liquid nitrogen). In some cases, it may be necessary to establish separate master cell banks for the expression vector and the host cells.

The working cell bank (WCB) is a homogeneous suspension of cells derived from the MCB(s) at a finite passage level, distributed as equal volumes in a single operation into individual containers for storage (e.g. in liquid nitrogen).

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For each type of cell bank, all containers are treated identically during storage and once removed from storage, are not returned to the cell stock.

The characterisation and testing of eukaryotic and prokaryotic cell banks are critical components of the control of rDNA-derived biological products. Cell banks are tested to confirm identity, purity and suitability of the cell substrate for the intended manufacturing use. The strategy for testing the cell banks may vary according to the nature and biological properties of the cells (e.g. growth properties) and their cultivation history (e.g. use of animal-derived raw material). Molecular methods are used to analyse the expression vector for copy number, insertions or deletions, and the number of integration sites. The nucleotide sequences of the coding region, flanking regions and promoters are shown to be identical to those determined for the expression vector. The coding region corresponds to that expected for the protein sequence. If any differences in nucleic acid sequences are identified, these must be clearly defined and the expression vector shown to be stable and capable of expressing the expected product consistently.

Cell banks must be characterised and tested at different stages including the MCB, the WCB and cells at or beyond the maximum population doubling level used for production.

For prokaryotic and yeast cell banks, characterisation and testing includes molecular identity of the gene being expressed, identity and purity of the cells including strain identification (e.g. by biochemical, genetic, or proteomic methods), phenotypic and genotypic strain characterisation, viability, presence of the plasmid (e.g. sequence, copy number, restriction map, percentage of cells retaining the plasmid), microbiological purity and, if appropriate, a test for bacteriophage. Additional tests may be relevant and shall be addressed on a case-by-case basis.

For animal cell banks, characterisation and testing includes morphology, identity, viability, genetic stability of the cells (e.g. copy number, integrity of the expression cassette) and testing for extraneous agents. Animal cell substrates have the capacity to propagate extraneous agents such as mycoplasma and viruses. In addition, animal cells may contain endogenous agents such as endogenous retroviruses. Consequently, a testing strategy with regard to extraneous agents should be developed based on a risk assessment taking into account the nature and the history of the cell line.

CULTURE MEDIA AND OTHER RAW MATERIALS

The quality of media and other raw materials used in the production of rDNA proteins is controlled, with consideration given to the impact of the raw material on the quality, safety and efficacy of the final medicinal product. In particular, the origin of the materials must be known and their traceability documented.

CULTURE AND HARVEST

The cell bank (e.g. 1 or more vials(s) of the WCB) is used to start the culture process. In-process controls (e.g. for population doubling levels, cell concentration, volumes, pH, cultivation times, temperature, microbial tests) are established to ensure suitable performance and consistency with regard to the culture process.

Criteria for harvesting and terminating the production must be defined by the manufacturer, and take into account the limit for *in vitro* cell age (e.g. limited number of passages or population doublings) for which the cell substrate has been demonstrated as stable and capable of producing the desired product/intermediate. Each harvest is tested to ensure absence of contamination.

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When prokaryotic or other microbial cells are used to manufacture the product, absence of contamination of the harvest is demonstrated primarily by establishing microbial purity. When animal cells are used, the absence of extraneous agents is verified using appropriate *in vitro* cell culture methods and/or molecular methods.

PURIFICATION

The extraction and purification procedure must be shown to yield the desired intermediates at a suitable purity. In this respect, an analysis of the step(s) taken to control the product-related impurities, and to remove or inactivate process-related impurities or contaminants is conducted.

In-process controls (e.g. for yield, volume, pH, processing time, temperature, elution profile and fraction selection, microbial tests) are established to ensure suitable performance and consistency with regard to the purification process.

Holding times and storage conditions of intermediates are to be defined where appropriate.

CHARACTERISATION

During development studies, the active substance is characterised extensively in order to determine its structure, physico-chemical properties, biological activity, immunochemical properties and purity.

Characterisation is necessary to identify the quality attributes that may be important for the safety and efficacy of the product. It provides the basis for release specifications, stability evaluation and for any testing that may have to be performed in support of process changes.

Structure

The characterisation should determine, as far as possible, the primary and higher-order structure of the protein, any post-translational modifications such as glycosylation, and any other intentional modification.

The amino-acid sequence is deduced from the DNA sequence of the expression vector and confirmed by analysis of the produced protein. The amino-acid sequence and the disulfide bridges of the substance are determined using a combination of techniques such as peptide mapping (2.2.55) and mass spectrometry (2.2.43).

The analysis of pegylated proteins should include, but not be limited to, the location of modification and the degree of site occupancy.

Glycosylation is characterised, and covers overall monosaccharide composition (neutral sugars, amino sugars and sialic acids), glycosylation site(s) and type (e.g. N- or O-linked), degree of site occupancy, and oligosaccharide structures of glycan chains (extensions, branching and linkage) using, for example, the principles and techniques described in general chapter 2.2.59. *Glycan analysis of glycoproteins*.

Due to their possible immunogenicity, particular attention is paid to glycan structures that are not known to be present in natural human proteins.

The higher-order structure of the substance is examined using physico-chemical methods such as circular dichroism spectroscopy, Fourier transform infrared spectroscopy, fluorescence, differential scanning calorimetry, proton nuclear magnetic resonance spectrometry and/or hydrogen-deuterium exchange mass spectrometry.

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Biological assays based on functional activity may also serve as additional confirmation of the higher-order structure.

Biological activity

The biological activity (i.e. the specific ability of a product to achieve a defined biological effect) is assessed by biological, biochemical (including immunochemical assays) or physico-chemical assays, as appropriate.

The mechanism of action is investigated and preferably reflected in the potency assay.

Immunochemical properties

Where relevant for the mechanism of action, e.g. in the case of antibodies, immunochemical properties (such as Fc-effector functions) are characterised extensively.

Product-related substances and impurities

Products of rDNA technology commonly display several sources of heterogeneity (e.g. N- or C-terminal processing, N-terminal pyroglutamation, deamidation, oxidation, isomerisation, fragmentation, disulfide bond mismatch, N-linked and O-linked glycosylation, glycation, aggregation), which leads to a complex product profile consisting of several molecular entities or variants. When the activity, safety and efficacy of these variants are comparable to those of the desired product, the variants are regarded as product-related substances. Other variants are considered as product-related impurities.

The methods used to assess product-related substances and impurities should be capable of detecting structural variants with different physico-chemical properties, e.g. charge, size and hydrophobicity. Typically, a combination of orthogonal methods is applied, e.g. chromatographic, electrophoretic and spectroscopic techniques.

Characterisation of charged variants, such as differentially sialylated or deamidated variants, is performed using appropriate methods (e.g. capillary electrophoresis, isoelectric focusing, ion-exchange chromatography), which may be coupled to other techniques such as mass spectrometry.

High-molecular-mass forms such as dimers and higher oligomers can be resolved and quantified by size-based separation procedures (e.g. size-exclusion chromatography, field flow fractionation, analytical ultracentrifugation) coupled with suitable detection methods (e.g. ultraviolet, fluorescence, light scattering).

Process-related impurities and contaminants

Process-related impurities derived from the upstream process may include host-cell proteins, host-cell DNA, or other media components (e.g. inducers, antibiotics, serum). They are to be evaluated qualitatively and quantitatively.

Host-cell proteins are investigated using a sensitive assay capable of detecting a wide range of protein impurities, and taking into account the recommendations given in general chapter *2.6.34. Host-cell protein assays*.

Residual host-cell DNA is determined using a suitably sensitive assay.

Process-related impurities derived from the downstream process may include enzymes, processing reagents (e.g. guanidine, dyes, oxidising and reducing agents), salts (e.g. heavy metals, non-metallic ions), solvents, carriers, ligands (e.g. protein A) and other leachables.

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Contaminants include all adventitiously introduced materials not intended to be part of the manufacturing process (e.g. micro-organisms, microbial proteases, bacterial endotoxins).

Process-related impurities and contaminants are controlled using appropriate strategies based on the principles of risk management.

Content

Content is determined by use of an appropriate physico-chemical or immunochemical assay. The total protein content (expressed in mass units) can be determined as described in general chapter *2.5.33. Total protein*. The protein content is determined using several methods, including absolute method(s).

CONTROL STRATEGY

Based on the understanding of the product and process, a planned set of controls that ensures process performance and product quality (i.e. a control strategy) is established. This control strategy includes the control of process parameters, in-process controls, control of raw materials, intermediates, active substance and finished product, as well as the methods used and the frequency of control.

The control strategy should ensure that the quality attributes relevant to the safety and efficacy of the product are within the appropriate range, limit or distribution to ensure the desired product quality.

The selection of tests and the stages at which they are performed are based on knowledge of the manufacturing process and extensive characterisation of the active substance and finished product. Some characterisation tests may be selected to become part of the specifications. The specifications for the active substance and finished product are only 1 part of the overall control strategy.

ACTIVE SUBSTANCE

The active substance is tested for appearance, identity, microbial quality and bacterial endotoxins, product-related substances, product- and process-related impurities, structural integrity, protein content and biological activity, with comparison to suitable reference standards where appropriate.

When the active substance is a conjugated or chemically modified protein, e.g. a pegylated protein, appropriate tests must be performed on both the modified and unmodified protein. Tests for product-related variants (e.g. proportion of modified and unmodified protein) and process-related impurities derived from the modification procedure (e.g. by-products of the modification reaction, reagents) are carried out and acceptance criteria should be established.

FINISHED PRODUCT

One or more batches of active substance may be combined to obtain the finished product. Suitable stabilisers and excipients may be added.

The finished product complies with the relevant dosage form monographs, with the relevant individual monograph as appropriate, and with the following considerations.

IDENTIFICATION

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The identity test(s) must be specific and must be based on unique aspects of the product's molecular structure or other specific properties such as the size of the molecule, its primary sequence, its isoelectric profile, its chromatographic properties and its functional conformation, with comparison of the product to a suitable reference standard where appropriate. Methods used in the determination of potency or purity may also contribute to the identification.

TESTS

Methods capable of determining process-related impurities and product-related substances and impurities (e.g. resulting from product truncation, fragmentation, aggregation, oxidation, deamidation) are applied and acceptance criteria established, as appropriate. Where impurities are controlled at a suitable earlier stage, the tests may be omitted at the finished product stage.

Tests applied to modified proteins

Suitable tests are carried out depending on the type of modification and the product complies with the approved limits.

ASSAY

Content

It complies with the limits approved for the particular product. It is usually based on protein content and expressed in mass units. The procedures described in general chapter *2.5.33. Total protein* may be applied. When appropriate, other methods using a suitable reference standard such as liquid chromatography (*2.2.29*) may also be used. For modified proteins, the content refers to the protein part of the molecule.

Potency

A potency assay is established using a suitable reference standard and carried out against this reference standard. General chapter *5.3. Statistical analysis of results of biological assays and tests* may be used to design the assay and calculate the results.

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Products with Risk of Transmitting Agents of Animal Spongiform Encephalopathies

General Notices

(Ph. Eur. monograph 1483)

Ph Eur

DEFINITION

Products with risk of transmitting agents of animal spongiform encephalopathies are those derived from tissues or secretions of animals susceptible to transmissible spongiform encephalopathies other than by experimental challenge. This monograph applies to all substances or preparations obtained from such animals and to all substances or preparations where products obtained from such animals are included as active substances or excipients or have been used during production, for example as raw or source materials, starting materials or reagents.

PRODUCTION

Production complies with chapter *5.2.8. Minimising the risk of transmitting animal spongiform encephalophathy agents via human and veterinary medicinal products*.

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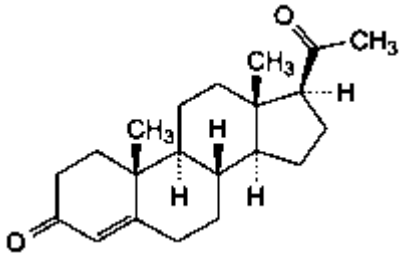
Progesterone

General Notices

(Ph. Eur. monograph 0429)



$C_{21}H_{30}O_2$ 314.5 *57-83-0*

Action and use

Progestogen.

Preparation

Progesterone Injection

Ph Eur

DEFINITION

Pregn-4-ene-3,20-dione.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in acetone and in fatty oils.

It shows polymorphism (*5.9*).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison progesterone CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in anhydrous ethanol R, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 1 volume of methanol R and 9 volumes of methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 10 mg of progesterone CRS in a mixture of 1 volume of methanol R and 9 volumes of methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Plate TLC silica gel F_{254} plate R.

Mobile phase ethyl acetate R, methylene chloride R (33:66 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Specific optical rotation (2.2.7)

+ 186 to + 194 (dried substance).

Dissolve 0.250 g in anhydrous ethanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in mobile phase B and dilute to 50.0 mL with mobile phase B.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase B.

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Reference solution (b) Dissolve 2 mg of *progesterone for system suitability CRS* (containing impurities B, C, G, I and M) in mobile phase B and dilute to 5.0 mL with mobile phase B.

Reference solution (c) Dissolve 2 mg of *progesterone for peak identification CRS* (containing impurities D, E, J, K and L) in mobile phase B and dilute to 5.0 mL with mobile phase B.

Reference solution (d) Dissolve 10.0 mg of *progesterone for impurity H identification CRS* (with an assigned content of impurity H) in mobile phase B and dilute to 25.0 mL with mobile phase B.

Reference solution (e) Dissolve 20.0 mg of *progesterone CRS* in mobile phase B and dilute to 50.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water R* (50:50 *V/V*);

— *mobile phase B*: *water R*, *acetonitrile R* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 27	100 → 0	0 → 100
27 - 45	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 241 nm and, for impurity H, at 286 nm.

Injection 10 µL of the test solution and reference solutions (a), (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *progesterone for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, G, I and M; use the chromatogram supplied with *progesterone for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D + E, J, K and L; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity H.

Relative retention With reference to progesterone (retention time = about 14 min): impurity B = about 0.60; impurity J = about 0.65; impurity H = about 0.82; impurity K = about 0.85; impurity C = about 0.93; impurity M = about 1.1; impurity L = about 1.90; impurity I = about 1.95; impurities D and E = about 2.05; impurity G = about 2.65.

System suitability Reference solution (b):

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— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to impurity M and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to progesterone.

Limits:

— *impurity I (sum of the 2 epimers)*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *sum of impurities D and E*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *impurities G, J, K, L, M*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *impurity H at 286 nm*: maximum 0.15 per cent, calculated from the area of the corresponding peak in the chromatogram obtained with reference solution (d) and taking into account the assigned content of impurity H in *progesterone for impurity H identification CRS*;

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than H*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C for 2 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (e).

Calculate the percentage content of $C_{21}H_{30}O_2$ taking into account the assigned content of *progesterone CRS*.

STORAGE

Protected from light.

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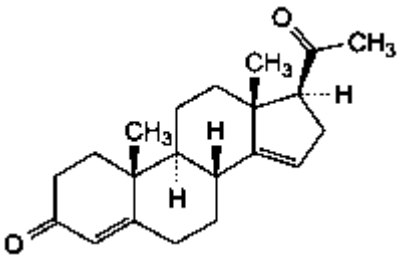
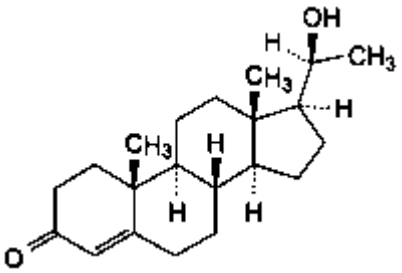
IMPURITIES

Specified impurities *B, C, D, E, G, H, I, J, K, L, M.*

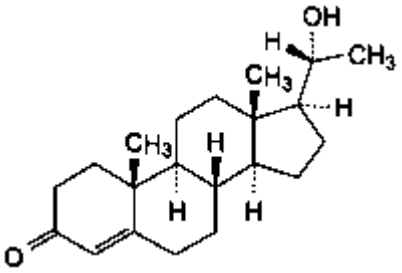
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



A. pregna-4,14-diene-3,20-dione,



B. (20*S*)-20-hydroxypregn-4-en-3-one,



C. (20*R*)-20-hydroxypregn-4-en-3-one,

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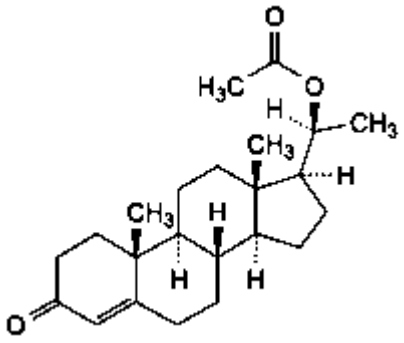
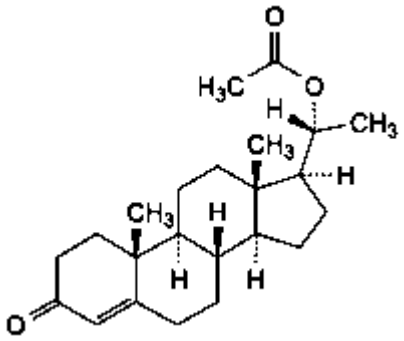
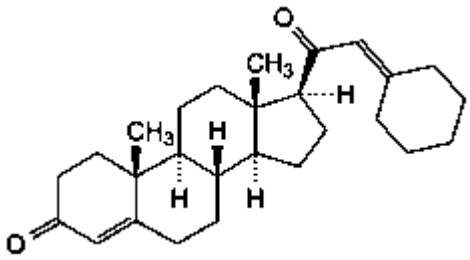


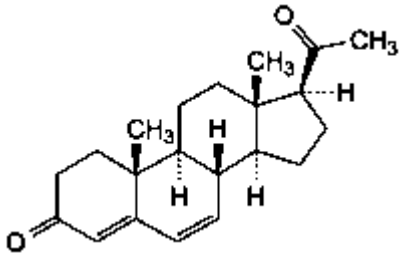
D. (20*S*)-3-oxopregn-4-en-20-yl acetate,



E. (20*R*)-3-oxopregn-4-en-20-yl acetate,



G. 21-(cyclohexylidene)pregn-4-ene-3,20-dione,



H. pregna-4,6-diene-3,20-dione (Δ6-progesterone),

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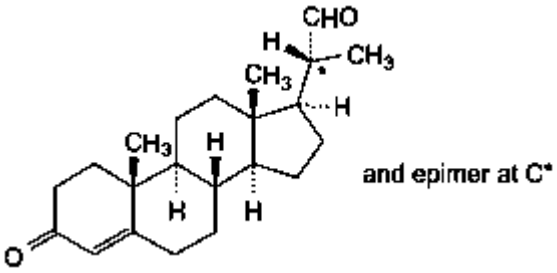
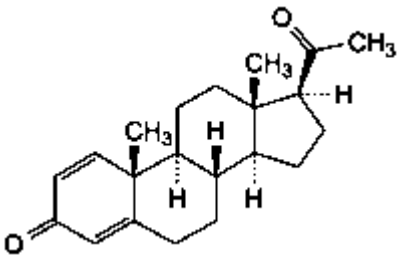
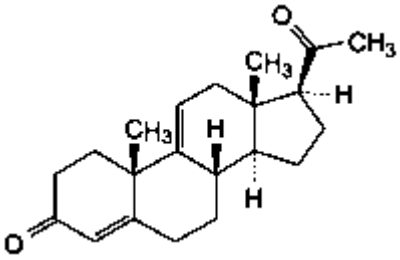


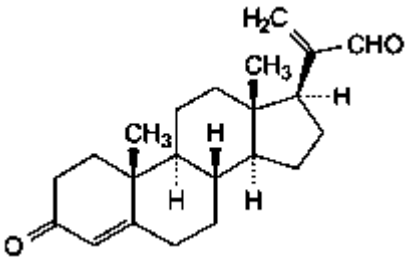
I. (20*RS*)-20-methyl-3-oxopregn-4-en-21-al,



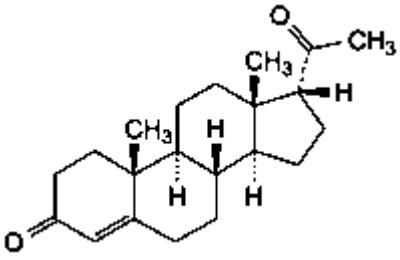
J. pregna-1,4-diene-3,20-dione,



K. pregna-4,9(11)-diene-3,20-dione,



L. 20-methylidene-3-oxopregn-4-en-21-al,



M. (17α)-pregn-4-ene-3,20-dione.

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Progesterone Injection

General Notices

Action and use

Progesterone

DEFINITION

Progesterone Injection is a sterile solution of Progesterone in Ethyl Oleate or other suitable esters, in a suitable fixed oil or in any mixture of these. It may contain suitable alcohols.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of progesterone, $C_{21}H_{30}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a volume containing 50 mg of Progesterone in 8 mL of *petroleum spirit* (*boiling range, 40° to 60°*) and extract with three 8-mL quantities of a mixture of 7 volumes of *glacial acetic acid* and 3 volumes of *water*. Wash the combined extracts with 10 mL of *petroleum spirit* (*boiling range, 40° to 60°*), dilute with *water* until the solution becomes turbid, allow to stand in ice for 2 hours and filter. Wash the residue with *water* and dry at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of progesterone (*RS 293*).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) To a quantity of the injection containing 40 mg of Progesterone add sufficient *methanol* to produce 100 mL.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.0040% w/v of *progesterone for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 100 Å is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 241 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A *water*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0→20	50	50	Isocratic
20→27	50→20	50→80	Linear Gradient
27→45	20	80	Isocratic
45→46	20→50	80→50	Linear Gradient
46→50	50	50	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to progesterone (retention time about 20 minutes) of impurity C is about 0.92.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peaks with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) To a weighed quantity of the injection containing 40 mg of Progesterone add sufficient *methanol* to produce 100 mL, dilute 1 volume of this solution to 10 volumes with *methanol*.

(2) 0.0040% w/v of *progesterone BPCRS*.

(3) 0.0040% w/v of each *progesterone BPCRS* and *progesterone for system suitability EPCRS*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 100 Å is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 241 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

45 volumes of *water* and 55 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the injection, Appendix V G, and calculate the content of $C_{21}H_{30}O_2$ using the declared content of $C_{21}H_{30}O_2$ in *progesterone BPCRS*.

STORAGE

Progesterone Injection should be protected from light. On standing, solid matter may separate; it should be redissolved by heating before use.

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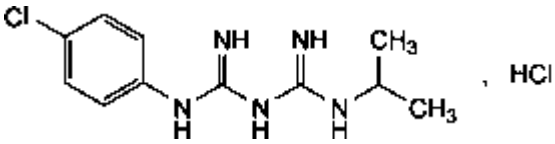
Proguanil Hydrochloride

General Notices

(Ph. Eur. monograph 2002)



$C_{11}H_{17}Cl_2N_5$ 290.2 *637-32-1*

Action and use

Antiprotozoal (malaria).

Preparation

Proguanil Tablets

Ph Eur

DEFINITION

N^1-(4-Chlorophenyl)-N^3-(propan-2-yl)imidodicarbonimidic diamide hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, C.

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Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *proguanil hydrochloride CRS*.

B. Dissolve 0.4 g in 50 mL of *water R* (solution A). To 15 mL of solution A add 2 mL of *dilute sodium hydroxide solution R*. Extract with 20 mL of *ethyl acetate R*. Wash the organic layer with *water R*, evaporate to dryness and dry at 105 °C. The melting point (2.2.14) of the residue is 130 °C to 133 °C.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Acidity or alkalinity

To 35 mL of *water R* maintained at 60-65 °C, add 0.2 mL of *methyl red mixed solution R*. Neutralise to a grey colour with either *0.01 M sodium hydroxide* or *0.01 M hydrochloric acid*. Add 0.4 g of the substance to be examined and stir until completely dissolved. The solution is grey or green. Not more than 0.2 mL of *0.01 M hydrochloric acid* is required to change the colour of the solution to reddish-violet.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *methanol R*, *water R* (20:20:60 *V/V/V*).

Test solution (a) Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Test solution (b) Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *proguanil for system suitability CRS* (containing impurity G) in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 4.0 mg of *proguanil impurity B CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

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— *mobile phase A*: dissolve 0.65 g of *sodium pentanesulfonate R* and 7.0 g of *sodium perchlorate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; adjust to pH 3.0 with a 1 per cent *V/V* solution of *trifluoroacetic acid R*;

— *mobile phase B*: dissolve 0.65 g of *sodium pentanesulfonate R* and 7.0 g of *sodium perchlorate R* in a mixture of 20 volumes of *water for chromatography R*, 40 volumes of *acetonitrile for chromatography R* and 40 volumes of *methanol R1* and dilute to 1000 mL with the same solvent mixture; add 4 mL of a 1 per cent *V/V* solution of *trifluoroacetic acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	75	25
3 - 23	75 → 40	25 → 60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *proguanil for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity G.

Relative retention With reference to proguanil (retention time = about 16 min): impurity G = about 1.05.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to proguanil.

Calculation of percentage contents:

— for each impurity, use the concentration of proguanil hydrochloride in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent, except for impurity B.

Impurity B

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

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Relative retention With reference to proguanil (retention time = about 16 min): impurity B = about 0.2.

System suitability Reference solution (c):

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity B.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (200 ppm).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Suspend 0.100 g in 20 mL of *anhydrous acetic acid R*, shake and heat at 50 °C for 5 min. Cool to room temperature and add 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 14.51 mg of $C_{11}H_{17}Cl_2N_5$.

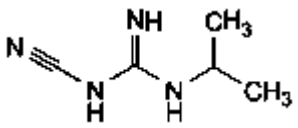
STORAGE

Protected from light.

IMPURITIES

Specified impurities *B*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, F, G.*



A. *N*-cyano-*N'*-(propan-2-yl)guanidine,

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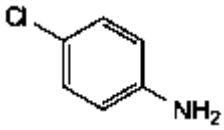
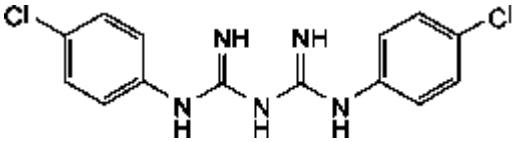
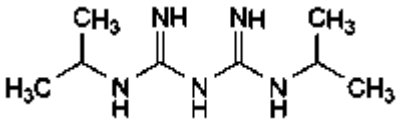


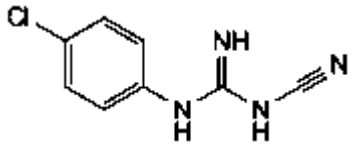
B. 4-chloroaniline,



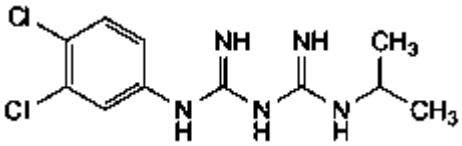
C. N^1,N^3-bis(4-chlorophenyl)imidodicarbonimidic diamide,



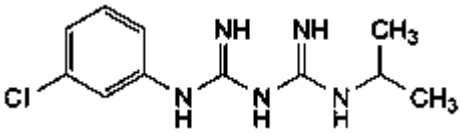
D. N^1,N^3-bis(propan-2-yl)imidodicarbonimidic diamide,



E. *N*-(4-chlorophenyl)-*N*′-cyanoguanidine,



F. N^1-(3,4-dichlorophenyl)-N^3-(propan-2-yl)imidodicarbonimidic diamide,



G. N^1-(3-chlorophenyl)-N^3-(propan-2-yl)imidodicarbonimidic diamide.

Ph Eur

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Proguanil Tablets

General Notices

Action and use

Antiprotozoal (malaria).

DEFINITION

Proguanil Tablets contain Proguanil Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of proguanil hydrochloride, $C_{11}H_{16}ClN_5,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 0.2 g of Proguanil Hydrochloride add 25 mL of *methanol*, shake for 10 minutes, filter, evaporate the filtrate to dryness and dry the residue at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of proguanil hydrochloride (*RS 294*).

B. Boil a quantity of the powdered tablets containing 0.5 g of Proguanil Hydrochloride with 5 mL of 2M *hydrochloric acid*, cool and filter. To the filtrate add a slight excess of 5M *sodium hydroxide*, extract with 30 mL of *ether*, evaporate the ether and dry the residue at 105°. The *melting point* of the residue is about 131°, Appendix V A.

TESTS

4-Chloroaniline

To a quantity of the powdered tablets containing 0.1 g of Proguanil Hydrochloride add 5 mL of *ethanol* (*96%*) and shake for 10 minutes. Add 2.5 mL of 2M *hydrochloric acid* and 15 mL of *water*, mix and filter through a moistened filter paper, washing the filter with 5 mL of *water*. Cool the filtrate to 5°, add 1 mL of 0.05M *sodium nitrite*, allow to stand at 5° for 5 minutes, add 2 mL of a 5% w/v solution of *ammonium sulfamate* and allow to stand for 10 minutes. Add 2 mL of a 0.1% w/v solution of N-*(1-naphthyl)ethylenediamine dihydrochloride*, dilute to 50 mL with *water* and allow to stand for 30 minutes. Any magenta colour produced is not more intense than that obtained by treating in the same manner and at the same time 20 mL of a solution containing 1.25 µg per mL of *4-chloroaniline* (250 ppm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Add 50 mL of *methanol* to a quantity of the powdered tablets containing 0.1 g of Proguanil Hydrochloride, shake for 10 minutes, dilute to 100 mL with *methanol*, mix, filter and dilute 5 mL of the filtrate to 50 mL with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 1 volume of a 0.05% w/v solution of *1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride BPCRS* in *methanol* with 9 volumes of a 0.010% w/v solution of *proguanil hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1.89 g of *sodium hexanesulfonate* in a mixture of 500 mL of *methanol*, 500 mL of *water* and 5 mL of *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated peaks due to proguanil hydrochloride and 1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.2M *hydrochloric acid* containing 0.2% w/v of *sodium chloride*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 withdraw a sample of 10 mL of the medium, filter and dilute 2 mL of the filtrate to 10 mL with dissolution medium. Measure the *absorbance* of this solution, Appendix II B, at 242 nm using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.001% w/v solution of *proguanil hydrochloride BPCRS* in dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of proguanil hydrochloride, $C_{11}H_{16}ClN_5$,HCl, in the medium from the absorbances obtained and from the declared content of $C_{11}H_{16}ClN_5$,HCl in *proguanil hydrochloride BPCRS*.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Weigh and powder 20 tablets, add 50 mL of *methanol* to a quantity of the powdered tablets containing 0.1 g of Proguanil Hydrochloride, shake for 10 minutes, dilute to 100 mL with *methanol*, mix and filter. To 5 mL of the filtrate add sufficient *methanol* to produce 50 mL and dilute 10 mL of the resulting solution to 50 mL with the mobile phase.

(2) 0.002% w/v of *proguanil hydrochloride BPCRS* in the mobile phase.

(3) 1 volume of a 0.05% w/v solution of *1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride BPCRS* in *methanol* with 9 volumes of a 0.010% w/v solution of *proguanil hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated peaks due to proguanil hydrochloride and 1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{16}ClN_5$,HCl in the tablets using the declared content of $C_{11}H_{16}ClN_5$,HCl in *proguanil hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Proguanil Hydrochloride.

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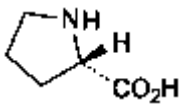
Proline

General Notices

(Ph. Eur. monograph 0785)



$C_5H_9NO_2$ 115.1 *147-85-3*

Action and use

Amino acid.

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DEFINITION

(2*S*)-Pyrrolidine-2-carboxylic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Specific optical rotation (see Tests).

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B. Infrared absorption spectrophotometry (2.2.24).

Comparison *proline CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 1 per cent *V*/*V* solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Reference solution Dissolve 10 mg of *proline CRS* in a 1 per cent *V*/*V* solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V*/*V*/*V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 2.5 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

-86.0 to -84.0 (dried substance).

Dissolve 1.00 g in *water R* and dilute to 25.0 mL with the same solvent.

Ninhydrin-positive substances

Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

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Solution A *dilute hydrochloric acid R1* or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dissolve 30.0 mg of *alanine R* (impurity A) in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* and 30 mg of *leucine R* in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of impurity A in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

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Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 11.51 mg of $C_5H_9NO_2$.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.

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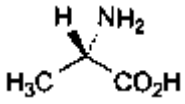
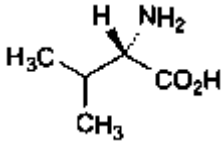


A. (2*S*)-2-aminopropanoic acid (alanine),



B. (2*S*)-2-amino-3-methylbutanoic acid (valine).

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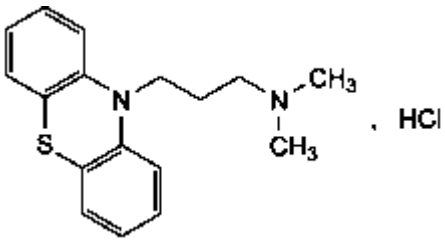
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Promazine Hydrochloride

General Notices

(Ph. Eur. monograph 1365)



$C_{17}H_{21}ClN_2S$ 320.9 *53-60-1*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparations

Promazine Injection

Promazine Tablets

Ph Eur

DEFINITION

N,*N*-Dimethyl-3-(10*H*-phenothiazin-10-yl)propan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

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Very soluble in water, in ethanol (96 per cent) and in methylene chloride.

mp

About 179 °C.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *promazine hydrochloride CRS*.
B. Identification test for phenothiazines by thin-layer chromatography (*2.3.3*): use *promazine hydrochloride CRS* to prepare the reference solution.
C. Dissolve about 5 mg in 2 mL of *sulfuric acid R* and allow to stand for 5 min. An orange colour is produced.
D. Dissolve 18 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

pH (*2.2.3*)

4.2 to 5.2, measured immediately after preparation.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions and protect from light*.

Buffer solution Dissolve 1.2 g of *ammonium hydrogen carbonate R* in *water for chromatography R* and dilute to 1000 mL with *water for chromatography R*. Adjust to pH 10.8 with *ammonia R*.

Test solution Dissolve 60.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 6 mg of *promazine impurity B CRS* and 6 mg of *promazine impurity C CRS* in mobile phase A, using sonication if necessary, and dilute to 100 mL with mobile phase A. Dilute 1 mL of the solution to 50 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

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— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: buffer solution, *acetonitrile R* (35:50 *V/V*);

— *mobile phase B*: buffer solution, *acetonitrile R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 22	100	0
22 - 37	100 → 0	0 → 100
37 - 60	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of peaks Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to promazine (retention time = about 22 min): impurity C = about 0.56; impurity B = about 0.68. The elution order of impurities C and B may be inverted.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities C and B.

Calculation of percentage content:

— use the concentration of promazine hydrochloride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

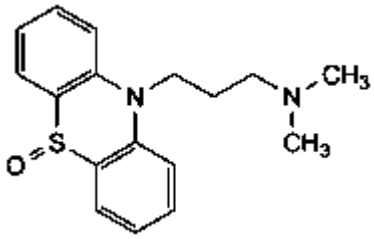
1 mL of *0.1 M sodium hydroxide* is equivalent to 32.09 mg of $C_{17}H_{21}ClN_2S$.

STORAGE

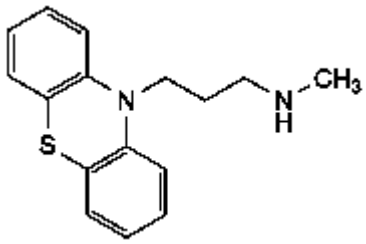
In an airtight container protected from light.

IMPURITIES

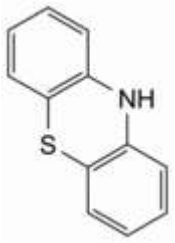
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10*. *Control of impurities in substances for pharmaceutical use*) *A, B, C, D*.



A. 10-[3-(dimethylamino)propyl]-5λ^4-phenothiazin-5(10*H*)-one (promazine sulfoxide),



B. *N*-methyl-3-(10*H*-phenothiazin-10-yl)propan-1-amine,



C. 10*H*-phenothiazine,

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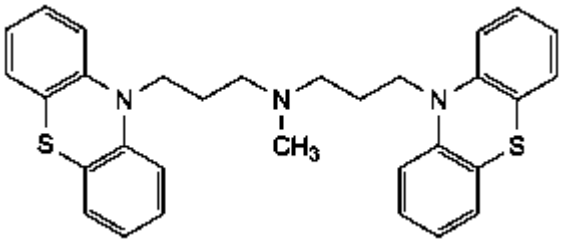

D. *N*-methyl-3-(10*H*-phenothiazin-10-yl)-*N*-[3-(10*H*-phenothiazin-10-yl)propyl]propan-1-amine.

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Promazine Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Promazine Injection is a sterile solution of Promazine Hydrochloride in Water for Injections free from dissolved air.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of promazine hydrochloride, $C_{17}H_{20}N_2S,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. To a volume containing 0.1 g of Promazine Hydrochloride add 20 mL of *water* and 2 mL of 10M *sodium hydroxide*. Shake and extract the mixture with 25 mL of *ether*. Wash the ether with two 5 mL quantities of *water*, dry with *anhydrous sodium sulfate* and evaporate the ether to dryness. Dissolve the residue in 1 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of promazine (*RS 295*).

B. To a volume containing 5 mg of Promazine Hydrochloride carefully add 2 mL of *sulfuric acid* and allow to stand for 5 minutes. An orange colour is produced.

C. To a volume containing 0.2 g of Promazine Hydrochloride add 1 mL of 1M *sodium hydroxide* and extract with four 10 mL quantities of *ether*. Wash the combined extracts with 10 mL of *water*, remove the ether and dissolve the residue in 4 mL of *methanol*. Heat on a water bath almost to boiling, immediately add 2 mL of a boiling 3.5% w/v solution of *picric acid* in *methanol* and boil for 2 minutes. Cool in ice, filter, wash the crystals with three quantities of *methanol*, dissolve in 10 mL of hot *methanol* and repeat the crystallisation and washing. The *melting point* of the rust-red crystals so obtained, after drying at 105° for 1 hour, is about 144°, Appendix V A.

TESTS

Acidity

pH, 4.4 to 5.2, Appendix V L.

Related substances

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Carry out the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and applying separately to the plate 10 µL of each of the following freshly prepared solutions. For solution (1) dilute a volume of the injection with sufficient *methanol* to produce a solution containing 1.0% w/v of Promazine Hydrochloride. For solution (2) dilute 1 volume of solution (1) to 40 volumes with *methanol*. For solution (3) dilute 1 volume of solution (1) to 200 volumes with *methanol*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (2.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Carry out the following procedure protected from light. To a quantity containing 50 mg of Promazine Hydrochloride add 5 mL of 2M *hydrochloric acid* and sufficient *water* to produce 1000 mL. To 10 mL add 10 mL of 0.1M *hydrochloric acid*, dilute to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 251 nm, Appendix II B. Calculate the content of $C_{17}H_{20}N_2S$,HCl taking 935 as the value of A(1%, 1 cm) at the maximum at 251 nm.

STORAGE

Promazine Injection should be protected from light.

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Promazine Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Promazine Tablets contain Promazine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of promazine hydrochloride, $C_{17}H_{20}N_2S,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 40 mg of Promazine Hydrochloride add 10 mL of *water* and 2 mL of 1M *sodium hydroxide*, shake and extract with 15 mL of *ether*. Wash the extract with 5 mL of *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 0.4 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of promazine (*RS 295*).

B. To a quantity of the powdered tablets containing 5 mg of Promazine Hydrochloride add 5 mL of *sulfuric acid* and allow to stand for 5 minutes. An orange colour is produced.

C. Triturate a quantity of the powdered tablets containing 0.2 g of Promazine Hydrochloride with 4 mL of *methanol*, centrifuge, filter the supernatant liquid, heat almost to boiling, immediately add 2 mL of a boiling 3.5% w/v solution of *picric acid* in *methanol* and boil for 2 minutes. Cool in ice, filter, wash the crystals with three quantities of *methanol*, dissolve in 10 mL of hot *methanol* and repeat the crystallisation and washing. The *melting point* of the rust red crystals so obtained, after drying at 105° for 1 hour, is about 144°, Appendix V A.

Related substances

Comply with the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and the following freshly prepared solutions. For solution (1) extract a quantity of the powdered tablets containing 0.1 g of Promazine Hydrochloride with 10 mL of *methanol* and filter. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *methanol*.

ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 tablets. Triturate a quantity of the powder containing 50 mg of Promazine Hydrochloride with 10 mL of 2M *hydrochloric acid* and then add 200 mL of *water*. Shake for 15 minutes, add sufficient *water* to

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produce 500 mL and centrifuge about 50 mL of the mixture. To 5 mL of the clear, supernatant liquid add 10 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 100 mL. Measure the *absorbance* of the resulting solution at the maximum at 251 nm, Appendix II B. Calculate the content of $C_{17}H_{20}N_2S$,HCl taking 935 as the value of A(1%, 1 cm) at the maximum at 251 nm.

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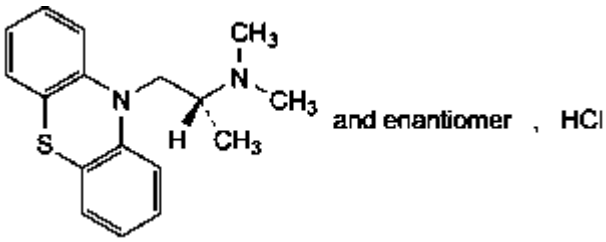
Promethazine Hydrochloride

General Notices

(Ph. Eur. monograph 0524)



$C_{17}H_{21}ClN_2S$ 320.9 *58-33-3*

Action and use

H_1 receptor antagonist; antihistamine.

Preparations

Promethazine Injection

Promethazine Oral Solution

Promethazine Hydrochloride Tablets

Ph Eur

DEFINITION

(2*RS*)-*N*,*N*-Dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or faintly yellowish, crystalline powder.

Solubility

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Very soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

mp

About 222 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison promethazine hydrochloride CRS.

B. Identification test for phenothiazines by thin-layer chromatography (2.3.3): use promethazine hydrochloride CRS to prepare the reference solution.

C. Dissolve 0.1 g in 3 mL of water R. Add dropwise 1 mL of nitric acid R. A precipitate is formed which rapidly dissolves to give a red solution, becoming orange and then yellow. Heat to boiling. The solution becomes orange and an orange-red precipitate is formed.

D. Dissolve 18 mg in 2 mL of methanol R. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

4.0 to 5.0, measured immediately after preparation.

Dissolve 1.0 g in carbon dioxide-free water R and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and carry out the test protected from light.*

Solvent mixture triethylamine R, methanol R (1:1000 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2.5 mg of promethazine for peak identification CRS (containing impurities A, B and C) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of promethazine impurity D CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

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— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography with embedded polar groups R* (5 µm).

Mobile phase Mix 20 volumes of *methanol R*, 30 volumes of *acetonitrile R* and 50 volumes of a 3.4 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with *potassium hydroxide R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 2.5 times the retention time of promethazine.

Identification of impurities Use the chromatogram supplied with *promethazine for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to promethazine (retention time = about 18 min): impurity D = about 0.2; impurity C = about 0.5; impurity B = about 1.4; impurity A = about 1.8.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities B and A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.5;

— *impurity B*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 12 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

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Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

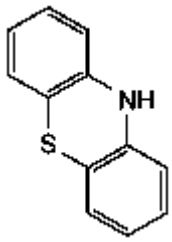
1 mL of *0.1 M sodium hydroxide* is equivalent to 32.09 mg of $C_{17}H_{21}ClN_2S$.

STORAGE

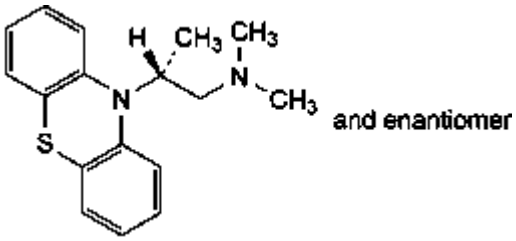
Protected from light.

IMPURITIES

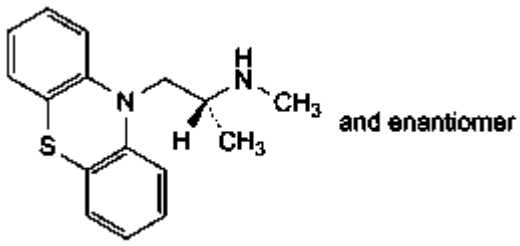
Specified impurities *A, B, C, D.*



A. phenothiazine,



B. (2*RS*)-*N*,*N*-dimethyl-2-(10*H*-phenothiazin-10-yl)propan-1-amine (isopromethazine),



C. (2*RS*)-*N*-methyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine,

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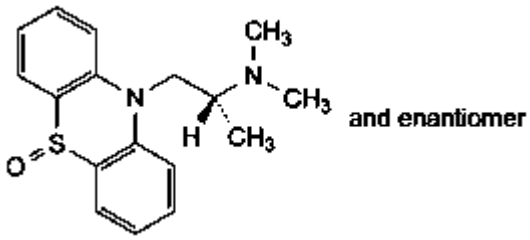

and enantiomer

D. 10-[(2*RS*)-2-(dimethylamino)propyl]-5λ^4-phenothiazin-5(10*H*)-one.

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Promethazine Hydrochloride Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Promethazine Hydrochloride Tablets contain Promethazine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of promethazine hydrochloride, $C_{17}H_{20}N_2S,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 40 mg of Promethazine Hydrochloride add 10 mL of *water* and 2 mL of 1M *sodium hydroxide*, shake and extract with 15 mL of *ether*. Wash the ether with 5 mL of *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 0.4 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of promethazine (*RS 297*).

B. To a quantity of the powdered tablets containing 5 mg of Promethazine Hydrochloride add 5 mL of *sulfuric acid* and allow to stand for 5 minutes. A red colour is produced.

C. Dissolve a quantity of the powdered tablets containing 0.2 g of Promethazine Hydrochloride in 2 mL of *water*, filter, saturate with *potassium carbonate sesquihydrate*, extract with two 10 mL quantities of *ether* and evaporate the combined extracts to dryness. Dissolve the residue in 2 mL of *methanol* and pour into a solution of 0.4 g of *picric acid* in 10 mL of *methanol* at about 50°. Cool, scratch the side of the tube to induce crystallisation, allow to stand for 3 to 4 hours and filter. The *melting point* of the crystals, after washing with *methanol* and drying, is about 160°, Appendix V A.

Related substances

Carry out the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase B* and applying separately to the plate 20 µL of each of the following freshly prepared solutions. For solution (1) extract a quantity of the powdered tablets containing 0.1 g of Promethazine Hydrochloride with 10 mL of a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine* and filter. Solution (2) contains 0.010% w/v of *isopromethazine hydrochloride BPCRS* in the same solvent. For solution (3) dilute 1 volume of solution (1) to 200 volumes with the same solvent. Any spot corresponding to isopromethazine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

ASSAY

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ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 tablets. Triturate a quantity of the powder containing 50 mg of Promethazine Hydrochloride with 10 mL of 2M *hydrochloric acid* and add 200 mL of *water*. Shake for 15 minutes, add sufficient *water* to produce 500 mL and centrifuge about 50 mL of the mixture. To 5 mL of the clear, supernatant liquid add 10 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 100 mL. Measure the *absorbance* of the resulting solution at the maximum at 249 nm, Appendix II B. Calculate the content of $C_{17}H_{20}N_2S,HCl$ taking 910 as the value of A(1%, 1 cm) at the maximum at 249 nm.

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Promethazine Injection

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Promethazine Injection is a sterile solution of Promethazine Hydrochloride in Water for Injections free from dissolved air.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of promethazine hydrochloride, $C_{17}H_{20}N_2S,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. To a volume containing 0.1 g of Promethazine Hydrochloride add 20 mL of *water* and 2 mL of 10M *sodium hydroxide*. Shake and extract the mixture with 25 mL of *ether*. Wash the ether layer with two 5 mL quantities of *water*, dry with *anhydrous sodium sulfate* and evaporate the ether. Dissolve the residue in 1 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of promethazine (*RS 297*).

B. To a volume containing 5 mg of Promethazine Hydrochloride carefully add 2 mL of *sulfuric acid* and allow to stand for 5 minutes. A red colour is produced.

C. To a volume containing 0.2 g of Promethazine Hydrochloride add sufficient *potassium carbonate sesquihydrate* to saturate the solution, extract with two 10-mL quantities of *ether* and evaporate the combined extracts to dryness. Dissolve the residue in 2 mL of *methanol* and pour into a solution of 0.4 g of *picric acid* in 10 mL of *methanol*, previously warmed to about 50°. Cool, scratch the side of the tube to induce crystallisation, allow to stand for 3 to 4 hours and filter. The *melting point* of the residue, after washing with *methanol* and drying, is about 160°, Appendix V A.

TESTS

Acidity

pH, 5.0 to 6.0, Appendix V L.

Related substances

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Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light under an atmosphere of nitrogen using *silica gel GF$_{254}$* as the coating substance (Merck silica gel 60 F$_{254}$ plates are suitable) and a mixture of 15 volumes of *diethylamine*, 45 volumes of *hexane* and 50 volumes of *acetone* as the mobile phase but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µL of each of the following freshly prepared solutions. For solution (1) use a volume of the injection diluted, if necessary, with a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol* to contain 1.0% w/v of Promethazine Hydrochloride. For solution (2) dilute 1 volume of solution (1) to 200 volumes with a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. Solution (3) contains 0.01% w/v of *isopromethazine hydrochloride BPCRS* in a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. Solution (4) contains 0.025% w/v of *promethazine sulfoxide BPCRS* in a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. After removal of the plate, allow it to dry in air, spray with a 20% w/v solution of *perchloric acid* and heat at 100° for 5 minutes. In the chromatogram obtained with solution (1) any spot corresponding to isopromethazine is not more intense than the principal spot in the chromatogram obtained with solution (3) (1%), any spot corresponding to promethazine sulfoxide is not more intense than the spot in the chromatogram obtained with solution (4) (2.5%) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%). Disregard any spot remaining on the line of application.

ASSAY

Carry out the following procedure protected from light. To a volume containing 25 mg of Promethazine Hydrochloride add sufficient 0.01M *hydrochloric acid* to produce 100 mL. Dilute 10 mL to 100 mL with 0.01M *hydrochloric acid*, dilute 10 mL of this solution to 50 mL with 0.01M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at 249 nm, Appendix II B. Calculate the content of $C_{17}H_{20}N_2S$,HCl taking 910 as the value of A(1%, 1 cm) at the maximum at 249 nm.

STORAGE

Promethazine Injection should be protected from light.

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Promethazine Oral Solution

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Promethazine Oral Solution is a solution containing Promethazine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of promethazine hydrochloride, $C_{17}H_{20}N_2S,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Carry out the method for *identification of phenothiazines*, Appendix III A, but applying as solution (1) 5 µL of a solution prepared by diluting a suitable volume of the oral solution with *water* to contain 0.08% w/v of Promethazine Hydrochloride.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light under an atmosphere of nitrogen using *silica gel* GF_{254} as the coating substance (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 15 volumes of *diethylamine*, 45 volumes of *hexane* and 50 volumes of *acetone* as the mobile phase but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µL of each of the following freshly prepared solutions. For solution (1) add 50 mL of *water* and 10 mL of a 5% w/v solution of *sodium hydroxide* to a quantity of the oral solution containing 20 mg of Promethazine Hydrochloride in a separating funnel and swirl to mix. Extract with two 100 mL quantities of *chloroform*, shaking vigorously for 1 minute each time, and filter successively through *anhydrous sodium sulfate*, washing the sodium sulfate with 50 mL of *chloroform*. Evaporate the combined extracts and washings to dryness at 30° using a rotary evaporator and dissolve the residue in 2 mL of a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. For solution (2) dilute 1 volume of solution (1) to 200 volumes with the same solvent. Solution (3) contains 0.01% w/v of *isopromethazine hydrochloride BPCRS* in the same solvent. Solution (4) contains 0.025% w/v of *promethazine sulfoxide BPCRS* in the same solvent. After removal of the plate, allow it to dry in air, spray with a 20% w/v solution of *perchloric acid* and heat at 100° for 5 minutes. In the chromatogram obtained with solution (1) any spot corresponding to isopromethazine is not more intense than the principal spot in the chromatogram obtained with solution (3) (1%), any spot corresponding to promethazine sulfoxide is not more intense than the principal spot in the chromatogram obtained with solution (4) (2.5%) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%). Disregard any spot remaining on the line of application.

ASSAY

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Carry out the following procedure protected from light. To a weighed quantity containing 10 mg of Promethazine Hydrochloride add 25 mL of *water* and 5 mL of a 5% w/v solution of *sodium hydroxide*. Extract the mixture with two 50 mL quantities of *chloroform*, shaking vigorously for 1 minute each time, evaporate the combined extracts to dryness at about 30° at a pressure of 2 kPa and dissolve the residue in sufficient *0.1M hydrochloric acid* to produce 50 mL (solution A). Dilute 10 mL of solution A to 50 mL with *water* (solution B). To a further 10 mL of solution A add 5 mL of *peroxyacetic acid solution*, allow to stand for 10 minutes and add sufficient *water* to produce 50 mL (solution C). Measure the *absorbance* of solution C at the maximum at 336 nm, Appendix II B, using solution B in the reference cell and measure the *absorbance* of solution B at the same wavelength using *water* in the reference cell. Repeat the procedure using a 0.02% w/v solution of *promethazine hydrochloride BPCRS* in *0.1M hydrochloric acid* in place of solution A and beginning at the words 'Dilute 10 mL of...'. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{17}H_{20}N_2S$,HCl, weight in volume, using the declared content of $C_{17}H_{20}N_2S$,HCl in *promethazine hydrochloride BPCRS*. The result is not valid if the absorbance of solution B is more than 0.10.

STORAGE

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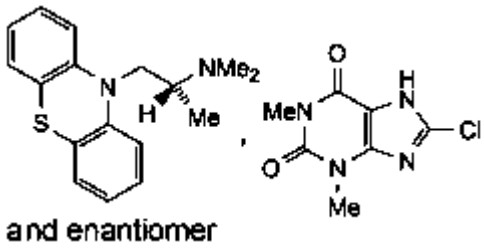
Promethazine Teoclate

General Notices



$C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$ 499.0 *17693-51-5*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparation

Promethazine Teoclate Tablets

DEFINITION

Promethazine Teoclate is the (*RS*)-dimethyl(2-phenothiazin-10-ylpropyl)amine salt of 8-chlorotheophylline. It contains not less than 98.0% and not more than 101.0% of $C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder.

Very slightly soluble in *water*; sparingly soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. Shake 0.15 g with 2.5 mL of *water*, add 1 mL of 5M *ammonia* and extract with 30 mL of *ether*. Wash the ether extract with 10 mL of *water*, dry with *anhydrous sodium sulfate* and evaporate the ether to dryness. Dissolve the residue in 1 mL of *chloroform IR*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of promethazine *(RS 297)*.

B. Dissolve 5 mg in 2 mL of *sulfuric acid* and allow to stand for 5 minutes. A red colour is produced.

C. Shake 0.4 g with 10 mL of *water*, add 4 mL of 5M *ammonia*, shake with two 30-mL quantities of *ether* and add 4 mL of *hydrochloric acid* to the aqueous solution. Filter the white precipitate, wash with *water* and dry at 105°. Dissolve 10 mg of the residue in 1 mL of *hydrochloric*

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acid, add 0.1 g of *potassium chlorate* and evaporate to dryness. A reddish residue remains which becomes purple on exposure to the vapour of ammonia.

TESTS

Chloride

Shake 0.3 g with 30 mL of *water* for 2 minutes and filter. 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII, but using 2 mL of *nitric acid* in place of the 1 mL of *dilute nitric acid* (350 ppm).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 5 volumes of *diethylamine*, 10 volumes of *acetone* and 85 volumes of *cyclohexane* as the mobile phase. Pour the mobile phase into an unlined tank, immediately place the prepared plate in the tank, close the tank and allow the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µL of each of the following solutions in a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. Solution (1) contains 2% w/v of the substance being examined. Solution (2) contains 0.02% w/v of *isopromethazine hydrochloride BPCRS*. For solution (3) dilute 1 volume of solution (1) to 200 volumes. For solution (4) dilute 1 volume of solution (1) to 500 volumes. Allow the plate to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to isopromethazine is not more intense than the spot in the chromatogram obtained with solution (2) (1%), any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%) and not more than three such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.2%). Disregard any spot remaining on the line of application.

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 1 g in 200 mL of *acetone* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 3 mL of a saturated solution of *methyl orange* in *acetone* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 49.90 mg of $C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$.

STORAGE

Promethazine Teoclate should be protected from light.

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Promethazine Teoclate Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Promethazine Teoclate Tablets contain Promethazine Teoclate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of promethazine teoclate, $C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 60 mg of Promethazine Teoclate add 10 mL of *water* and 2 mL of 1M *sodium hydroxide*, shake and extract with 15 mL of *ether*. Wash the extract with 5 mL of *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 0.4 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of promethazine (*RS 297*).

B. To a quantity of the powdered tablets containing 5 mg of Promethazine Teoclate add 5 mL of *sulfuric acid* and allow to stand for 5 minutes. A red colour is produced.

C. Extract a quantity of the powdered tablets containing 0.2 g of Promethazine Teoclate with *chloroform*, filter and evaporate the filtrate to dryness. Shake the residue with 10 mL of *water*, add 4 mL of 5M *ammonia* and extract with two 30 mL quantities of *ether*. Wash the combined extracts with 10 mL of *water* and reserve the aqueous layer and washings. To the combined aqueous layer and washings add 4 mL of *hydrochloric acid*; a white precipitate is produced. Filter, wash the residue with *water* and dry at 105°. Dissolve 10 mg of the residue in 1 mL of *hydrochloric acid*, add 0.1 g of *potassium chlorate* and evaporate to dryness. A reddish residue remains which becomes purple on exposure to the vapour of 5M *ammonia*.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 5 volumes of *diethylamine*, 10 volumes of *acetone* and 85 volumes of *cyclohexane* as the mobile phase. Pour the mobile phase into an unlined tank, immediately place the prepared plate in the tank, close the tank and allow the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.2 g of Promethazine Teoclate with 10 mL of a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol* for 5 minutes, filter (Whatman GF/C filter paper is suitable) and use the filtrate. Solution (2) contains 0.02% w/v of *isopromethazine hydrochloride BPCRS* in a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. For solution (3) dilute 1

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volume of solution (1) to 200 volumes with a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. For solution (4) dilute 1 volume of solution (1) to 500 volumes with a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*. Allow the plate to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to isopromethazine hydrochloride is not more intense than the spot in the chromatogram obtained with solution (2) (1%), any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%) and not more than three such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.2%). Disregard any spot remaining on the line of application.

ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 tablets. To a quantity of the powder containing 50 mg of Promethazine Teoclate add 5 mL of *water* and 1 mL of 13.5M *ammonia* and allow to stand for 5 minutes. Add 50 mL of *absolute ethanol*, shake for 5 minutes and filter, washing the residue with five 5 mL quantities of *absolute ethanol*. Add sufficient *absolute ethanol* to the filtrate to produce 100 mL. Dilute 10 mL to 100 mL with *absolute ethanol* and dilute 10 mL of this dilution to 100 mL with *absolute ethanol*. Measure the *absorbance* of the resulting solution at the maximum at 255 nm, Appendix II B. Calculate the content of $C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$ taking 755 as the value of A(1%, 1 cm) at the maximum at 255 nm.

STORAGE

Promethazine Teoclate Tablets should be protected from light.

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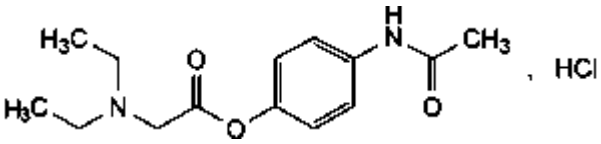
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Propacetamol Hydrochloride

General Notices

(Ph. Eur. monograph 1366)



$C_{14}H_{21}ClN_2O_3$ 300.8 *66532-86-3*

Action and use

Analgesic; antipyretic.

Ph Eur

DEFINITION

4-(Acetylamino)phenyl (diethylamino)acetate hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in anhydrous ethanol, practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of propacetamol hydrochloride*.

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B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Prepare the solution immediately before use Dissolve 1.75 g in water R and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 or BY_6 (2.2.2, Method II).

Absorbance (2.2.25)

Maximum 0.05, determined at 390 nm on solution S.

Impurity B

Thin-layer chromatography (2.2.27).

Test solution Suspend 4.00 g of the substance to be examined in 8 mL of acetonitrile R. Shake for 30 min and filter. Dilute to 10 mL with acetonitrile R.

Reference solution (a) Dissolve 25 mg of 4-aminophenol R (impurity B) in acetonitrile R and dilute to 50 mL with the same solvent. Dilute 10 mL of this solution to 50 mL with acetonitrile R.

Reference solution (b) Dilute 5 mL of reference solution (a) to 50 mL with acetonitrile R.

Reference solution (c) Dilute 0.2 mL of reference solution (a) to 5 mL with the test solution.

Plate TLC silica gel F_{254} plate R.

Mobile phase anhydrous formic acid R, water R, methanol R, methylene chloride R (3:4:30:64 *V/V/V/V*).

Application 50 µL of the test solution and of reference solutions (b) and (c).

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm. Spray with a 10 g/L solution of dimethylaminobenzaldehyde R in ethanol (96 per cent) R.

Identification of spots Reference solution (c) shows 2 spots, one visible in ultraviolet light due to propacetamol and the other one yellow, visible after spraying due to impurity B. An additional spot may appear in ultraviolet light and corresponds to impurity A.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots.

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Limit:

— *impurity B*: any yellow spot due to impurity B not visible in ultraviolet light is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (25 ppm).

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 2.16 g of *sodium octanesulfonate R* in 900 mL of *water R* and dilute to 1000 mL with the same solvent. Adjust to pH 3.0 with *acetic acid R*.

Test solution Suspend 1.00 g of the substance to be examined in 10.0 mL of *acetonitrile R*. Shake for 10 min. Allow to stand. Take 3.0 mL of the supernatant and dilute to 10.0 mL with solution A. Inject immediately.

Reference solution (a) Dissolve 50 mg of *paracetamol R* (impurity A) in *acetonitrile R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *acetonitrile R*. Dilute 3.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 10 mg of *paracetamol R* (impurity A) and 0.100 g of *4-aminophenol R* (impurity B) in *acetonitrile R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *acetonitrile R*. Dilute 3.0 mL of this solution to 10.0 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, solution A (30:70 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 246 nm.

Injection 20 µL.

Run time Twice the retention time of propacetamol.

Identification of impurities The chromatogram obtained with reference solution (b) shows a peak due to impurity A (1st peak) and a peak due to impurity B (2nd peak).

Relative retention With reference to impurity A: impurity B = about 1.6.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (200 ppm);

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— *unspecified impurities*: for each impurity, not more than 3.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent taking into account the response factor of paracetamol of 1.6);

— *total*: not more than 6.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent taking into account the relative response factor of paracetamol of 1.6);

— *disregard limit*: 0.01 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3 ppm taking into account the relative response factor of paracetamol of 1.6).

Methanol

Gas chromatography (*2.2.28*).

Internal standard solution Dilute 2.0 mL of *propanol R* to 20.0 mL with *water R*. Dilute 1.0 mL of the solution to 25.0 mL with *water R*. Dilute 1.0 mL of this solution to 25.0 mL with *water R*.

Test solution Dissolve 2.00 g of the substance to be examined in *water R*, add 2.0 mL of the internal standard solution and dilute to 10.0 mL with *water R*.

Reference solution Dilute 0.8 mL of *methanol R* to 50.0 mL with *water R*. Dilute 1.0 mL of the solution to 25.0 mL with *water R*. To 2.0 mL of this solution, add 2.0 mL of the internal standard solution and dilute to 10.0 mL with *water R*.

Column:

— *material*: glass;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: carbon molecular sieve impregnated with 0.2 per cent of macrogol 1500.

Carrier gas *nitrogen for chromatography R*.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1.5	60
	1.5 - 5.5	60 → 80
	5.5 - 15.5	80
Injection port		170
Detector		220

Detection Flame ionisation.

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Injection 2 µL.

Limit:

— *methanol*: calculate the ratio (*R*) of the area of the peak due to methanol to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the area of any peak due to methanol to the area of the peak due to the internal standard: this ratio is not greater than *R* (500 ppm).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 25 mL of *anhydrous acetic acid R* and 25 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

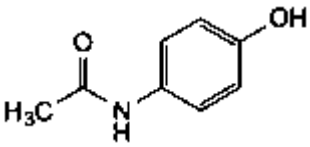
1 mL of *0.1 M perchloric acid* is equivalent to 30.08 mg of $C_{14}H_{21}ClN_2O_3$.

STORAGE

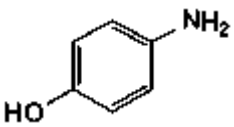
Protected from humidity.

IMPURITIES

Specified impurities *A, B.*



A. *N*-(4-hydroxyphenyl)acetamide (paracetamol),



B. 4-aminophenol.

Ph Eur

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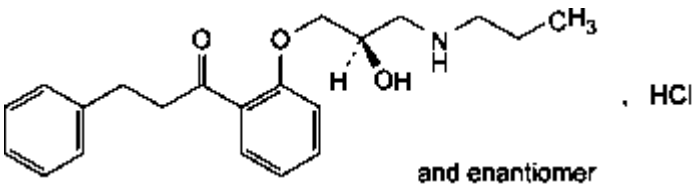
Propafenone Hydrochloride

General Notices

(Ph. Eur. monograph 2103)



$C_{21}H_{28}ClNO_3$ 377.9 *34183-22-7*

Action and use

Class I antiarrhythmic.

Ph Eur

DEFINITION

1-[2-[(2*RS*)-2-Hydroxy-3-(propylamino)propoxy]phenyl]-3-phenylpropan-1-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Colourless crystals or white or almost white powder.

Solubility

Slightly soluble in cold water, soluble in methanol and in hot water, practically insoluble in ethanol (96 per cent).

mp

About 173 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *propafenone hydrochloride CRS*.

B. To 5.0 mL of solution S (see Tests) add 2 drops of *dilute nitric acid R*. A precipitate is formed. After 10 min, filter. 2.0 mL of the clear filtrate gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

To 0.500 g in a 100 mL volumetric flask add 50 mL of *water R*, and heat to boiling for 5 min. Allow to cool to room temperature and dilute to 100.0 mL with *carbon dioxide-free water R*.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.0 to 6.2 for solution S.

Optical rotation (*2.2.7*)

-0.05° to + 0.05°.

Dissolve 1.00 g in *methanol R* and dilute to 100.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase B, mobile phase A (35:65 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of the substance to be examined and 5.0 mg of *propafenone impurity B CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 320-350 m^2/g and a pore size of 12-13 nm,

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— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 3.42 g/L solution of *dipotassium hydrogen phosphate trihydrate R* adjusted to pH 2.5 with *phosphoric acid R*,

— *mobile phase B*: *acetonitrile for chromatography R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	65	35
8 - 20	65 → 30	35 → 70
20 - 30	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Equilibration 60 min with the mobile phase at the initial composition, before each series of injections.

Injection 20 µL of the test solution, reference solutions (a), (b) and (c) and of the solvent mixture as a blank.

Relative retention With reference to propafenone (retention time = about 5 min): impurity B = about 0.8; impurity D = about 2.3; impurity G = about 3.6; impurity C = about 4.1; impurity F = about 5.3.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurity B and propafenone.

Limits:

— *impurities B, C, D, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

— *disregard limit*: 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating during the titration, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

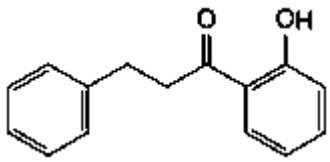
Dissolve 0.300 g in 2 mL of *anhydrous formic acid R*. Add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 37.79 mg of $C_{21}H_{28}ClNO_3$.

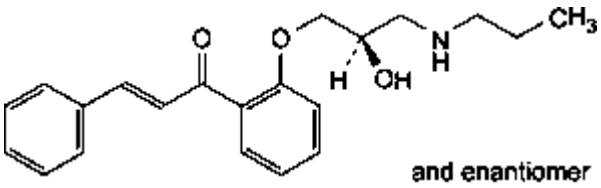
IMPURITIES

Specified impurities *B, C, D, F, G.*

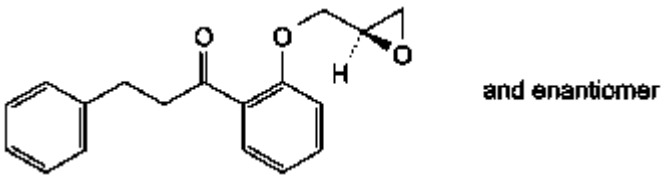
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, E, H.*



A. 1-(2-hydroxyphenyl)-3-phenylpropan-1-one,



B. (2*E*)-1-[2-[(2*RS*)-2-hydroxy-3-(propylamino)propoxy]phenyl]-3-phenylprop-2-en-1-one,



C. 1-[2-[[(2*RS*)-oxiranyl]methoxy]phenyl]-3-phenylpropan-1-one,

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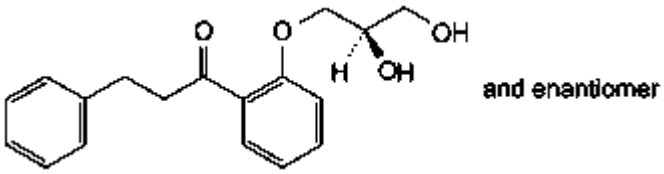
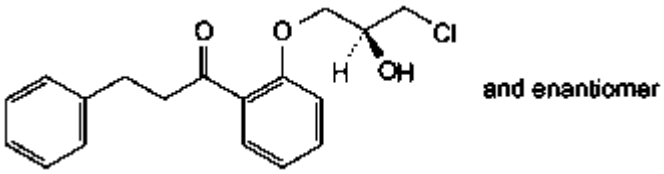
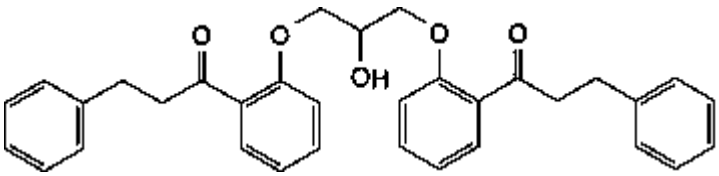


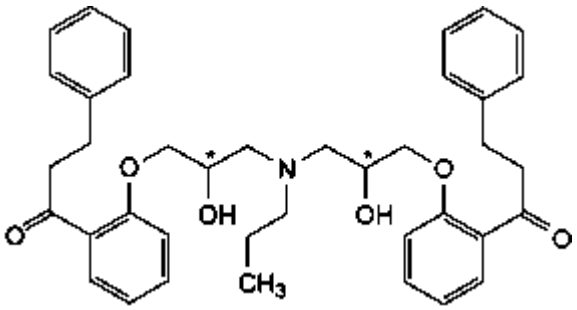
D. 1-[2-[(2*RS*)-2,3-dihydroxypropoxy]phenyl]-3-phenylpropan-1-one,



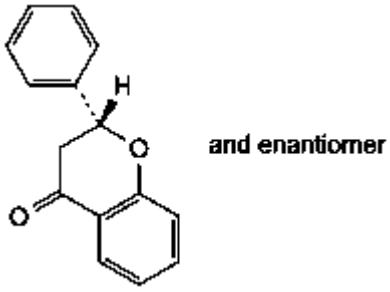
E. 1-[2-[(2*RS*)-3-chloro-2-hydroxypropoxy]phenyl]-3-phenylpropan-1-one,



F. 1,1′-[2-hydroxypropane-1,3-diylbis(oxy-2,1-phenylene)]bis(3-phenylpropan-1-one),



G. 1,1′-[propyliminobis[(2-hydroxypropane-3,1-diyl)oxy-2,1-phenylene]]bis(3-phenylpropan-1-one),



H. (2*RS*)-2-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Propanol

General Notices

(Ph. Eur. monograph 2036)

C_3H_8O 60.1 *71-23-8*

Ph Eur

DEFINITION

Propan-1-ol.

CHARACTERS

Appearance

Clear, colourless liquid.

Solubility

Miscible with water and with anhydrous ethanol.

IDENTIFICATION

First identification: C, B.

Second identification: A, B, D.

A. Refractive index (2.2.6): 1.384 to 1.387.

B. Boiling point (2.2.12): 96 °C to 98 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of propanol*.

D. To 1.0 mL add 0.10 g of *dinitrobenzoyl chloride R* and 0.05 mL of *sulfuric acid R*. Boil under reflux for 30 min. Evaporate until the excess of propanol is removed, add 5 mL of *heptane R* to the residue and heat to boiling. Filter the hot solution. Wash the crystals formed

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on cooling with *heptane R* and dry in vacuum (2 kPa, at room temperature for 24 h). The small, colourless, shiny plates melt (*2.2.14*) between 71 °C and 74 °C.

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and colourless (*2.2.2, Method II*). Dilute 2 mL to 10 mL with *water R*. After 5 min, the solution is clear (*2.2.1*).

Acidity or alkalinity

To 10.0 mL of *carbon dioxide-free water R* add 0.1 mL of *phenolphthalein solution R* and *0.01 M sodium hydroxide* until the solution becomes pale pink. After addition of 5.0 mL of the substance to be examined the colour of the solution does not become more intense. If the colour fades, add 0.2 mL of *0.01 M sodium hydroxide*. The solution is pink.

Absorbance (*2.2.25*)

Measure the absorbance between 230 nm and 310 nm using *water R* as the compensation liquid. The absorbance *A* is not greater than the following values.

Wavelength (nm)	Absorbance *A*
230	0.300
250	0.100
270	0.030
290	0.020
310	0.010

The absorption curve does not show any peaks.

Reducing substances

Place 10.0 mL in a test tube of about 20 mm in diameter in a water bath at 20 °C. Keep protected from actinic light and add 1.0 mL of a freshly prepared 0.16 g/L solution of *potassium permanganate R*. The mixture, maintained at 20 °C, slowly changes its colour from violet to red. After 30 min, the test solution is not less intensely coloured (*2.2.2, Method II*) than 10.0 mL of a reference solution prepared as follows: to 5.5 mL of primary solution yellow, add 13.0 mL of primary solution red and dilute to 100.0 mL with *water R*.

Related substances

Gas chromatography (*2.2.28*).

Test solution The substance to be examined.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *heptane R*. Dilute 1.0 mL of this solution to 10.0 mL with *heptane R*.

Reference solution (b) Mix 0.1 mL of *acetone R* and 0.1 mL of *2-propanol R* and dilute to 100 mL with the test solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 1.4 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 25 cm/s.

Split ratio 1:200.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 12	40
	12 - 28	40 → 200
	28 - 38	200
Injection port		240
Detector		240

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities D and E.

Limits:

— *any impurity*: not more than the area of the peak due to propanol in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 3 times the area of the peak due to propanol in the chromatogram obtained with reference solution (a) (0.3 per cent);

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— *disregard limit*: 0.1 times the area of the peak due to propanol in the chromatogram obtained with reference solution (a) (0.01 per cent).

Non-volatile matter

Maximum 0.004 per cent.

Evaporate 50 mL of the substance to be examined to dryness at 100 °C and dry the residue in an oven at 100-105 °C to constant mass. The residue weighs a maximum of 2 mg.

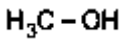
Water (*2.5.12*)

Maximum 0.2 per cent, determined on 10 g.

STORAGE

Protected from light.

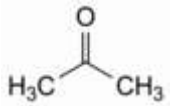
IMPURITIES



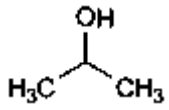
A. methanol,

B. ethanol,

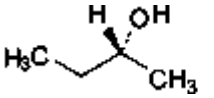
C. propanal,



D. propanone (acetone),



E. isopropyl alcohol (2-propanol),



F. butan-2-ol (*sec*-butanol),

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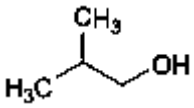
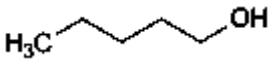


G. 2-methylpropan-1-ol (isobutanol),

H. butan-1-ol (*n*-butanol),



I. pentan-1-ol (*n*-pentanol),

J. hexan-1-ol (*n*-hexanol).

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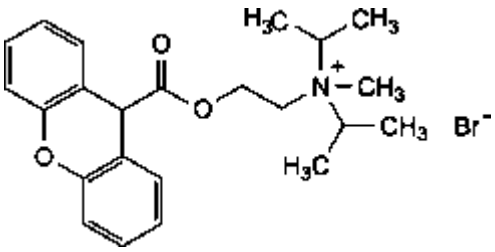
Propantheline Bromide

General Notices

(Ph. Eur. monograph 0857)



$C_{23}H_{30}BrNO_3$ 448.4 *50-34-0*

Action and use

Anticholinergic.

Preparation

Propantheline Tablets

Ph Eur

DEFINITION

N-Methyl-*N*,*N*-bis(1-methylethyl)-2-[(9*H*-xanthen-9-ylcarbonyl)oxy]ethanaminium bromide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, slightly hygroscopic powder.

Solubility

Very soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

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A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 60 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *methanol R*.

Spectral range 230-350 nm.

Absorption maxima At 246 nm and 282 nm.

Specific absorbance at the absorption maxima:

— at 246 nm: 115 to 125;

— at 282 nm: 57 to 63.

B. Dissolve 0.2 g in 15 mL of *water R* and add 1 mL of *strong sodium hydroxide solution R*. Boil for 2 min and cool slightly. Add 7.5 mL of *dilute hydrochloric acid R* and filter. Wash the residue with *water R* and recrystallise from *ethanol (50 per cent V/V) R*. Dry at 100-105 °C for 1 h. Dissolve about 10 mg of the residue in 5 mL of *sulfuric acid R*. The solution has an intense yellow colour and shows an intense yellowish-green fluorescence when examined in ultraviolet light at 365 nm.

C. Dissolve 50 mg in 0.1 mL of *water R* in a 25 mL flask and add 1 mL of a saturated solution of *potassium permanganate R*. Attach a fractionating column and a condenser, with the end of the delivery tube immersed in 1 mL of *water R* in a test-tube placed in a bath of iced water. Distil fairly vigorously and continue heating for 1 min after a dry residue has been obtained in the flask. Prepare a blank by introducing into an identical test-tube a volume of *water R* equal to that of the distillate. Place the tubes in a bath of iced water. To each tube, add 0.5 mL of a 20 per cent *V/V* solution of *morpholine R* and 0.5 mL of a freshly prepared 50 g/L solution of *sodium nitroprusside R*. Mix and allow to stand at 0 °C for 5 min, and then at room temperature for 3 min. No blue colour develops in either tube. Add 1 g of *ammonium sulfate R*, mix and allow to stand for 15 min. A stable, intense pink colour develops in the test solution. A brownish-yellow colour develops in the blank.

D. It gives reaction (a) of bromides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 0.6 g in *water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (40:60 *V/V*).

Test solution (a) Dissolve 6 mg of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Test solution (b) Dissolve 6 mg of the substance to be examined in 30 mL of the solvent mixture. Add 5 mL of reference solution (b) and dilute to 50 mL with the solvent mixture.

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Test solution (c) Dissolve 6 mg of *xanthydrol R1* and 6 mg of the substance to be examined in the solvent mixture, then dilute to 50 mL with the solvent mixture.

Reference solution (a) Dissolve 6 mg of *xanthydrol R1* in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (b) Dilute 5 mL of reference solution (a) to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mixture of equal volumes of *acetonitrile R* and of a solution containing 28 g/L of *sodium perchlorate R* and 11 g/L of *phosphoric acid R*, adjusted to pH 3.8 with *strong sodium hydroxide solution R* and then with *0.1 M sodium hydroxide*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 206 nm.

Injection 20 µL of test solutions (a), (b), (c) and reference solution (a).

Run time Twice the retention time of propantheline.

System suitability Test solution (c):

— in the chromatogram obtained with test solution (a), there is no peak corresponding to the principal peak in the chromatogram obtained with reference solution (a);

— *resolution*: minimum 8.0 between the peaks due to propantheline and xanthydrol.

Limits Test solution (b):

— *any impurity*: for each impurity, not more than the area of the peak due to xanthydrol (1.0 per cent), and not more than one such peak has an area greater than or equal to 0.5 times the area of the peak due to xanthydrol (0.5 per cent);

— *disregard limit*: disregard any peak with a retention time relative to propantheline of less than 0.2 (bromide); disregard the peak due to xanthydrol.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

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1 mL of *0.1 M perchloric acid* corresponds to 44.84 mg of $C_{23}H_{30}BrNO_3$.

STORAGE

In an airtight container.

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Propantheline Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Propantheline Tablets contain Propantheline Bromide. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of propantheline bromide, $C_{23}H_{30}BrNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Triturate a quantity of the powdered tablets containing 75 mg of Propantheline Bromide with 10 mL of *chloroform*, filter, evaporate the chloroform and stir the residue with 5 mL of *ether* until it solidifies. The solid complies with the following tests.

A. Dissolve 60 mg in 2 mL of *water*, add 2 mL of 5M *sodium hydroxide*, boil for 2 minutes, cool slightly, acidify with 2M *hydrochloric acid*, heat to boiling, add *ethanol* (*96%*) drop wise until the precipitate just dissolves, cool and filter. The *melting point* of the residue, after washing with *water*, recrystallising from *ethanol* (*50%*) and drying at 105° for 1 hour, is about 215°, Appendix V A. The crystals dissolve in *sulfuric acid* to produce a bright yellow solution which fluoresces strongly in ultraviolet light (365 nm).

B. Yields the reactions characteristic of *bromides*, Appendix VI.

TESTS

Xanthanoic acid

Shake the combined ether extracts reserved in the Assay with two 30 mL quantities of 0.1M *sodium hydroxide* containing 1.5% w/v of *sodium chloride*. Remove the ether from the combined aqueous extracts by heating on a water bath, add sufficient 0.1M *sodium hydroxide* to produce 100 mL and dilute 25 mL to 100 mL with 0.1M *sodium hydroxide*. The *absorbance* of the resulting solution at the maximum at 248 nm is not more than 0.31, Appendix II B.

ASSAY

Weigh and powder 20 tablets or more if necessary. Place a quantity of the powder containing 0.5 g of Propantheline Bromide on a sintered-glass filter, add 10 mL of *peroxide-free ether*, dried over sodium and distilled before use, stir and filter. Repeat the extraction with four

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10 mL quantities of the ether and reserve the combined ether extracts for the test for Xanthanoic acid. Extract the residue on the filter with four 10 mL quantities of *chloroform*, evaporate the combined chloroform extracts to about 10 mL, add 10 mL of *mercury(II) acetate solution* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 44.84 mg of $C_{23}H_{30}BrNO_3$.

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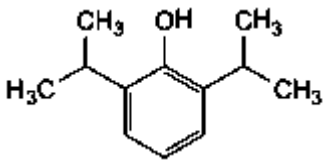
Propofol

General Notices

(Ph. Eur. monograph 1558)



$C_{12}H_{18}O$ 178.3 *2078-54-8*

Action and use

Intravenous general anaesthetic.

Preparation

Propofol Injection

Ph Eur

DEFINITION

2,6-Bis(1-methylethyl)phenol.

Content

98.0 per cent to 102.0 per cent.

This monograph applies to propofol prepared using distillation for purification.

CHARACTERS

Appearance

Colourless or very light yellow, clear liquid.

Solubility

Very slightly soluble in water, miscible with hexane and with methanol.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison propofol CRS.

TESTS

Refractive index (2.2.6)

1.5125 to 1.5145.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 1.00 g of the substance to be examined in hexane R and dilute to 10.0 mL with the same solvent.

Test solution (b) Dissolve 0.240 g of the substance to be examined in hexane R and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 5 µL of the substance to be examined and 15 µL of propofol impurity J CRS in hexane R and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 0.1 mL of propofol for peak identification CRS (containing impurities E and G) to 1.0 mL with hexane R.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with hexane R. Dilute 1.0 mL of this solution to 10.0 mL with hexane R.

Reference solution (d) Dissolve 0.240 g of propofol CRS in hexane R and dilute to 100.0 mL with the same solvent.

Column:

— *size*: *l* = 0.20 m, Ø = 4.6 mm;

— *stationary phase*: silica gel for chromatography R (5 µm).

Mobile phase anhydrous ethanol R, acetonitrile R, hexane R (1.0:7.5:990 *V/V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time 7 times the retention time of propofol.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities G and E.

Relative retention With reference to propofol (retention time = about 3 min): impurity G = about 0.5; impurity I = about 0.6; impurity B = about 0.7; impurity N = about 2.3; impurity D = about 2.5; impurity P = about 2.9; impurity A = about 3.0; impurity C = about 3.4; impurity E = about 4.0; impurity F = about 5.8; impurity H = about 6.4.

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System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity J and propofol.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.25; impurity G = 5.0;

— *impurity G*: not more than twice the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity E*: not more than 0.1 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.01 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.05 per cent);

— *total*: not more than 3 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *disregard limit*: 0.3 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.03 per cent), except for impurity E.

Impurities J, K, L and O

Gas chromatography (*2.2.28*).

Test solution Dissolve 40.0 mg of the substance to be examined in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 10.0 mL with *methylene chloride R*.

Reference solution (b) Dissolve 5 µL of *propofol impurity J CRS* (corresponding to 5 mg) in *methylene chloride R* and dilute to 100 mL with the same solvent. Dilute 1.0 mL of this solution to 25 mL with *methylene chloride R*.

Reference solution (c) Dissolve 4 mg of *propofol CRS* in reference solution (b) and dilute to 1 mL with the same solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.7 mL/min.

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Split ratio 1:5.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3	80
	3 - 25	80 → 210
	25 - 40	210
Injection port		100
Detector		270

Detection Flame ionisation.

Injection 1 µL of the test solution and reference solutions (a) and (c).

Relative retention With reference to propofol (retention time = about 17 min): impurity K = about 0.76; impurity L = about 0.81; impurity J = about 1.01; impurity O = about 1.03.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity J, and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to propofol.

Limits:

— *impurities J, K, L, O*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{12}H_{18}O$ using the declared content of *propofol CRS*.

STORAGE

Protected from light under an inert gas.

IMPURITIES

Specified impurities *E, G, J, K, L, O.*

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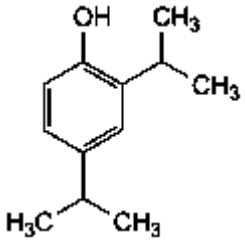
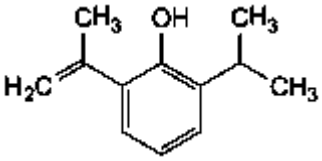
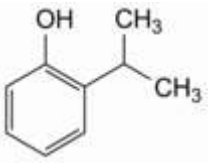
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, F, H, I, N, P.



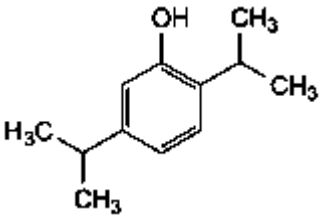
A. 2,4-bis(1-methylethyl)phenol,



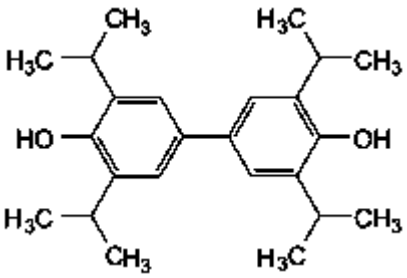
B. 2-(1-methylethenyl)-6-(1-methylethyl)phenol,



C. 2-(1-methylethyl)phenol,



D. 2,5-bis(1-methylethyl)phenol,



E. 3,3′,5,5′-tetrakis(1-methylethyl)biphenyl-4,4′-diol,

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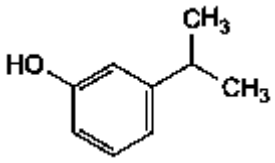
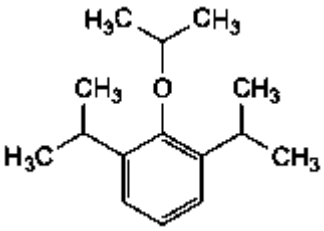
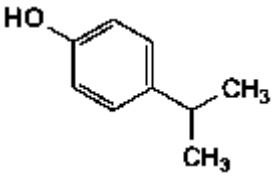


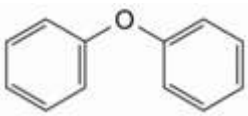
F. 3-(1-methylethyl)phenol,



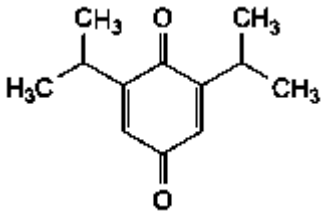
G. 2-(1-methylethoxy)-1,3-bis(1-methylethyl)benzene,



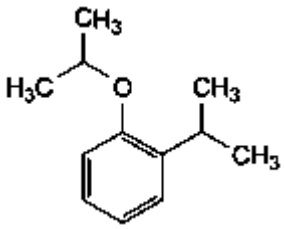
H. 4-(1-methylethyl)phenol,



I. oxydibenzene,



J. 2,6-bis(1-methylethyl)benzene-1,4-dione,



K. 1-(1-methylethoxy)-2-(1-methylethyl)benzene,

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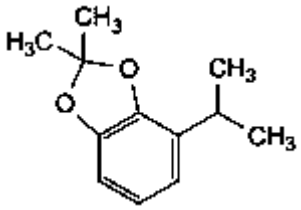
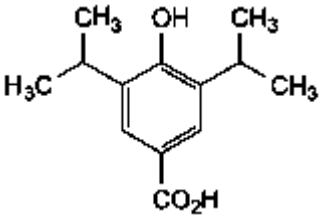
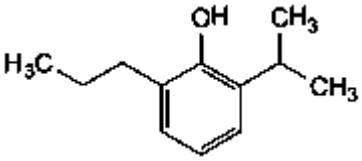


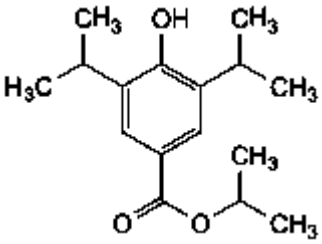
L. 2,2-dimethyl-4-(1-methylethyl)-1,3-benzodioxole,



N. 4-hydroxy-3,5-bis(1-methylethyl)benzoic acid,



O. 2-(1-methylethyl)-6-propylphenol,



P. 1-methylethyl 4-hydroxy-3,5-bis(1-methylethyl)benzoate.

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Propofol Injection

General Notices

Action and use

Intravenous general anaesthetic.

DEFINITION

Propofol Injection is a sterile emulsion of Propofol in a suitable basis.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

PRODUCTION

The methods of formulation and production of Propofol Injection are designed such that the globule size distribution, when tested by a method that has been approved by the relevant competent authority, does not exceed the approved limit.

Where soya lecithins are present in the formulation, a suitable test is carried out to demonstrate that the content of soya lysolecithin is not more than 0.2% w/v.

Content of propofol, $C_{12}H_{18}O$

95.0 to 105.0% of the stated amount.

Shake the injection vigorously before carrying out the following tests.

IDENTIFICATION

Extract a volume of the injection containing 0.1 g of Propofol with three 25-mL quantities of *hexane* and filter the combined extracts (Whatman GF/C is suitable). Extract the filtrate with two 20-mL quantities of *methanol* (90%) and evaporate the combined extracts under reduced pressure. Dissolve the residue obtained in 2 mL of *absolute ethanol* and evaporate to dryness under reduced pressure. Dry the residue at 50° over *phosphorus pentoxide* for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Propofol (*RS 416*).

TESTS

Acidity or alkalinity

pH, 6.0 to 8.5, Appendix V L.

Propofol quinone and propofol dimer

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection with *propan-2-ol* to produce a solution containing 0.08% w/v of Propofol.

(2) 0.0008% w/v of *propofol BPCRS*, 0.00008% w/v of *propofol impurity J BPCRS* and 0.0002% w/v of *propofol dimer BPCRS* in *propan-2-ol* containing 6.8% v/v of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for at least three times the retention time of the principal peak.

MOBILE PHASE

40 volumes of *tetrahydrofuran* and 60 volumes of *water*.

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to propofol (retention time about 7 minutes) are: impurity J, about 0.8 and impurity E, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to impurity J and propofol is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E (propofol dimer) is not greater than the area of the peak due to impurity E in the chromatogram obtained with solution (2) (0.25%);

the area of any peak corresponding to impurity J (propofol quinone) is not greater than the area of the peak due to impurity J in the chromatogram obtained with solution (2) (0.1%).

Free fatty acid

Not greater than 7 millimoles per litre, when determined by the following method. To 5 mL of the injection add 25 mL of a mixture of 40 volumes of *propan-2-ol*, 10 volumes of *n-heptane* and 1 volume of 0.5M *sulfuric acid* and shake for 1 minute. Allow to stand for 10 minutes, add 15 mL of *n-heptane* and 15 mL of *water*. Mix by inverting the container 10 times and allow to stand for 15 minutes. To 15 mL of the upper phase add 5 mL of *aqueous nile blue A solution* and pass a stream of *nitrogen*, previously passed through 0.1M *sodium hydroxide*, through the solution. Titrate with *0.02M sodium hydroxide VS*, using a microburette. Calculate the content of free fatty acid from a calibration curve prepared from quantities of 1, 2, 4, 6 and 8 mL of a 1.282% w/v solution of *palmitic acid* in *n-heptane*, each diluted to 50 mL with *n-heptane*. Carry out the method described above, using 5 mL of each solution and beginning at the words ‘add 25 mL of a mixture…’.

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Lysolecithin

For injections containing egg lecithins

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection with *ethanol* to produce a solution containing 0.1% w/v of Propofol. Centrifuge and filter the supernatant liquid through a 0.45-µm nylon filter.

(2) 0.01% w/v of *lysophosphatidylcholine from egg yolk EPCRS* (lysolecithin) in *ethanol*.

(3) 0.1% w/v each of *lysophosphatidylcholine from egg yolk EPCRS* (lysolecithin) and L-α-lecithin from egg yolk in *ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 2.1 mm) packed with *silica gel for chromatography* (5 µm) (Kromasil Sil is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 268 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

16 volumes of *water*, 16.5 volumes of *hexane* and 67 volumes of *propan-2-ol*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to lysolecithin (retention time about 9 minutes) is: L-α-lecithin, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless the *resolution* between the peaks due to L-α-lecithin and lysolecithin is at least 2.0.

LIMITS

The content of lysolecithin is not greater than 0.2% w/v, calculated using the following expression:

$$\frac{A_1 \times C_2 \times f}{A_2}$$

where:

A_1	=	peak area of lysolecithin in solution (1)
A_2	=	peak area of lysolecithin in solution (2)
C_2	=	concentration of lysolecithin in solution (2)
f	=	dilution factor used for solution (1)

Bacterial endotoxins

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Carry out the test for *Bacterial endotoxins*, Appendix XIV C. Dilute the injection in *water BET* to give an emulsion containing 5 mg per mL (solution A). The endotoxin limit concentration of solution A is 1.65 IU endotoxin per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed volume of the well shaken injection with *propan-2-ol* to produce a solution containing 0.08% w/v of Propofol.

(2) 0.08% w/v of *propofol BPCRS* in *propan-2-ol* containing 6.8% v/v of *water*.

(3) 0.0008% w/v of *propofol BPCRS* and 0.00008% w/v of *propofol impurity J BPCRS* in *propan-2-ol* containing 6.8% v/v of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Propofol quinone and propofol dimer may be carried out but using a detection wavelength of 275 nm.

SYSTEM SUITABILITY

The test is not valid unless the *resolution* between the peaks due to propofol and propofol impurity J is at least 2.5.

DETERMINATION OF CONTENT

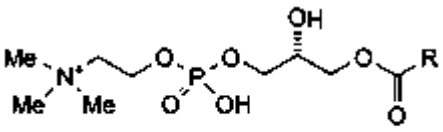
Determine the *weight per mL* of the Injection, Appendix V G, and calculate the content of $C_{12}H_{18}O$, in the injection, weight in volume, using the declared content of $C_{12}H_{18}O$ in *propofol BPCRS*.

STORAGE

Propofol Injection should be stored at a temperature not exceeding 25°. It should not be allowed to freeze.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities E and J listed under Propofol and:



where R is a variable fatty acid chain

1. 2-({[(2*R*)-3-acyloxy-2-hydroxypropoxy]hydroxyphosphoryl}oxy)-*N*,*N*,*N*-trimethylethanaminium (lysophosphatidylcholine, lysolecithin)

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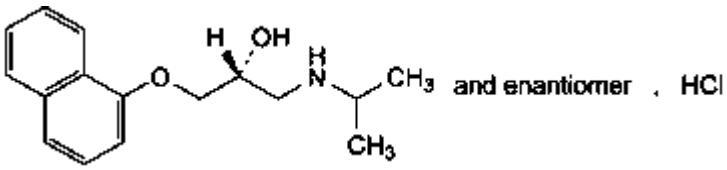
Propranolol Hydrochloride

General Notices

(Ph. Eur. monograph 0568)



$C_{16}H_{22}ClNO_2$ 295.8 *318-98-9*

Action and use

Beta-adrenoceptor antagonist.

Preparations

Propranolol Prolonged-release Capsules

Propranolol Injection

Propranolol Oral Solution

Propranolol Tablets

Ph Eur

DEFINITION

(2*RS*)-1-[(Propan-2-yl)amino]-3-[(naphthalen-1-yl)oxy]propan-2-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Soluble in water and in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 163 °C to 166 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison propranolol hydrochloride CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 1 mL of methanol R.

Reference solution Dissolve 10 mg of propranolol hydrochloride CRS in 1 mL of methanol R.

Plate TLC silica gel G plate R.

Mobile phase concentrated ammonia R1, methanol R (1:99 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying At 100-105 °C.

Detection Spray with anisaldehyde solution R and heat at 100-105 °C until the colour of the spots reaches maximum intensity (10-15 min).

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

Dissolve 2.0 g in methanol R and dilute to 20 mL with the same solvent.

Acidity or alkalinity

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Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent. Add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M hydrochloric acid*; the solution is red. Add 0.4 mL of *0.01 M sodium hydroxide*; the solution is yellow.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *propranolol for system suitability CRS* (containing impurity A) in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m; Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate R* and 1.6 g of *sodium laurilsulfate R* in a mixture of 1 mL of *sulfuric acid R*, 450 mL of *water for chromatography R* and 550 mL of *acetonitrile R*; adjust to pH 3.3 with *dilute sodium hydroxide solution R*.

Flow rate 1.8 mL/min.

Detection Spectrophotometer at 292 nm.

Injection 20 µL.

Run time 7 times the retention time of propranolol.

Identification of impurities Use the chromatogram supplied with *propranolol for system suitability CRS* and the chromatogram obtained with reference solution (a)to identify the peak due to impurity A.

Relative retention With reference to propranolol (retention time = about 3 min): impurity A = about 0.6.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity A and propranolol.

Calculation of percentage contents:

— for each impurity, use the concentration of propranolol hydrochloride in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

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— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

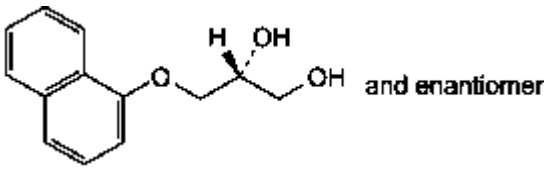
ASSAY

Dissolve 0.250 g in 25 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

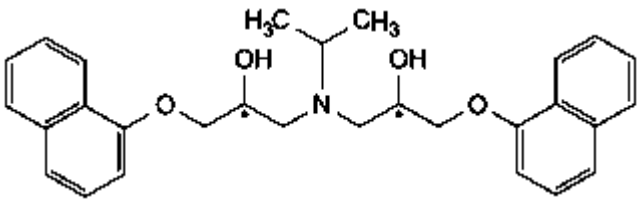
1 mL of *0.1 M sodium hydroxide* is equivalent to 29.58 mg of $C_{16}H_{22}ClNO_2$.

IMPURITIES

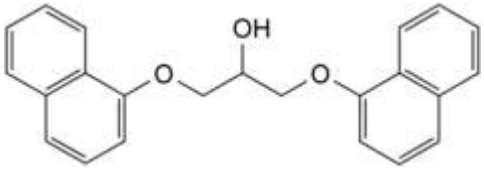
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.



A. (2*RS*)-3-[(naphthalen-1-yl)oxy]propane-1,2-diol,



B. 1,1′-[(propan-2-yl)azanediyl]bis[(2Ξ)-3-[(naphthalen-1-yl)oxy]propan-2-ol,



C. 1,3-bis[(naphthalen-1-yl)oxy]propan-2-ol.

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Propranolol Injection

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Propranolol Injection is a sterile solution of Propranolol Hydrochloride in Water for Injections containing Citric Acid or Citric Acid Monohydrate.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of propranolol hydrochloride, $C_{16}H_{21}NO_2$,HCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Make alkaline with 1M *sodium hydroxide* a volume containing 10 mg of Propranolol Hydrochloride and extract with three 5-mL quantities of *ether*. Wash the combined extracts with *water* until the washings are free from alkali, dry with *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness and dry the residue at 50° at a pressure of 2 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of propranolol (*RS 298*).

TESTS

Acidity

pH, 3.0 to 3.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D,protected from light, using the following solutions prepared in the mobile phase.

(1) Dilute the injection being examined with *acetonitrile*, if necessary, to produce a solution containing 0.1% w/v of Propranolol Hydrochloride.
(2) Dilute 2 volume of solution (1) to 500 volumes.
(3) 0.01% w/v of *propranolol for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 292 nm.

(f) Inject 40 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for seven times the retention time of the principal peak.

MOBILE PHASE

Add 1.6 g of *sodium laurilsulfate* and 0.31 g of *tetrabutylammonium dihydrogen orthophosphate* to a mixture of 1 mL of *sulfuric acid*, 450 mL of *water* and 550 mL of *acetonitrile*, adjusted to pH 3.3 with 2M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to propranolol (retention time, about 3 minutes) are impurity A, about 0.6; impurity B, about 4.5; impurity C, about 6.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and propranolol is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

To a volume containing 2 mg of Propranolol Hydrochloride add sufficient *methanol* to produce 100 mL and measure the *absorbance* of the resulting solution at the maximum at 290 nm, Appendix II B. Calculate the content of $C_{16}H_{21}NO_2$,HCl taking 206 as the value of A (1%, 1 cm) at the maximum at 290 nm.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Propranolol Hydrochloride.

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Propranolol Oral Solution

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Propranolol Oral Solution contains Propranolol Hydrochloride.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of propranolol hydrochloride, $C_{16}H_{21}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the oral solution containing 10 mg of Propranolol Hydrochloride add sufficient 1M *sodium hydroxide* to make the solution alkaline. Extract this solution with three 5-mL quantities of *ether*, wash the combined extracts with *water* until the washings are no longer alkaline, dry with *anhydrous sodium sulfate* and filter. Evaporate the filtrate to dryness and dry the residue at 50° at a pressure of 2 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of propranolol (*RS 298*).

TESTS

Acidity

pH, 2.5 to 3.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in the mobile phase.

(1) Dilute the oral solution, if necessary, to produce a solution containing 0.05% w/v of Propranolol Hydrochloride.
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of this solution to 5 volumes.
(3) 0.01% w/v of *propranolol for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 292 nm.

(f) Inject 80 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for eight times the retention time of the principal peak.

MOBILE PHASE

Add 1.6 g of *sodium laurilsulfate* and 0.31 g of *tetrabutylammonium dihydrogen orthophosphate* to a mixture of 1 mL of *sulfuric acid*, 450 mL of *water* and 550 mL of *acetonitrile*, adjusted to pH 3.3 with 2M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to propranolol (retention time, about 3 minutes) are impurity A, about 0.6; impurity B, about 4.5; impurity C, about 6.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and propranolol is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in the mobile phase.

(1) Dilute a weighed quantity of the oral solution, if necessary, to produce a solution containing 0.05% w/v of Propranolol Hydrochloride.

(2) 0.05% w/v of *propranolol hydrochloride BPCRS*.

(3) 0.1% w/v of *propranolol hydrochloride for performance test EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used but with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and propranolol is at least 1.5.

DETERMINATION OF CONTENT

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Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{16}H_{21}NO_2$,HCl, weight in volume, using the declared content of $C_{16}H_{21}NO_2$,HCl in *propranolol hydrochloride BPCRS*.

STORAGE

Propranolol Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Propranolol Hydrochloride.

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Propranolol Prolonged-release Capsules

General Notices

Prolonged-release Propranolol Capsules

Propranolol Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Propranolol Prolonged-release Capsules contain Propranolol Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Propranolol Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of propranolol hydrochloride, $C_{16}H_{21}NO_2$,HCl

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. The *light absorption* of the solution obtained in the Assay, Appendix II B, exhibits two maxima, at 290 nm and 319 nm, and a shoulder at 306 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

(1) Shake a quantity of the powdered capsule contents containing 20 mg of Propranolol Hydrochloride with 10 mL of *methanol* for 5 minutes and filter (Whatman No. 1 paper is suitable).

(2) 0.2% w/v of *propranolol hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia* and 99 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that of the principal spot in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in the mobile phase.

(1) Add 100 mL of *methanol* to a quantity of the powdered capsule contents containing 0.1 g of Propranolol Hydrochloride, mix with the aid of ultrasound for 15 minutes, shaking occasionally, filter through a glass-microfibre filter (Whatman GF/C is suitable) and use the filtrate.

(2) Dilute 1 volume of solution (1) to 500 volumes.

(3) 0.01% w/v of *propranolol for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 292 nm.

(f) Inject 40 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for seven times the retention time of the principal peak.

MOBILE PHASE

Add 1.6 g of *sodium laurilsulfate* and 0.31 g of *tetrabutylammonium dihydrogen orthophosphate* to a mixture of 1 mL of *sulfuric acid*, 450 mL of *water* and 550 mL of *acetonitrile*, adjusted to pH 3.3 with 2M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to propranolol (retention time, about 3 minutes) are impurity A, about 0.6; impurity B, about 4.5; impurity C, about 6.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and propranolol is at least 1.5.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. To a quantity of the mixed capsule contents containing 80 mg of Propranolol Hydrochloride add about 150 mL of *methanol*, heat to boiling and boil for 2 minutes, remove from the heat, shake for 20 minutes, cool to 20° and add sufficient *methanol* to produce 200 mL. Filter (Whatman No. 1 paper is suitable), discard the first 20 mL of filtrate, and dilute 10 volumes of the filtrate to 200 volumes with *methanol*. Measure the *absorbance* of the resulting solution at the maximum at 290 nm, Appendix II B, using *methanol* in the reference cell. Calculate the content of $C_{16}H_{21}NO_2$,HCl taking 206 as the value of A(1%, 1 cm) at the maximum at 290 nm.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Propranolol Hydrochloride.

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Propranolol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Propranolol Tablets contain Propranolol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of propranolol hydrochloride, $C_{16}H_{21}NO_2,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Suspend a quantity of the powdered tablets containing 0.1 g of Propranolol Hydrochloride in 20 mL of *water*, filter, make the filtrate alkaline with 1M *sodium hydroxide* and extract with three 10-mL quantities of *ether*. Wash the combined extracts with *water* until the washings are free from alkali, dry with *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness and dry the residue at 50° at a pressure of 2 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of propranolol (*RS 298*)

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in mobile phase.

(1) Add 25 mL of *methanol* to a quantity of the powdered tablets containing 0.1 g of Propranolol Hydrochloride and dilute to 100 mL. Filter through glass-microfibre paper (Whatman GF/C is suitable) and use the filtrate.
(2) Dilute 2 volumes of solution (1) to 100 volumes. Dilute 1 volume of this solution to 10 volumes.
(3) 0.01% w/v of *propranolol for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable).
(b) Use isocratic elution and the mobile phase described below.

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(c) Use a flow rate of 1.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 292 nm.

(f) Inject 40 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for seven times the retention time of the principal peak.

MOBILE PHASE

Add 1.6 g of *sodium laurilsulfate* and 0.31 g of *tetrabutylammonium dihydrogen orthophosphate* to a mixture of 1 mL of *sulfuric acid*, 450 mL of *water* and 550 mL of *acetonitrile*, adjusted to pH 3.3 with 2M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to propranolol (retention time, about 3 minutes) are impurity A, about 0.6; impurity B, about 4.5; impurity C, about 6.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and propranolol is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 20 mg of Propranolol Hydrochloride with 20 mL of *water* for 10 minutes. Add 50 mL of *methanol*, shake for a further 10 minutes, add sufficient *methanol* to produce 100 mL and filter. Dilute 10 mL of the filtrate to 50 mL with *methanol* and measure the *absorbance* of the resulting solution at the maximum at 290 nm, Appendix II B. Calculate the content of $C_{16}H_{21}NO_2$,HCl taking 206 as the value of A(1%, 1 cm) at the maximum at 290 nm.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Propranolol Hydrochloride.

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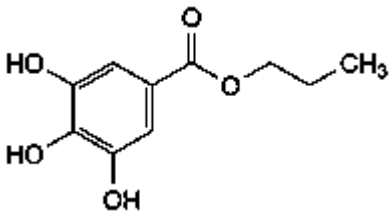
Propyl Gallate

General Notices

(Ph. Eur. monograph 1039)



$C_{10}H_{12}O_5$ 212.2 *121-79-9*

Action and use

Antioxidant.

Ph Eur

DEFINITION

Propyl 3,4,5-trihydroxybenzoate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

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A. Melting point (2.2.14): 148 °C to 151 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison propyl gallate for ID and assay CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in acetone R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 5 mg of propyl gallate for ID and assay CRS in acetone R and dilute to 5 mL with the same solvent.

Plate TLC silica gel G plate R.

Mobile phase anhydrous formic acid R, ethyl formate R, toluene R (10:40:50 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air for 10 min.

Detection Spray with a mixture of 1 volume of ferric chloride solution R1 and 9 volumes of ethanol (96 per cent) R.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in 10 mL of water R by heating to about 70 °C. Cool and add 1 mL of bismuth subnitrate solution R. A bright yellow precipitate is formed.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

Dissolve 1.0 g in ethanol (96 per cent) R and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in methanol R and dilute to 25.0 mL with the same solvent.

Test solution (b) Dilute 2.0 mL of test solution (a) to 20.0 mL with methanol R.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with methanol R. Dilute 1.0 mL of this solution to 10.0 mL with methanol R.

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Reference solution (b) Dissolve 25.0 mg of *propyl gallate for ID and assay CRS* in *methanol R* and dilute to 25.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with *methanol R*.

Reference solution (c) Dissolve 25 mg of *methyl parahydroxybenzoate R* in *methanol R* and dilute to 25 mL with the same solvent. Mix 1 mL of the solution and 1 mL of test solution (a), and dilute to 100 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (3.5 µm);

— *temperature*: 28 °C.

Mobile phase:

— *mobile phase A*: 6.8 g/L solution of *potassium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	95	5
6 - 25	95 → 45	5 → 55
25 - 40	45	55

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (c).

Identification of peaks Use the chromatogram obtained with reference solution (c) to identify the peak due to methyl parahydroxybenzoate.

Relative retention With reference to propyl gallate (retention time = about 20 min): methyl parahydroxybenzoate = about 1.05.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to propyl gallate and methyl parahydroxybenzoate.

Calculation of percentage contents:

— for each impurity, use the concentration of propyl gallate in reference solution (a).

Limits:

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— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.15 per cent;

— *reporting threshold*: 0.05 per cent.

Total chlorine

Maximum 200 ppm.

Mix 0.5 g with 2 g of *calcium carbonate R1*. Dry and ignite at 700 ± 50 °C. Take up the residue with 20 mL of *dilute nitric acid R* and dilute to 30 mL with *water R*. 15 mL of the solution, without further addition of *dilute nitric acid R*, complies with the test for chlorides (*2.4.4*).

Chlorides (*2.4.4*)

Maximum 100 ppm.

To 1.65 g add 50 mL of *water R*. Shake for 5 min. Filter.

Zinc

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution To 2.5 mL of the test solution prepared as described in general chapter *2.4.8* (method C) using 2.0 g of the substance to be examined, add 2.5 mL of *water R*.

Reference solutions Prepare the reference solutions using *zinc standard solution (10 ppm Zn) R*, diluting with *water R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (b).

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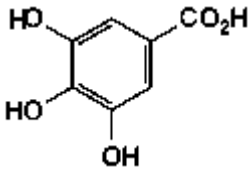
Calculate the percentage content of $C_{10}H_{12}O_5$ taking into account the assigned content of *propyl gallate for ID and assay CRS*.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



A. 3,4,5-trihydroxybenzoic acid (gallic acid).

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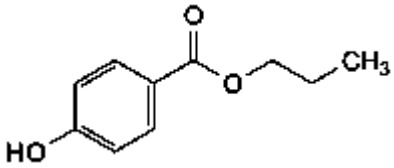
Propyl Hydroxybenzoate[1]

General Notices

Propylparaben

(Propyl Parahydroxybenzoate, Ph. Eur. monograph 0431)



$C_{10}H_{12}O_3$ 180.2 *94-13-3*

Action and use

Antimicrobial preservative.

Ph Eur

DEFINITION

Propyl 4-hydroxybenzoate.

Content

98.0 per cent to 102.0 per cent.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent) and in methanol.♦

IDENTIFICATION

First identification: A, B.

◊ *Second identification: A, C.*◊

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A. Melting point (2.2.14): 96 °C to 99 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison propyl parahydroxybenzoate CRS.

◊ C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.10 g of the substance to be examined in acetone R and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with acetone R.

Reference solution (a) Dissolve 10 mg of propyl parahydroxybenzoate CRS in acetone R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of ethyl parahydroxybenzoate CRS in 1 mL of test solution (a) and dilute to 10 mL with acetone R.

Plate TLC octadecylsilyl silica gel F_{254} plate R.

Mobile phase glacial acetic acid R, water R, methanol R (1:30:70 *V/V/V*).

Application 2 µL of test solution (b) and reference solutions (a) and (b).

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).◊

TESTS

Solution S

Dissolve 1.0 g in ethanol (96 per cent) R and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Acidity

To 2 mL of solution S add 3 mL of ethanol (96 per cent) R, 5 mL of carbon dioxide-free water R and 0.1 mL of bromocresol green solution R. Not more than 0.1 mL of 0.1 M sodium hydroxide is required to change the colour of the indicator to blue.

Related substances

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Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of 4-hydroxybenzoic acid R (impurity A), 5 mg of ethyl parahydroxybenzoate R (impurity C) and 5 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50.0 mg of propyl parahydroxybenzoate CRS in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase 6.8 g/L solution of potassium dihydrogen phosphate R, methanol R (35:65 *V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 2.5 times the retention time of propyl parahydroxybenzoate.

Relative retention With reference to propyl parahydroxybenzoate (retention time = about 4.5 min): impurity A = about 0.3; impurity C = about 0.7.

System suitability Reference solution (a):

— resolution: minimum 3.0 between the peaks due to impurity C and propyl parahydroxybenzoate.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

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— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

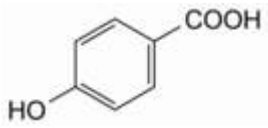
Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{10}H_{12}O_3$ from the declared content of *propyl parahydroxybenzoate CRS*.

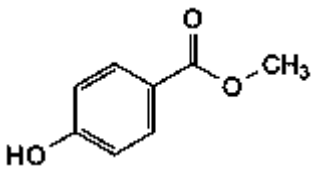
IMPURITIES

Specified impurities *A*.

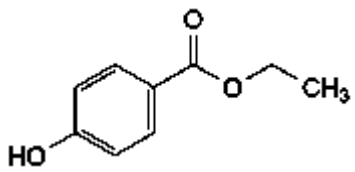
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D*.



A. 4-hydroxybenzoic acid,



B. methyl 4-hydroxybenzoate (methyl parahydroxybenzoate),



C. ethyl 4-hydroxybenzoate (ethyl parahydroxybenzoate),

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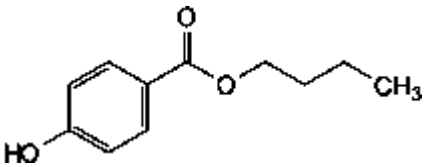

D. butyl 4-hydroxybenzoate (butyl parahydroxybenzoate).

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

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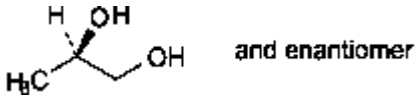
Propylene Glycol

General Notices

(Ph. Eur. monograph 0430)



and enantiomer

$C_3H_8O_2$ 76.1 *57-55-6*

Action and use

Excipient.

Preparation

Propylene Glycol Solution

Ph Eur

DEFINITION

Propylene glycol is (*RS*)-propane-1,2-diol.

CHARACTERS

A viscous, clear, colourless, hygroscopic liquid, miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Relative density (see Tests).

B. Refractive index (see Tests).

C. Boiling point (*2.2.12*): 184 °C to 189 °C.

D. To 0.5 mL add 5 mL of *pyridine R* and 2 g of finely ground *nitrobenzoyl chloride R*. Boil for 1 min and pour into 15 mL of cold *water R* with shaking. Filter, wash the precipitate with 20 mL of a saturated solution of *sodium hydrogen carbonate R* and then with *water R* and dry. Dissolve in boiling *ethanol (80 per cent V/V) R* and filter the hot solution. On cooling, crystals are formed which, after drying at 100-105 °C, melt (*2.2.14*) at 121 °C to 128 °C.

TESTS

Appearance

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It is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Relative density (*2.2.5*)

1.035 to 1.040.

Refractive index (*2.2.6*)

1.431 to 1.433.

Acidity

To 10 mL add 40 mL of *water R* and 0.1 mL of *bromothymol blue solution R1*. The solution is greenish-yellow. Not more than 0.05 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Oxidising substances

To 10 mL add 5 mL of *water R*, 2 mL of *potassium iodide solution R* and 2 mL of *dilute sulfuric acid R* and allow to stand in a ground-glass-stoppered flask protected from light for 15 min. Titrate with *0.05 M sodium thiosulfate*, using 1 mL of *starch solution R* as indicator. Not more than 0.2 mL of *0.05 M sodium thiosulfate* is required.

Reducing substances

To 1 mL add 1 mL of *dilute ammonia R1* and heat in a water-bath at 60 °C for 5 min. The solution is not yellow. Immediately add 0.15 mL of *0.1 M silver nitrate* and allow to stand for 5 min. The solution does not change its appearance.

Water (*2.5.12*)

Not more than 0.2 per cent, determined on 5.00 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Heat 50 g until it burns and ignite. Allow to cool. Moisten the residue with *sulfuric acid R* and ignite; repeat the operations. The residue weighs not more than 5 mg (0.01 per cent).

STORAGE

Store in an airtight container.

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Propylene Glycol Dicaprylocaprate

General Notices

(Ph. Eur. monograph 2122)

Action and use

Excipient.

Ph Eur

DEFINITION

Propylene glycol diesters of saturated fatty acids, mainly caprylic (octanoic) acid and capric (decanoic) acid, of vegetable origin.

CHARACTERS

Appearance

Almost colourless or light yellow, oily liquid.

Solubility

Practically insoluble in water, soluble in fatty oils and in light petroleum, slightly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: C, D.

Second identification: A, B, C, E.

A. Refractive index (*2.2.6*): 1.439 to 1.442.

B. Relative density (*2.2.5*): 0.910 to 0.930.

C. Viscosity (*2.2.9*): 9 mPa·s to 13 mPa·s.

D. Composition of fatty acids (see Tests).

E. Saponification value (see Tests).

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acid value (*2.5.1*)

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Acid value (2.5.1)

Maximum 0.2.

Hydroxyl value (*2.5.3, Method A*)

Maximum 10.

Iodine value (*2.5.4*)

Maximum 1.0.

Peroxide value (*2.5.5, Method A*)

Maximum 1.0.

Saponification value (*2.5.6*)

315 to 340.

Alkaline impurities

Dissolve 2.00 g of the substance to be examined in a mixture of 1.5 mL of *ethanol (96 per cent) R* and 3.0 mL of *ether R*. Add 0.05 mL of *bromophenol blue solution R*. Not more than 0.15 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*). Prepare reference solution (a) as indicated in Table 2.4.22.-2.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.3 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	70
	1 - 35	70 → 240

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	Time (min)	Temperature (°C)
	35 - 50	240
Injection port		250
Detector		250

Detection Flame ionisation.

Composition of the fatty-acid fraction of the substance:

— *caproic acid*: maximum 2.0 per cent;

— *caprylic acid*: 50.0 per cent to 80.0 per cent;

— *capric acid*: 20.0 per cent to 50.0 per cent;

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 1.0 per cent.

Water (*2.5.12*)

Maximum 0.1 per cent, determined on 5.00 g.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 2.0 g.

STORAGE

Protected from light.

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Propylene Glycol Dilaurate

General Notices

(Ph. Eur. monograph 2087)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of propylene glycol ((2*RS*)-propane-1,2-diol) mono- and diesters of lauric (dodecanoic) acid.

Content

Minimum 70.0 per cent of diesters and maximum 30.0 per cent of monoesters.

CHARACTERS

Appearance

Clear, oily liquid at 20 °C, colourless or slightly yellow.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent), in methanol and in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.1 g of the substance to be examined in *methylene chloride R* and dilute to 2 mL with the same solvent.

Reference solution Dissolve 0.1 g of *propylene glycol dilaurate CRS* in *methylene chloride R* and dilute to 2 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

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Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine 6 G R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The spots in the chromatogram obtained with the test solution are similar in position to those in the chromatogram obtained with the reference solution.

B. Composition of fatty acids (see Tests).

C. It complies with the assay (content of diesters).

TESTS

Acid value (*2.5.1*)

Maximum 4.0, determined on 5.00 g.

Iodine value (*2.5.4, Method A*)

Maximum 1.0.

Saponification value (*2.5.6*)

230 to 250.

Composition of fatty acids (*2.4.22, Method C*)

Use the mixture of calibrating substances in Table 2.4.22.-2.

Composition of the fatty acid fraction of the substance:

— *caprylic acid*: maximum 0.5 per cent;

— *capric acid*: maximum 2.0 per cent;

— *lauric acid*: minimum 95.0 per cent;

— *myristic acid*: maximum 3.0 per cent;

— *palmitic acid*: maximum 1.0 per cent.

Free propylene glycol

Maximum 2.0 per cent, determined as prescribed under Assay.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Size-exclusion chromatography (2.2.30).

Stock solution Introduce 0.100 g of propylene glycol R into a flask and dilute to 25.0 mL with tetrahydrofuran R.

Test solution In a 15 mL flask, weigh 0.200 g (*m*). Add 5.0 mL of tetrahydrofuran R and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions Into four 15 mL flasks, introduce respectively 0.25 mL, 0.5 mL, 1.0 mL and 2.5 mL of stock solution and add 5.0 mL of tetrahydrofuran R. Weigh each flask and calculate the concentration of propylene glycol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm,

— *stationary phase*: styrene-divinylbenzene copolymer R (5 µm) with a pore size of 10 nm.

Mobile phase tetrahydrofuran R.

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to propylene glycol: diesters = about 0.85; monoesters = about 0.90.

Calculations:

— *free propylene glycol*: from the calibration curve obtained with the reference solutions, determine the concentration of propylene glycol (*C*) in milligrams per gram in the test solution and calculate the percentage content of free propylene glycol (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 200}{56.11 \times 10}$$

I_A = acid value (see Tests);

200 = rounded molar mass of lauric acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

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— *monoesters*: calculate the percentage content of monoesters using the following expression:

$$\left[\frac{X}{X+Y}\,(100 - A - B)\right] - D$$

A	=	percentage content of free propylene glycol;
B	=	percentage content of water (see Tests);
D	=	percentage content of free fatty acids;
X	=	area of the peak due to monoesters and free fatty acids;
Y	=	area of the peak due to diesters.

— *diesters*: calculate the percentage content of diesters using the following expression:

$$\frac{Y}{X+Y}\,(100 - A - B)$$

STORAGE

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Propylene Glycol Monocaprylate

General Notices

(Ph. Eur. monograph 2799)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of propylene glycol ((2*RS*)-propane-1,2-diol) mono- and diesters of caprylic (octanoic) acid obtained by esterification of propylene glycol with caprylic acid. Propylene glycol monocaprylate type II is obtained by further distillation.

Content

— *propylene glycol monocaprylate (type I)*: 55.0 per cent to 80.0 per cent of monoesters and 20.0 per cent to 45.0 per cent of diesters;

— *propylene glycol monocaprylate (type II)*: minimum 90.0 per cent of monoesters and maximum 10.0 per cent of diesters.

CHARACTERS

Appearance

Clear, oily liquid at 20 °C, colourless or slightly yellow.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent), with methanol and with methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.5 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.5 g of *propylene glycol monocaprylate CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

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Mobile phase *heptane R*, *ethyl acetate R* (30:70 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine 6 G R* in *ethanol (96 per cent) R*. Examine in ultraviolet light at 365 nm.

Results The spots in the chromatogram obtained with the test solution are similar in position to those in the chromatogram obtained with the reference solution.

B. It complies with the test for composition of fatty acids (see Tests).

C. It complies with the Assay (content of monoesters).

TESTS

Acid value (*2.5.1*)

Maximum 1.5, determined on 5.00 g.

Iodine value (*2.5.4, Method A*)

Maximum 1.0.

Peroxide value (*2.5.5, Method A*)

Maximum 6.0.

Saponification value (*2.5.6*)

285 to 315 for propylene glycol monocaprylate (type I) and 270 to 295 for propylene glycol monocaprylate (type II).

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*).

Use the mixture of calibrating substances in Table 2.4.22.-2.

Composition of the fatty acid fraction of the substance:

— *caprylic acid*: minimum 90 per cent;

— *capric acid*: maximum 3.0 per cent;

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 3.0 per cent;

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— *palmitic acid*: maximum 1.0 per cent.

Free propylene glycol

Maximum 1.5 per cent, determined as prescribed under Assay.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g.

Total ash (2.4.16)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Size-exclusion chromatography (2.2.30).

Stock solution Into a weighed flask, introduce 0.100 g of propylene glycol R, add stabilised tetrahydrofuran R and dilute to 25.0 mL with the same solvent. Reweigh the flask.

Test solution Into a weighed flask, introduce 0.200 g (*m*) of the substance to be examined. Add 5.0 mL of stabilised tetrahydrofuran R and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions Into four weighed flasks, introduce respectively 0.25 mL, 0.5 mL, 1.0 mL and 2.5 mL of stock solution and add 5.0 mL of stabilised tetrahydrofuran R. In a fifth weighed flask, introduce 5.0 mL of stock solution. Reweigh the flasks and calculate the concentration of propylene glycol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7.0 mm;

— *stationary phase*: styrene-divinylbenzene copolymer R (5 µm) with a pore size of 10 nm.

Mobile phase stabilised tetrahydrofuran R.

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to propylene glycol (retention time = about 16 min): diesters = about 0.85; monoesters = about 0.90.

Calculations:

— *free propylene glycol*: determine the concentration of propylene glycol (*C*) in milligrams per gram in the test solution from the calibration curve obtained with the reference solutions. Calculate the percentage content of free propylene glycol (*A*) in the substance to be examined using the following expression:

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$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 144.21}{(56.11 \times 10)}$$

I_A = acid value (see Tests);

144.21 = molar mass of caprylic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoesters*: calculate the percentage content of monoesters using the following expression:

$$\left[\frac{X}{(X+Y)}\left(100 - A - B\right)\right] - D$$

X = area of peak due to monoesters;

Y = area of peak due to diesters;

A = percentage content of free propylene glycol;

B = percentage content of water (see Tests);

D = percentage content of free fatty acids.

— *diesters*: calculate the percentage content of diesters using the following expression:

$$\frac{Y}{(X+Y)}\left(100 - A - B\right)$$

STORAGE

Protected from moisture.

LABELLING

The label states the type of propylene glycol monocaprylate (type I or type II).

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Propylene Glycol Monolaurate

General Notices

(Ph. Eur. monograph 1915)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of propylene glycol ((2*RS*)-propane-1,2-diol) mono- and diesters of lauric (dodecanoic) acid.

Content

— *propylene glycol monolaurate (type I)*: 45.0 per cent to 70.0 per cent of monoesters and 30.0 per cent to 55.0 per cent of diesters,

— *propylene glycol monolaurate (type II)*: minimum 90.0 per cent of monoesters and maximum 10.0 per cent of diesters.

CHARACTERS

Appearance

Clear, oily liquid at 20 °C, colourless or slightly yellow.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent), in methanol and in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.1 g of the substance to be examined in *methylene chloride R* and dilute to 2 mL with the same solvent.

Reference solution Dissolve 0.1 g of *propylene glycol monolaurate CRS* in *methylene chloride R* and dilute to 2 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

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Development Over a path of 15 cm.

Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine 6 G R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The spots in the chromatogram obtained with the test solution are similar in position to those in the chromatogram obtained with the reference solution.

B. Composition of fatty acids (see Tests).

C. It complies with the assay (content of monoesters).

TESTS

Acid value (*2.5.1*)

Maximum 4.0, determined on 5.00 g.

Iodine value (*2.5.4, Method A*)

Maximum 1.0.

Saponification value (*2.5.6*)

210 to 245 for propylene glycol monolaurate (type I) and 200 to 230 for propylene glycol monolaurate (type II).

Composition of fatty acids (*2.4.22, Method C*)

Use the mixture of calibrating substances in Table 2.4.22.-2.

Composition of the fatty acid fraction of the substance:

— *caprylic acid*: maximum 0.5 per cent;

— *capric acid*: maximum 2.0 per cent;

— *lauric acid*: minimum 95.0 per cent;

— *myristic acid*: maximum 3.0 per cent;

— *palmitic acid*: maximum 1.0 per cent.

Free propylene glycol

Maximum 5.0 per cent for propylene glycol monolaurate (type I) and maximum 1.0 per cent for propylene glycol monolaurate (type II), determined as prescribed under Assay.

Water (*2.5.12*)

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Maximum 1.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Size-exclusion chromatography (*2.2.30*).

Stock solution Introduce 0.100 g of *propylene glycol R* into a vial and dilute to 25.0 mL with *tetrahydrofuran R*.

Test solution In a 15 mL flask, weigh 0.200 g (*m*). Add 5.0 mL of *tetrahydrofuran R* and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions Into four 15 mL flasks, introduce respectively 0.25 mL, 0.5 mL, 1.0 mL and 2.5 mL of stock solution and add 5.0 mL of *tetrahydrofuran R*. In a fifth 15 mL flask, introduce 5.0 mL of stock solution. Weigh each flask and calculate the concentration of propylene glycol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to propylene glycol: diesters = about 0.85; monoesters = about 0.90.

Calculations:

— *free propylene glycol*: from the calibration curve obtained with the reference solutions, determine the concentration of propylene glycol (*C*) in milligrams per gram in the test solution and calculate the percentage content of free propylene glycol (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 200}{56.11 \times 10}$$

I_A = acid value (see Tests);

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200 = rounded molar mass of lauric acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoesters*: calculate the percentage content of monoesters using the following expression:

$$\left[\frac{X}{X+Y}\ (100 - A - B)\right] - D$$

A = percentage content of free propylene glycol;

B = percentage content of water (see Tests);

D = percentage content of free fatty acids;

X = area of the peak due to monoesters and free fatty acids;

Y = area of the peak due to diesters.

— *diesters*: calculate the percentage content of diesters using the following expression:

$$\frac{Y}{X+Y}\ (100 - A - B)$$

STORAGE

Protected from moisture.

LABELLING

The label states the type of propylene glycol monolaurate (type I or type II).

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Propylene Glycol Monopalmitostearate

General Notices

Propylene Glycol Monostearate

(Ph. Eur. monograph 1469)

Action and use

Excipient.

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DEFINITION

Mixture of propylene glycol ((2*RS*)-propane-1,2-diol) mono- and diesters of palmitic (hexadecanoic) and stearic (octadecanoic) acids, produced by the condensation of propylene glycol and stearic acid 50 of vegetable or animal origin (see *Stearic acid (1474)*).

Content

Minimum 50.0 per cent of monoesters.

CHARACTERS

Appearance

White or almost white, waxy solid.

Solubility

Practically insoluble in water, soluble in acetone and in hot ethanol (96 per cent).

IDENTIFICATION

A. Melting point (see Tests).

B. Composition of fatty acids (see Tests).

C. It complies with the assay (content of monoesters).

TESTS

Melting point (*2.2.15*)

33 °C to 40 °C.

Acid value (2.5.1)

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Acid value (2.5.1)

Maximum 4.0.

Iodine value (2.5.4)

Maximum 3.0.

Saponification value (2.5.6)

170 to 185, determined on 2.0 g.

Composition of fatty acids (2.4.22, Method A)

Composition of the fatty-acid fraction of the substance:

— *stearic acid*: 40.0 per cent to 60.0 per cent;

— *sum of contents of palmitic acid and stearic acid*: minimum 90.0 per cent.

Free propylene glycol

Maximum 5.0 per cent, determined as prescribed under Assay.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g. Use a mixture of equal volumes of *methanol R* and *methylene chloride R* as the solvent.

Total ash (2.4.16)

Maximum 0.1 per cent.

ASSAY

Size-exclusion chromatography (2.2.30).

Test solution In a 15 mL flask, weigh 0.200 g (*m*). Add 5.0 mL of *tetrahydrofuran R* and shake to dissolve. Heat gently, if necessary. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions In four 15 mL flasks, weigh respectively 2.5 mg, 5.0 mg, 10.0 mg and 20.0 mg of *propylene glycol R*. Add 5.0 mL of *tetrahydrofuran R* and shake to dissolve. Weigh the flasks again and calculate the concentration of propylene glycol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7.5 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1 mL/min.

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Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to propylene glycol: diesters = about 0.78; monoesters = about 0.84.

Calculations:

— *free propylene glycol*: from the calibration curve obtained with the reference solutions, determine the concentration of propylene glycol (*C*) in milligrams per gram in the test solution and calculate the percentage content of free propylene glycol (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 270}{56.11 \times 10}$$

I_A = acid value (see Tests);

270 = average rounded molar mass of palmitic acid and stearic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoesters*: calculate the percentage content of monoesters using the following expression:

$$\left[\frac{X}{X+Y}(100 - A - B)\right] - D$$

A = percentage content of free propylene glycol;

B = percentage content of water (see Tests);

D = percentage content of free fatty acids;

X = area of the peak due to monoesters and free fatty acids;

Y = area of the peak due to diesters.

STORAGE

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Propylene Glycol Solution

General Notices

Propylene Glycol Cutaneous Solution

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Excipient; emollient.

DEFINITION

Propylene Glycol Solution is a *cutaneous solution*. It contains Propylene Glycol in Purified Water.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements. Where appropriate, the solution also complies with the requirements stated under Unlicensed Medicines.

Content of propylene glycol, $C_3H_8O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of propylene glycol (*RS 437*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

To 10 mL of the solution add 40 mL of *water* and 0.1 mL of *bromothymol blue solution R1*; the solution is greenish-yellow. Not more than 0.1 mL of 0.1M *sodium hydroxide* is required to change the colour of the solution to blue.

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Dilute a quantity of the solution with sufficient *water* to contain 5% w/v of Propylene Glycol.

(2) 1% w/v of *diethylene glycol* in *water*.

(3) Dilute 1 volume of solution (2) to 10 volumes with solution (1) and further dilute 1 volume of this solution to 20 volumes with solution (1).

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(4) Dilute 1 volume of a 40% w/v solution of *propylene glycol BPCRS* in *water* and 5 volumes of solution (2) to 100 volumes with *water*; further dilute 1 volume to 10 volumes with *water*.

(5) 0.05% w/v of *diethylene glycol* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a film (3 µm) of 6% cyanopropylphenyl siloxane and 94% polydimethylsiloxane (DB-624 is suitable).

(b) Use *helium* as the carrier gas at 4.5 mL per minute.

(c) Use an oven maintained at an initial temperature of 100°, increasing linearly to 220° at a rate of 7.5° per minute, then maintained at 220° for 4 minutes.

(d) Use an inlet temperature of 220°.

(e) Use a flame ionisation detector maintained at a temperature of 250°.

(f) Use a split ratio of 1:10.

(g) Inject 0.5 µL of each solution.

SYSTEM SUITABILITY

The chromatogram obtained with solution (4) shows a peak due to propylene glycol (retention time about 4.2 minutes) and a peak due to diethylene glycol with a retention relative to propylene glycol of about 1.8. The test is not valid unless the *symmetry factor* of both peaks is not less than 0.8 and not more than 1.2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to diethylene glycol is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than five times the area of the peak due to diethylene glycol in the chromatogram obtained with solution (3) (0.5%);

the sum of the areas of all the peaks is not greater than 10 times the area of the peak due to diethylene glycol in the chromatogram obtained with solution (3) (1%).

Disregard any peak with an area less than 0.05 times the area of the peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Dilute a quantity of the solution with sufficient *water* to contain 0.04% w/v of Propylene Glycol.

(2) 0.04% w/v of *propylene glycol BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a film (3 µm) of 6% cyanopropylphenyl siloxane and 94% polydimethylsiloxane (DB-624 is suitable).

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(b) Use *helium* as the carrier gas at 4.5 mL per minute.

(c) Use an oven maintained at an initial temperature of 100°, increasing linearly to 220° at a rate of 7.5° per minute, then maintained at 220° for 4 minutes.

(d) Use an inlet temperature of 220°.

(e) Use a flame ionisation detector maintained at a temperature of 250°.

(f) Use a split ratio of 1:10.

(g) Inject 0.5 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_3H_8O_2$ in the solution using the declared content of $C_3H_8O_2$ in *propylene glycol BPCRS*.

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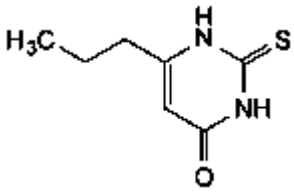
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Propylthiouracil

General Notices

(Ph. Eur. monograph 0525)



$C_7H_{10}N_2OS$ 170.2 *51-52-5*

Action and use

Thiourea antithyroid drug.

Preparation

Propylthiouracil Tablets

Ph Eur

DEFINITION

6-Propyl-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

Very slightly soluble in water, sparingly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides.

IDENTIFICATION

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First identification: B.

Second identification: A, C.

A. Melting point (2.2.14): 217 °C to 221 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *propylthiouracil CRS*.

C. To about 20 mg add 8 mL of *bromine water R* and shake for a few minutes. Boil until the mixture is decolourised, allow to cool and filter. To the filtrate add 2 mL of *barium chloride solution R1*. A white precipitate is formed whose colour does not become violet on the addition of 5 mL of *dilute sodium hydroxide solution R*.

TESTS

Impurity A

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *acetonitrile R* (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution Dissolve 2.5 mg of *propylthiouracil impurity A CRS* in 70 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography, alkyl-bonded for use with highly aqueous mobile phases R* (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: to 1000 mL of *water for chromatography R*, add 1 mL of *phosphoric acid R* and mix. Mix 900 mL of this solution and 100 mL of *acetonitrile for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 15	100 → 70	0 → 30
15 - 25	70	30

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Flow rate 0.6 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Run time 1.5 times the retention time of propylthiouracil.

Identification of impurities Use the chromatogram obtained with the reference solution to identify the peak due to impurity A.

Relative retention With reference to propylthiouracil (retention time = about 16 min): impurity A = about 0.27.

Calculation of percentage content:

— for impurity A, use the concentration of impurity A in the reference solution.

Limit:

— *impurity A*: maximum 0.05 per cent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 20 mL of methanol R, sonicate to dissolve and dilute to 100.0 mL with methanol R.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with methanol R. Dilute 1.0 mL of the solution to 100.0 mL with methanol R.

Reference solution (b) Dissolve 25 mg of the substance to be examined and 25 mg of methylthiouracil R (impurity B) in 50 mL of methanol R and dilute to 100 mL with the same solvent. Dilute 0.5 mL of the solution to 50 mL with methanol R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase To 1000 mL of water for chromatography R, add 1 mL of phosphoric acid R and mix. Mix 900 mL of this solution and 100 mL of acetonitrile R.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL.

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Run time 1.5 times the retention time of propylthiouracil.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to propylthiouracil (retention time = about 19 min): impurity B = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 20 between the peaks due to impurity B and propylthiouracil.

Calculation of percentage contents:

— for each impurity, use the concentration of propylthiouracil in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: maximum 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.300 g add 30 mL of *water R* and 30.0 mL of *0.1 M sodium hydroxide*. Boil and shake until dissolution is complete. Add 50 mL of *0.1 M silver nitrate* while stirring, boil gently for 5 min and cool. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). The volume of *0.1 M sodium hydroxide* used is equal to the sum of the volume added initially and the volume used in the final titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 8.511 mg of $C_7H_{10}N_2OS$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A*.

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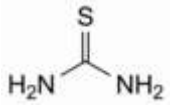
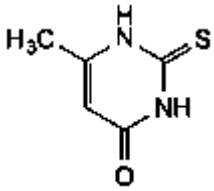
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. thiourea,



B. 6-methyl-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one (methylthiouracil).

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Propylthiouracil Tablets

General Notices

Action and use

Thiourea antithyroid drug.

DEFINITION

Propylthiouracil Tablets contain Propylthiouracil.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of propylthiouracil, $C_7H_{10}N_2OS$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Propylthiouracil with 20 mL of *methanol* for 10 minutes, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of propylthiouracil (*RS 300*).

B. Shake a quantity of the powdered tablets containing 50 mg of Propylthiouracil with 60 mL of *methanol* for 20 minutes, dilute to 100 mL with *methanol* and filter. Dilute 5 mL of this solution to 250 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum only at 274 nm.

C. Extract a quantity of the powdered tablets in a continuous extraction apparatus with *ether* and evaporate the solution to dryness. The *melting point* of the residue, after drying at 105°, is about 219°, Appendix V A.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 0.2 volume of *glacial acetic acid*, 12 volumes of *propan-2-ol* and 100 volumes of *chloroform* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 50 mg of Propylthiouracil with 5 mL of *methanol* for 15 minutes, filter and use the filtrate. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *methanol*. Solution (3) contains 0.0010% w/v of *thiourea* in *methanol*. After removal of the plate, allow it to dry in air, examine under *ultraviolet light (254 nm)* and expose to iodine vapour for 10 minutes. Any spot corresponding to thiourea in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.1%) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (1%). Disregard any spot remaining on the line of application.

ASSAY

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Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.15 g of Propylthiouracil in a mixture of 20 mL of *0.1M sodium hydroxide VS* and 75 mL of *water* with the aid of gentle heat. Cool, add 4 g of *sodium acetate*, just acidify the solution to *litmus paper* with 6 M *acetic acid*, add 0.5 mL of a freshly prepared 0.5% w/v solution of *1,5-diphenylcarbazone* in *ethanol* (*96%*) and titrate with 0.02M *mercury nitrate VS* until a pinkish violet colour persists for 2 to 3 minutes. Each mL of 0.02M *mercury nitrate VS* is equivalent to 6.808 mg of $C_7H_{10}N_2OS$.

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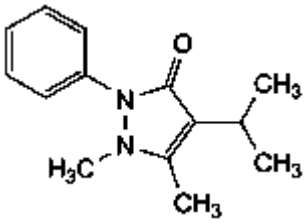
Propyphenazone

General Notices

(Ph. Eur. monograph 0636)



$C_{14}H_{18}N_2O$ 230.3 *479-92-5*

Action and use

Pyrazolone analgesic.

Ph Eur

DEFINITION

1,5-Dimethyl-2-phenyl-4-(propan-2-yl)-1,2-dihydro-3*H*-pyrazol-3-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

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A. Melting point (2.2.14): 102 °C to 106 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison propyphenazone CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 80 mg of the substance to be examined in methanol R and dilute to 5 mL with the same solvent.

Reference solution Dissolve 80 mg of propyphenazone CRS in methanol R and dilute to 5 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase butanol R, cyclohexane R, ethyl acetate R (10:45:45 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In a current of hot air for 15 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 1 mL of solution S (see Tests) add 0.1 mL of ferric chloride solution R1. A brownish-red colour appears which becomes yellow on addition of 1 mL of dilute hydrochloric acid R.

TESTS

Solution S

Dissolve 2 g in a mixture of equal volumes of carbon dioxide-free water R and ethanol (96 per cent) R and dilute to 50 mL with the same mixture of solvents.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of phenolphthalein solution R. The solution is colourless. Add 0.2 mL of a 0.40 g/L solution of sodium hydroxide R; the solution becomes pink. Add 0.4 mL of a 1.03 g/L solution of hydrochloric acid R; the solution becomes colourless. Add 0.2 mL of methyl red solution R; the solution becomes orange or red.

Related substances

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Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 1 mg of *phenazone R* (impurity A) in the mobile phase, add 1 mL of the test solution and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 13.7 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 5.2 with *dilute sodium hydroxide solution R* and dilute to 1000 mL with *water for chromatography R*. Mix 60 volumes of the solution and 40 volumes of *acetonitrile R1*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time 4 times the retention time of propyphenazone.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to propyphenazone (retention time = about 7 min): impurity A = about 0.4.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity A and propyphenazone.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 0.5 g.

ASSAY

Dissolve 0.175 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

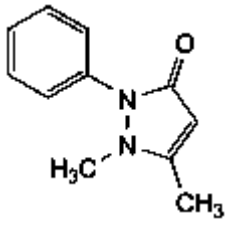
1 mL of *0.1 M perchloric acid* is equivalent to 23.03 mg of $C_{14}H_{18}N_2O$.

STORAGE

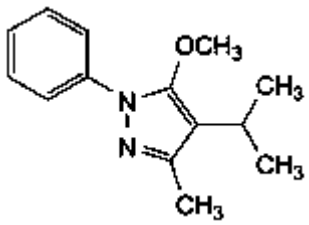
Protected from light.

IMPURITIES

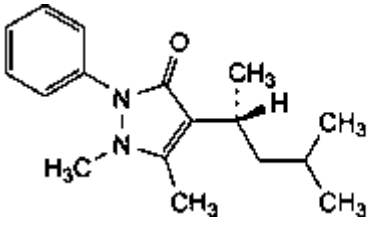
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.



A. 1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (phenazone),



B. 5-methoxy-3-methyl-1-phenyl-4-(propan-2-yl)-1*H*-pyrazole,



C. 1,5-dimethyl-4-[(2*RS*)-4-methylpentan-2-yl]-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one.

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Protamine Sulfate

General Notices

Protamine Sulphate

(Ph. Eur. monograph 0569)

9009-65-8

Action and use

Antidote to heparin.

Preparation

Protamine Sulfate Injection

Ph Eur

DEFINITION

Sulfated forms of basic peptides, comprising 4 major chemical species, extracted from the sperm or roe of *Salmonidae*. It binds with heparin in solution, inhibiting its anticoagulant activity; under the conditions of the potency assay this binding gives rise to a precipitate.

Content

90.0 per cent to 110.0 per cent (dried, sulfuric acid-free substance).

Potency

1 mg of protamine sulfate precipitates not less than 100 IU of heparin (dried substance).

PRODUCTION

The animals from which protamine sulfate is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent).

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IDENTIFICATION

A. Examine the chromatograms obtained in the test for related substances and calculate individually the relative amounts of protamine peptides A, B, C and D.

Results:

— the principal peaks in the chromatogram obtained with the test solution (protamine peptides A to D) are similar in retention time to the principal peaks in the chromatogram obtained with reference solution (a);

— protamine peptide A content: 13-18 per cent;

— protamine peptide B content: 21-28 per cent;

— protamine peptide C content: 31-38 per cent;

— protamine peptide D content: 19-24 per cent.

B. It gives the appropriate response when examined as described in the potency assay.

C. It complies with the test for sulfate (see Tests).

TESTS

Solution S

Dissolve 0.20 g in *water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_6 or Y_6 (*2.2.2, Method II*).

To 2.5 mL of solution S add 7.5 mL of *water R*.

Absorbance (*2.2.25*)

Maximum 0.1 between wavelengths of 260 nm and 280 nm.

Dilute 2.5 mL of solution S to 5.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 30 mg of the substance to be examined in 400 µL of a 618 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with a 1.03 g/L solution of *hydrochloric acid R*.

Reference solution (a) Dissolve the contents of a vial of *protamine sulfate CRS* in 40 µL of a 618 g/L solution of *hydrochloric acid R* and dilute to 10.0 mL with a 1.03 g/L solution of *hydrochloric acid R*.

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Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with a 1.03 g/L solution of *hydrochloric acid R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (3.6 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *acetonitrile R1*, *water for chromatography R* (0.1:5:95 *V/V/V*); degas;

— *mobile phase B*: *trifluoroacetic acid R*, *acetonitrile R1*, *water for chromatography R* (0.1:50:50 *V/V/V*); degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	95	5
2 - 17	95 → 80	5 → 20
17 - 17.2	80 → 20	20 → 80
17.2 - 20	20	80

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 5 °C.

Injection 30 µL.

Relative retention With reference to protamine peptide A (retention time = about 9-13 min): protamine peptide B = about 1.05; protamine peptide C = about 1.10; protamine peptide D = about 1.15.

System suitability:

— the 4 principal peaks (protamine peptides A to D) are eluted between 8 min and 16.5 min in the chromatogram obtained with reference solution (a);

— *resolution*: minimum 2.0 between each of the adjacent principal peaks in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 10 for the peak due to protamine peptide A in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.8 for the peak due to protamine peptide A, maximum 1.5 for the peak due to protamine peptide B, maximum 2.5 for the peak due to protamine peptide C and maximum 2.2 for the peak due to protamine peptide D in the chromatogram obtained with reference solution (a).

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Calculate the percentage content of related substances using the following expression (use the vertical drop approach for integration):

$$100 - \left(\frac{r_A + r_B + r_C + r_D}{r_T} \times 100 \right)$$

$r_{A\text{-}D}$ = areas of the peaks due to protamine peptides A to D;

r_T = sum of the areas of all peaks in the chromatogram.

Limit:

— *total*: maximum 8.0 per cent;

— *reporting threshold*: 0.50 per cent.

Sulfate

16 per cent to 24 per cent (dried substance).

Dissolve 0.150 g in 15 mL of *distilled water R* in a beaker. Add 5 mL of *dilute hydrochloric acid R*. Heat to boiling and slowly add to the boiling solution 10 mL of a 100 g/L solution of *barium chloride R*. Cover the beaker and heat on a water-bath for 1 h. Filter. Wash the precipitate several times with small quantities of hot *water R*. Dry and ignite the residue at 600 ± 50 °C to constant mass.

1.0 g of residue is equivalent to 0.4117 g of SO_4.

Iron (2.4.9)

Maximum 10 ppm.

Dissolve 1.0 g with heating in *water R* and dilute to 10 mL with the same solvent.

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Protein

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the total area of the peaks above the reporting threshold with a relative retention with reference to protamine peptide A of 0.80-1.30, determined on 6 injections.

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Calculate the percentage content of protamine from the areas of all peaks above the reporting threshold with a relative retention with reference to protamine peptide A of 0.80-1.30, taking into account the assigned content of *protamine sulfate CRS*.

Potency

Test solution (a) Dissolve 15.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 2.0 mL of test solution (a) to 3.0 mL with *water R*.

Test solution (c) Dilute 1.0 mL of test solution (a) to 3.0 mL with *water R*.

Use as titrant a 6-fold dilution of *heparin sodium BRP* in *water R* (for example, 1.7 mL diluted to 10.0 mL with *water R*). Titrate each test solution in duplicate as follows: introduce an accurately measured volume of the solution to be titrated, for example 1.5 mL, into the cell of a suitable colorimeter and set the apparatus for measurement at a suitable wavelength (none is critical) in the visible range. Add the titrant in small volumes until there is a sharp increase in the absorbance and note the volume of titrant added.

Carry out 3 independent assays. For each individual titration, calculate the number of International Units of heparin in the volume of titrant added at the end-point per milligram of the substance to be examined. Calculate the potency of the substance as the average of the 18 values. Test the linearity of the response by the usual statistical methods (for example, *5.3*). Calculate the 3 standard deviations for the results obtained with each of the 3 test solutions. Calculate the 3 standard deviations for the results obtained with each of the 3 independent assays. The assay is not valid unless each of the 6 standard deviations is less than 5 per cent of the average result.

STORAGE

In an airtight, tamper-evident container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

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Protamine Sulfate Injection

General Notices

Protamine Sulphate Injection

Action and use

Antidote to heparin.

DEFINITION

Protamine Sulfate Injection is a sterile solution of Protamine Sulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of protamine sulfate

Not less than 80.0% of the stated amount.

IDENTIFICATION

A. Produces a precipitate under the conditions of the Assay.

B. Dilute the injection with *water* to give a solution containing 0.2% w/v of Protamine Sulfate. To 5 mL add 1 mL of a 10% w/v solution of *sodium hydroxide* and 1 mL of a 0.02% w/v solution of *1-naphthol* and mix. Cool to 5° and add 0.5 mL of *sodium hypobromite solution*. An intense pink colour is produced.

C. Heat 2 mL in a water bath at 60° and add 0.1 mL of mercury (II) sulfate solution; no precipitate is produced. Cool the mixture in ice; a white precipitate is produced.

D. Yields reaction A characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

pH, 2.5 to 3.5, Appendix V L.

Optical rotation

Dilute the injection with 0.5M *hydrochloric acid* to produce a solution containing 0.8% w/v of Protamine Sulfate. The *optical rotation* of the resulting solution is –0.52° to –0.68°, Appendix V F.

Light absorption

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Dilute the injection, if necessary, with *water* to produce a solution containing 1% w/v of Protamine Sulfate. The *absorbance* at 260 to 280 nm is not more than 0.1, Appendix II B.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing 10 mg of Protamine Sulfate per mL (solution A). The endotoxin limit concentration of solution A is 70 IU of endotoxin per mL. Carry out the test using the maximum allowable concentration of solution A calculated from the declared sensitivity of the lysate used in the test.

ASSAY

Carry out the Potency Assay described under Protamine Sulfate using solutions prepared by diluting the injection with *water* to contain (1) 0.015% w/v, (2) 0.010% w/v and (3) 0.005% w/v of Protamine Sulfate.

Use as titrant a 6-fold dilution of heparin sodium BRP in water R (for example, 1.7 mL diluted to 10.0 mL with water R). Titrate each test solution in duplicate as follows: introduce an accurately measured volume of the solution to be titrated, for example 1.5 mL, into the cell of a suitable UV/visible spectrophotometer and set the apparatus for measurement at a suitable wavelength (none is critical) in the visible range. Add the titrant in small volumes until there is a sharp increase in the absorbance and note the volume of titrant added.

Carry out 3 independent assays. For each individual titration, calculate the number of International Units of heparin in the volume of titrant added at the end-point per milligram of the substance to be examined. Calculate the potency of the substance as the average of the 18 values. Test the linearity of the response by the usual statistical methods (for example, 5.3). Calculate the 3 standard deviations for the results obtained with each of the 3 test solutions. Calculate the 3 standard deviations for the results obtained with each of the 3 independent assays. The assay is not valid unless each of the 6 standard deviations is less than 5 per cent of the average result.

LABELLING

The label states that the dose is calculated from the results of determinations of the amount required to produce an acceptable blood clotting time in the patient.

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Protamine Zinc Insulin Injection

General Notices

Protamine Zinc Insulin

Action and use

Hormone; treatment of diabetes' mellitus.

DEFINITION

Protamine Zinc Insulin Injection is a sterile buffered suspension of bovine, porcine or human insulin complexed with Protamine Sulfate or another suitable protamine and Zinc Chloride or another suitable zinc salt.

The injection complies with the requirements stated under Injectable Insulin Preparations and with the following requirements.

PRODUCTION

Protamine Zinc Insulin Injection is prepared by carrying out the procedures described under Insulin Preparations. A suitable protamine is added in the proportion of 1.0 to 1.7 mg of protamine sulfate per 100 IU of insulin.

DESCRIPTION

A white suspension which on standing deposits a white sediment and leaves a colourless or almost colourless supernatant liquid; the sediment is readily resuspended by shaking. When examined under a microscope, approximately 50% of the particles are seen to have no uniform shape, with a maximum diameter rarely exceeding 2 µm. The remaining particles are seen to be rod-shaped crystals, the majority with a maximum dimension greater than 10 µm but rarely exceeding 100 µm.

IDENTIFICATION

In the Assay the position of the peak due to insulin in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the appropriate reference solution.

Total zinc

20 to 25 mg per 100 IU of insulin, determined as described under Insulin Preparations.

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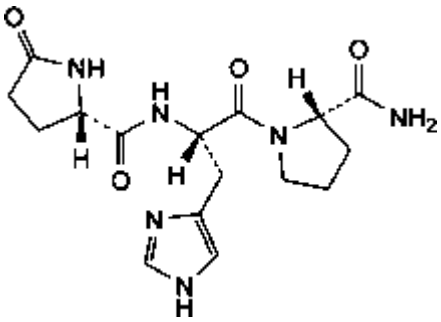
Protirelin

General Notices

(Ph. Eur. monograph 1144)



$C_{16}H_{22}N_6O_4$ 362.4 *24305-27-9*

Action and use

Thyrotrophin-releasing hormone.

Ph Eur

DEFINITION

5-Oxo-L-prolyl-L-histidyl-L-prolinamide.

Synthetic tripeptide with the same sequence of amino acids as the natural hypothalamic neurohormone, which stimulates the release and synthesis of thyrotropin.

Content

97.0 per cent to 102.0 per cent (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic.

Solubility

Very soluble in water, freely soluble in methanol.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison protirelin CRS.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

A 10 g/L solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, Method II).

Specific optical rotation (2.2.7)

-62 to -70 (anhydrous and acetic acid-free substance).

Dissolve 10 mg in 1.0 mL of water R.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 5.0 mg of the substance to be examined in mobile phase A and dilute to 5.0 mL with mobile phase A.

Reference solution (a) Dissolve the contents of a vial of D-His-protirelin CRS in an appropriate volume of mobile phase A to obtain a concentration of 1 mg/mL. Mix equal volumes of this solution and the test solution.

Reference solution (b) Dilute 0.2 mL of the test solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm,

— *stationary phase*: spherical octadecylsilyl silica gel for chromatography R (5 µm) with a pore size of 12 nm.

Mobile phase:

— *mobile phase A*: a mixture of 100 mL of acetonitrile for chromatography R, 1900 mL of water R and 2.0 g of sodium octanesulfonate R, containing 2.5 mL/L of tetraethylammonium hydroxide solution R; adjust to pH 3.5 with phosphoric acid R,

— *mobile phase B*: a mixture of 300 mL of acetonitrile for chromatography R, 1700 mL of water R and 2.0 g of sodium octanesulfonate R, containing 2.5 mL/L of tetraethylammonium hydroxide solution R; adjust to pH 3.5 with phosphoric acid R,

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	74 → 41	26 → 59
30 - 35	41 → 74	59 → 26
35 - 50	74	26

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Relative retention With reference to protirelin (retention time = about 18 min): impurity C = about 0.2; impurity D = about 0.68; impurity A = about 0.91; impurity B = about 0.95; impurity E = about 1.08.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity A and protirelin,

— *symmetry factor*: 0.9 to 1.2 for the peak due to protirelin.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent),

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Acetic acid (*2.5.34*)

Maximum 2.0 per cent.

Test solution Dissolve 40.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of solvents.

Water (*2.5.12*)

Maximum 7.0 per cent, determined on 0.200 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.7 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

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Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Reference solution Dissolve the contents of a vial of *protirelin CRS* in an appropriate volume of mobile phase A to obtain a concentration of 1.0 mg/mL.

Calculate the content of protirelin ($C_{16}H_{22}N_6O_4$) using the peak areas of the chromatograms obtained with the test solution and the reference solution and the declared content of $C_{16}H_{22}N_6O_4$ in *protirelin CRS*.

STORAGE

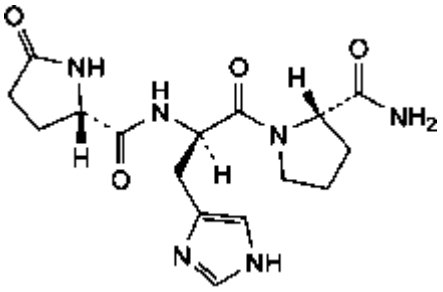
In an airtight container, protected from light at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

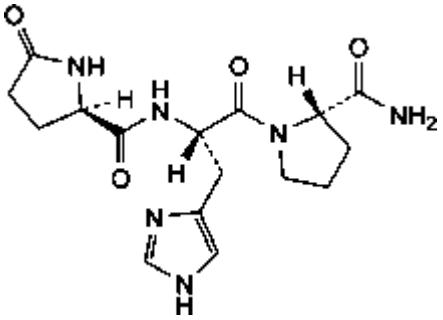
The label states the mass of peptide in the container.

IMPURITIES

Specified impurities *A, B, C, D, E.*



A. 5-oxo-L-prolyl-D-histidyl-L-prolinamide,



B. 5-oxo-D-prolyl-L-histidyl-L-prolinamide,

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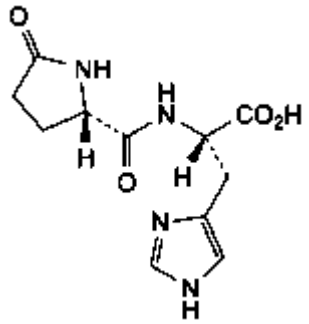
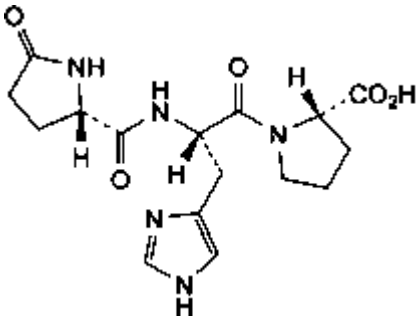
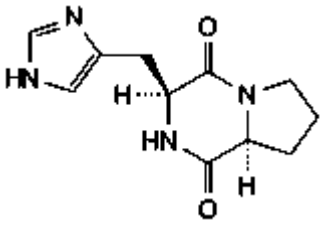


C. 5-oxo-L-prolyl-L-histidine,



D. 5-oxo-L-prolyl-L-histidyl-L-proline,



E. (3*S*,8a*S*)-3-(1*H*-imidazol-4-ylmethyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (cyclo(-L-histidyl-L-prolyl-)).

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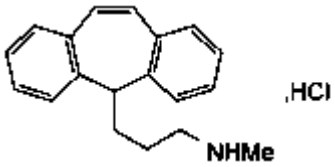
Protriptyline Hydrochloride

General Notices



$C_{19}H_{21}N$,HCl 299.8 *1225-55-4*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Protriptyline Hydrochloride is 3-(5*H*-dibenzo[*a,d*]cyclohept-5-yl)propyl(methyl)amine hydrochloride. It contains not less than 99.0% and not more than 101.0% of $C_{19}H_{21}N$,HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white to yellowish white powder.

Freely soluble in *water* and in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. Dissolve 0.1 g in 10 mL of *water*, make alkaline with 1M *sodium hydroxide*, extract with 5 mL of *chloroform*, dry with *anhydrous sodium sulfate* and evaporate the solvent using a current of nitrogen. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of protriptyline *(RS 301)*.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH of a 1% w/v solution, 5.0 to 6.5, Appendix V L.

Loss on drying

When dried to constant weight at 60° at a pressure not exceeding 0.7 kPa, loses not more than 0.5% of its weight. Use 1 g.

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Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.7 g and *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 29.98 mg of $C_{19}H_{21}N,HCl$.

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Proxymetacaine Eye Drops

General Notices

Action and use

Local anaesthetic.

DEFINITION

Proxymetacaine Eye Drops are a sterile solution of Proxymetacaine Hydrochloride in Purified Water. They may contain Glycerol.

With the exception that they may be supplied in containers not exceeding 15 mL in capacity, the eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of proxymetacaine hydrochloride, $C_{16}H_{26}N_2O_3$,HCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 250 to 350 nm of the solution used in the Assay exhibits two maxima, at 268 nm and 310 nm.

B. To a volume containing 50 mg of Proxymetacaine Hydrochloride add 2 mL of 2M *hydrochloric acid* and extract with 25 mL of *chloroform*. Discard the chloroform layer, make alkaline with 5M *sodium hydroxide* and extract with two 25 mL quantities of *chloroform*. Filter the combined extracts through *anhydrous sodium sulfate* and evaporate the filtrate to dryness using a rotary evaporator. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of proxymetacaine (*RS 302*).

C. A volume containing 5 mg of Proxymetacaine Hydrochloride yields the reaction characteristic of *primary aromatic amines*, Appendix VI.

TESTS

Related substances

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the eye drops, diluted if necessary to contain 0.5% w/v of Proxymetacaine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) Dilute 1 volume of solution (2) with an equal volume of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat it at 105° for 10 minutes, allow to cool and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *diethylamine*, 30 volumes of *ethyl acetate* and 75 volumes of *toluene*

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (1%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

Disregard any spot remaining on the line of application.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the eye drops, diluted if necessary to contain 0.5% w/v of Proxymetacaine Hydrochloride.

(2) 0.020% w/v *3-amino-4-propoxybenzoic acid BPCRS* in *methanol*.

(3) 0.0050% w/v *3-amino-4-propoxybenzoic acid BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

A mixture of 4 volumes of *glacial acetic acid*, 20 volumes of *cyclohexane* and 80 volumes of *1,4-dioxan*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (4%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (1%).

The principal spot remains on or near the line of application.

ASSAY

Dilute a volume containing 10 mg of Proxymetacaine Hydrochloride to 200 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 310 nm, Appendix II B. Calculate the content of $C_{16}H_{26}N_2O_3$,HCl taking 162 as the value of A(1%, 1 cm) at the maximum at 310 nm.

STORAGE

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Proxymetacaine Eye Drops should be protected from light, stored at a temperature of 2° to 8° and should not be allowed to freeze.

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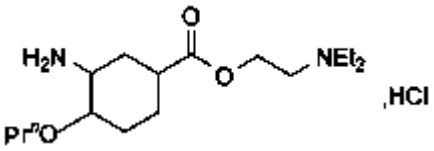
Proxymetacaine Hydrochloride

General Notices



$C_{16}H_{26}N_2O_3HCl$ 330.9 *5875-06-9*

Action and use

Local anaesthetic.

Preparation

Proxymetacaine Eye Drops

DEFINITION

Proxymetacaine Hydrochloride is 2-diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride. It contains not less than 98.0% and not more than 102.0% of $C_{16}H_{26}N_2O_3$,HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Soluble in *water*; very soluble in *absolute ethanol*; practically insoluble in *ether*.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 220 to 350 nm of a 0.002% w/v solution exhibits three maxima, at 231, 268 and 310 nm. The *absorbances* at the maxima at 268 nm and at 310 nm are about 0.58 and about 0.32, respectively.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of proxymetacaine hydrochloride *(RS 303)*.

C. A 5% w/v solution yields the reaction characteristic of *primary aromatic amines* and the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

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pH of a 1% w/v solution, 5.7 to 6.4, Appendix V L.

Related substances

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions of the substance being examined in *methanol*.

(1) 2.0% w/v of the substance being examined.

(2) 0.020% w/v of the substance being examined.

(3) 0.010% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, heat at 105° for 10 minutes, allow to cool and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *diethylamine*, 30 volumes of *ethyl acetate* and 75 volumes of *toluene*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1);

is not more intense than the spot in the chromatogram obtained with solution (2) (1%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.5%). Disregard any spot remaining on the line of application.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) 2.0% w/v of the substance being examined.

(2) 0.0050% w/v of *3-amino-4-propoxybenzoic acid BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *glacial acetic acid*, 20 volumes of *cyclohexane* and 80 volumes of *1,4-dioxan*.

LIMITS

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Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%). The principal spot remains on or near the line of application.

Loss on drying

When dried at 105° for 3 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.15%, Appendix IX A.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.25 g, 20 mL of *mercury(II) acetate solution* and *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 16.54 mg of $C_{16}H_{26}N_2O_3$,HCl.

STORAGE

Proxymetacaine Hydrochloride should be protected from light.

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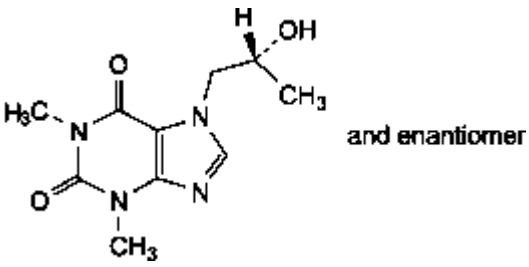
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Proxyphylline

General Notices

(Ph. Eur. monograph 0526)



$C_{10}H_{14}N_4O_3$ 238.2 *603-00-9*

Action and use

Non selective phospho-diesterase inhibitor; treatment of reversible airways obstruction.

Ph Eur

DEFINITION

Proxyphylline contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 7-[(2*RS*)-2-hydroxypropyl]-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 134 °C to 136 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *proxyphylline CRS*. Examine the substances as discs prepared using 0.5 mg to 1 mg of the substance to be examined in 0.3 g of *potassium bromide R*.

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C. Dissolve 1 g in 5 mL of *acetic anhydride R* and boil under a reflux condenser for 15 min. Allow to cool and add 100 mL of a mixture of 20 volumes of *ether R* and 80 volumes of *light petroleum R*. Cool in iced water for at least 20 min, shaking from time to time. Filter, wash the precipitate with a mixture of 20 volumes of *ether R* and 80 volumes of *light petroleum R*, recrystallise from *alcohol R* and dry *in vacuo*. The crystals melt (*2.2.14*) at 87 °C to 92 °C.

D. It gives the reaction of xanthines (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.25 mL of *bromothymol blue solution R1*. The solution is yellow or green. Not more than 0.4 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel HF_{254} R* as the coating substance.

Test solution Dissolve 0.3 g of the substance to be examined in a mixture of 20 volumes of *water R* and 30 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents. Prepare immediately before use.

Reference solution (a) Dilute 1 mL of the test solution to 100 mL with *methanol R*.

Reference solution (b) Dilute 0.2 mL of the test solution to 100 mL with *methanol R*.

Reference solution (c) Dissolve 10 mg of *theophylline R* in *methanol R*, add 0.3 mL of the test solution and dilute to 10 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *concentrated ammonia R*, 10 volumes of *ethanol R* and 90 volumes of *chloroform R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1 per cent) and at most one such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated spots.

Chlorides (*2.4.4*)

Dilute 2.5 mL of solution S to 15 mL with *water R*. The solution complies with the limit test for chlorides (400 ppm).

Loss on drying (*2.2.32*)

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Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.200 g in 3.0 mL of *anhydrous formic acid R* and add 50.0 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 23.82 mg of $C_{10}H_{14}N_4O_3$.

STORAGE

Store protected from light.

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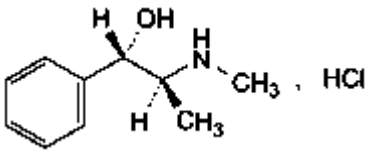
Pseudoephedrine Hydrochloride

General Notices

(Ph. Eur. monograph 1367)



$C_{10}H_{16}ClNO$ 201.7 *345-78-8*

Action and use

Adrenoceptor agonist.

Preparations

Pseudoephedrine Oral Solution

Pseudoephedrine Tablets

Ph Eur

DEFINITION

(1*S*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride.

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About 184 °C.

IDENTIFICATION

First identification: A, B, D.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *pseudoephedrine hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *pseudoephedrine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *ephedrine hydrochloride CRS* in reference solution (a) and dilute to 5 mL with reference solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *methylene chloride R*, *concentrated ammonia R*, *2-propanol R* (5:15:80 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 110 °C for 5 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.25 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

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Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

Dilute 2 mL of solution S to 10 mL with *carbon dioxide-free water R*. Add 0.1 mL of *methyl red solution R* and 0.1 mL of *0.01 M sodium hydroxide*; the solution is yellow. Add 0.2 mL of *0.01 M hydrochloric acid*; the solution is red.

Specific optical rotation (*2.2.7*)

+ 61.0 to + 62.5 (dried substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of *ephedrine hydrochloride CRS* (impurity A) in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

Reference solution (c) Dissolve 10 mg of *ephedrine hydrochloride CRS* (impurity A) in 5 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 6 volumes of *methanol R* and 94 volumes of an 11.6 g/L solution of *ammonium acetate R* previously adjusted to pH 4.0 with *glacial acetic acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 257 nm.

Injection 20 µL.

Run time 1.5 times the retention time of pseudoephedrine.

Relative retention With reference to pseudoephedrine (retention time = about 18 min): impurity A = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurity A and pseudoephedrine; if necessary, reduce the content of methanol in the mobile phase.

Limits:

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— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.170 g in 30 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

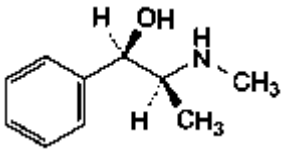
1 mL of *0.1 M sodium hydroxide* is equivalent to 20.17 mg of $C_{10}H_{16}ClNO$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A*.



A. (1*R*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol (ephedrine).

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Pseudoephedrine Oral Solution

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Pseudoephedrine Oral Solution is a solution of Pseudoephedrine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of pseudoephedrine hydrochloride, $C_{10}H_{15}NO,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the Oral Solution containing 0.3 g of Pseudoephedrine Hydrochloride, add 4 mL of *2M hydrochloric acid*, extract with two 40-mL quantities of *ether* and discard the ether. Add sufficient 5M *ammonia* to the aqueous phase to make it alkaline, extract with two 60-mL quantities of *ether*, wash the combined ether extracts with three 30-mL quantities of *water*, dry with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, in the range 1550 to 1350 cm^{-1} and in the range 1250 to 400 cm^{-1} is concordant with the *reference spectrum* of pseudoephedrine *(RS 304)*.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add sufficient 5M *ammonia* to a volume of the oral solution containing 10 mg of Pseudoephedrine Hydrochloride to make it alkaline, extract with two 100-mL quantities of *ether*, wash the combined extracts with 10 mL of *water*, dry with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. Dissolve the oily residue in sufficient *methanol* to produce 5 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.05% w/v each of *ephedrine hydrochloride BPCRS* and *pseudoephedrine hydrochloride BPCRS* in the mobile phase.

(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

(5) Dilute 1 volume of solution (2) to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (30 cm × 3.9 mm) packed with particles of *phenylsilyl silica gel for chromatography* (µBondapak Phenyl is suitable).

(b) Use isocratic elution and the mobile phase below.

(c) Use a flow rate of 1 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 257 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of 6 volumes of *methanol* and 94 volumes of 0.15M *ammonium acetate*, adjusted to pH 4.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of the peak due to ephedrine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (4) (0.2%);

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution containing 60 mg of Pseudoephedrine Hydrochloride to 50 mL with *methanol (65%)*.

(2) 0.12% w/v of *pseudoephedrine hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution containing 0.005M *dioctyl sodium sulfosuccinate* in a mixture of 1 volume of *glacial acetic acid*, 35 volumes of *water* and 65 volumes of *methanol*.

DETERMINATION OF CONTENT

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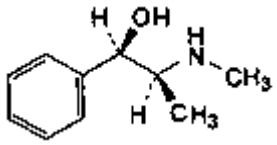
Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{10}H_{15}NO,HCl$, weight in volume, using the declared content of $C_{10}H_{15}NO,HCl$ in *pseudoephedrine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include:



Ephedrine.

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Pseudoephedrine Tablets

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Pseudoephedrine Tablets contain Pseudoephedrine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pseudoephedrine hydrochloride, $C_{10}H_{15}NO,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 60 mg of Pseudoephedrine Hydrochloride with 10 mL of *water* and filter. Shake the filtrate with 10 mL of *ether*, discard the ether, add 1 mL of 1M *sodium hydroxide* to the aqueous layer and extract with two 10 mL quantities of *ether*. Dry the combined ether extracts with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pseudoephedrine (*RS 304*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel precoated plate (Merck silica gel 60 plates are suitable) and a mixture of 10 volumes of 5M *ammonia*, 10 volumes of *methanol*, 20 volumes of *acetone*, 20 volumes of *butan-1-ol* and 40 volumes of *butyl acetate* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. Remove any film coating from the tablets before proceeding. For solution (1) add 25 mL of *methanol* to a quantity of the powdered tablets containing 0.5 g of Pseudoephedrine Hydrochloride, shake for 5 minutes, filter, wash the filter with *methanol* and evaporate the combined filtrate and washings to dryness. Dissolve the residue as completely as possible in 5 mL of *methanol*, centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with *methanol*. Solution (2) contains 1.0% w/v of *pseudoephedrine hydrochloride BPCRS* in *methanol*. After removal of the plate, allow it to dry in a current of warm air, spray with a solution containing 0.3 g of *ninhydrin* in a mixture of 100 mL of *butan-1-ol* and 3 mL of *glacial acetic acid* and heat at 120° for 20 minutes. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Remove any film coating from the tablets before proceeding. For solution (1) add 25 mL of *methanol* to a quantity of the powdered tablets containing 0.5 g of Pseudoephedrine Hydrochloride, shake for 5 minutes, filter, wash the filter with *methanol* and evaporate the combined filtrate and washings to dryness. Dissolve the residue as completely as possible in 5 mL of *methanol*, centrifuge and dilute 1 mL of the supernatant liquid to 50 mL with the

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mobile phase. Solution (2) contains 0.002% w/v of *ephedrine hydrochloride BPCRS* in the mobile phase. Solution (3) contains 0.05% w/v of *ephedrine hydrochloride BPCRS* and 0.05% w/v of *pseudoephedrine hydrochloride BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with particles of silica the surface of which has been modified with chemically bonded phenyl groups (µBondapak Phenyl is suitable), (b) a mixture of 6 volumes of *methanol* and 94 volumes of 0.15M *ammonium acetate*, adjusted to pH 4.0 with *glacial acetic acid*, as the mobile phase with a flow rate of 1.0 mL per minute and (c) a detection wavelength of 257 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.0.

In the chromatogram obtained with solution (1) the area of any peak corresponding to ephedrine is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) is a 0.12% w/v solution of *pseudoephedrine hydrochloride BPCRS* in *methanol* (*50%*). For solution (2) add 50 mL of 0.1M *hydrochloric acid* to a quantity of the powdered tablets containing 0.12 g of Pseudoephedrine Hydrochloride, mix with the aid of ultrasound for 15 minutes, add sufficient *methanol* to produce 100 mL, filter and use the filtrate.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable), (b) 0.005M *dioctyl sodium sulfosuccinate* in a mixture of 65 volumes of *methanol*, 35 volumes of *water* and 1 volume of *glacial acetic acid* as the mobile phase with a flow rate of 1.5 mL per minute and (c) a detection wavelength of 258 nm.

Calculate the content of $C_{10}H_{15}NO,HCl$ using the declared content of $C_{10}H_{15}NO,HCl$ in *pseudoephedrine hydrochloride BPCRS*.

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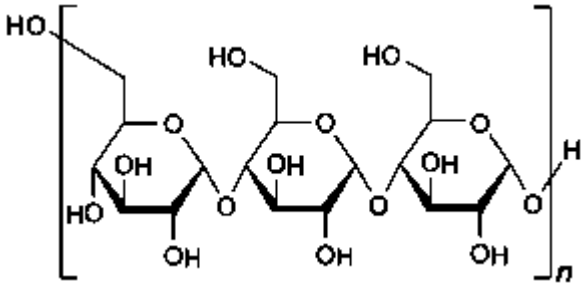
Pullulan

General Notices

(Ph. Eur. monograph 2603)



$C_{18n}H_{30n+2}O_{15n+1}$ *9057-02-7*

Action and use

Excipient.

Ph Eur

DEFINITION

Neutral polysaccharide produced by the growth of *Aureobasidium pullulans*. It has a chain structure consisting of α-(1→6)-linked maltotriose units, each of which is composed of three α-(1→4)-linked D-glucopyranose units. It may contain some maltotetraose units.

CHARACTERS

Appearance

White or almost white, very hygroscopic powder.

Solubility

Freely soluble in water, practically insoluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Dissolve 10 g in 100 mL of *water R*, adding the substance to be examined in small quantities while stirring. A viscous solution is produced.

B. Mix 10 mL of the solution obtained in identification test A with 0.1 mL of a 10 units/mL solution of *pullulanase R*. Incubate at 25 °C for about 20 min. A substantial decrease in viscosity is observed.

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C. Dissolve 2 g in 100 mL of *water R*. To 10 mL of the solution, add 2 mL of *macrogol 600 R*. A white precipitate is formed immediately.

TESTS

pH (*2.2.3*)

4.5 to 6.5.

Dissolve 1.0 g in 10 mL of *carbon dioxide-free water R*.

Viscosity (*2.2.9*)

100 $mm^2 \cdot s^{-1}$ to 180 $mm^2 \cdot s^{-1}$.

Dissolve 10.0 g (dried substance) in *water R* to make 100 g of solution, adding the substance to be examined in small quantities while stirring. Carry out the test at 30 ± 0.1 °C.

Mono-, di- and oligosaccharides

Maximum 10.0 per cent for the sum of mono-, di- and oligosaccharides.

Stock solution Dissolve 0.80 g (dried substance) in *water R*, adding the substance to be examined in small quantities while stirring, and dilute to 100.0 mL with the same solvent.

Test solution To 1.0 mL of the stock solution, add 0.1 mL of a saturated solution of *potassium chloride R* (2 g in 5 mL). Mix vigorously with 3 mL of *methanol R*. Centrifuge at 12 000-16 000 *g* for 10 min maintaining at 4 °C. Use the supernatant.

Reference solution Dilute 1.0 mL of the stock solution to 50.0 mL with *water R*.

Blank solution *water R*.

Transfer 0.2 mL of the test solution, the reference solution and the blank solution to separate test tubes, placed in a bath of iced water with each containing 5 mL of a 2 g/L solution of *anthrone R* in *sulfuric acid R1*. Stir immediately, then heat at 90 °C for 10 min. Cool the tubes under running water.

Measure the absorbance (*2.2.25*) of the test solution, the reference solution and the blank solution at 620 nm, using *water R* as the compensation liquid.

Calculate the percentage content of mono-, di- and oligosaccharides using the following expression:

$$100 \times \frac{4.1}{50} \times \frac{A_1 - A_2}{A_3 - A_2}$$

4.1	=	dilution factor for the test solution;
50	=	dilution factor for the reference solution;
A_1	=	absorbance of the test solution;

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A_2 = absorbance of the blank solution;

A_3 = absorbance of the reference solution.

Loss on drying (2.2.32)

Maximum 6.0 per cent, determined on 1.000 g by drying *in vacuo* at 90 °C for 6 h.

Sulfated ash (2.4.14)

Maximum 0.3 per cent, determined on 2.0 g.

Nitrogen (2.5.9)

Maximum 0.05 per cent (dried substance), determined on 4.0 g.

Carry out the determination of nitrogen using 40 mL of *sulfuric acid R* and heating until a green colour is obtained (about 1.5 h) to complete the decomposition and add *strong sodium hydroxide solution R* until a dark brown colour is obtained (about 90 mL).

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

STORAGE

In an airtight container.

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Purified Talc[1]

General Notices

(Talc, Ph. Eur. monograph 0438)

◊ *14807-96-6*◊

Preparation

Talc Dusting Powder

Ph Eur

DEFINITION

Powdered, selected, natural, hydrated magnesium silicate. Pure talc has the formula $Mg_3Si_4O_{10}(OH)_2$ (M_r 379.3). It may contain variable amounts of associated minerals among which chlorites (hydrated aluminium and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate) and dolomite (calcium and magnesium carbonate) are predominant.

♦ PRODUCTION

Talc derived from deposits that are known to contain associated asbestos is not suitable for pharmaceutical use. The manufacturer is responsible for demonstrating by the test for amphiboles and serpentines that the product is free from asbestos. The presence of amphiboles and of serpentines is revealed by X-ray diffraction or by infrared spectrophotometry (see A and B). If detected, the specific morphological criteria of asbestos are investigated by a suitable method of optical microscopy to determine whether tremolite asbestos or chrysotile is present, as described below.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs of *potassium bromide R*.

In the range 740 cm^{-1} to 760 cm^{-1} using scale expansion, any absorption band at 758 ± 1 cm^{-1} may indicate the presence of tremolite or of chlorite. If the absorption band remains after ignition of the substance to be examined at 850 ± 50 °C for at least 30 min, it indicates the presence of the tremolite. In the range 600 cm^{-1} to 650 cm^{-1} using scale expansion, any absorption band or shoulder may indicate the presence of serpentines.

B. X-ray diffraction.

Preparation Place the sample on the sample holder; pack and smooth its surface with a polished glass microscope slide.

Radiation Cu Kα monochromatic, 40 kV, 24-30 mA.

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Incident slit 1°.

Detection slit 0.2°.

Goniometer speed 1/10° 2 θ/min.

Scanning range 10-13° 2 θ and 24-26° 2 θ.

Sample Not oriented.

Results The presence of amphiboles is detected by a diffraction peak at 10.5 ± 0.1° 2 θ, the presence of serpentines is detected by diffraction peaks at 24.3 ± 0.1° 2 θ and at 12.1 ± 0.1° 2 θ.

If, by one of the 2 methods, amphiboles and/or serpentine are detected, examine by a suitable method of optical microscopy to determine the asbestos character.

The presence of asbestos is shown if the following 2 criteria are met:

— a range of length to width ratios of 20:1 to 100:1, or higher for fibres longer than 5 µm;

— capability of splitting into very thin fibrils;

and if at least 2 of the following 4 criteria are met:

— parallel fibres occurring in bundles;

— fibre bundles displaying frayed ends;

— fibres in the form of thin needles;

— matted masses of individual fibres and/or fibres showing curvature.

CHARACTERS

Appearance

Light, homogeneous, white or almost white powder, greasy to the touch (non abrasive).

Solubility

Practically insoluble in water, in ethanol (96 per cent) and in dilute solutions of acids and alkali hydroxides.♦

IDENTIFICATION

First identification: A.

◊ *Second identification: B, C.*◊

A. Infrared absorption spectrophotometry (2.2.24).

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Preparation Discs of *potassium bromide R*.

Absorption bands At 3677 ± 2 cm^{-1}, 1018 ± 2 cm^{-1} and 669 ± 2 cm^{-1}.

◊ B. In a platinum crucible, melt a mixture of 0.2 g of *anhydrous sodium carbonate R* and 2.0 g of *potassium carbonate R*. To the melted mass add 0.1 g of the substance to be examined and heat until the mixture is completely melted. Allow to cool and transfer the melted mass into an evaporating dish with 50 mL of hot *water R*. Add *hydrochloric acid R* until effervescence ceases. Add 10 mL of *hydrochloric acid R* and evaporate to dryness on a water-bath. Allow to cool. Add 20 mL of *water R*, heat to boiling and filter (the residue is used for identification test C). To 5 mL of the filtrate add 1 mL of *ammonia R* and 1 mL of *ammonium chloride solution R* and filter. To the filtrate add 1 mL of *disodium hydrogen phosphate solution R*. A white, crystalline precipitate is formed.

C. The residue obtained in identification test B gives the reaction of silicates (*2.3.1*).◊

TESTS

Solution S1

Weigh 10.0 g into a conical flask fitted with a reflux condenser, gradually add 50 mL of *0.5 M hydrochloric acid* while stirring and heat on a water-bath for 30 min. Allow to cool. Transfer the mixture to a beaker and allow the undissolved material to settle. Filter the supernatant through medium-speed filter paper into a 100 mL volumetric flask, retaining as much as possible of the insoluble material in the beaker. Wash the residue and the beaker with 3 quantities, each of 10 mL, of hot *water R*. Wash the filter with 15 mL of hot *water R*, allow the filtrate to cool and dilute to 100.0 mL with the same solvent.

Solution S2

Perchlorates mixed with heavy metals are known to be explosive. Take proper precautions while performing this procedure Weigh 0.5 g in a 100 mL polytetrafluoroethylene dish, add 5 mL of *hydrochloric acid R*, 5 mL of *lead-free nitric acid R* and 5 mL of *perchloric acid R*. Stir gently then add 35 mL of *hydrofluoric acid R* and evaporate slowly to dryness on a hot plate. To the residue, add 5 mL of *hydrochloric acid R*, cover with a watch-glass, heat to boiling and allow to cool. Rinse the watch-glass and the dish with *water R*. Transfer into a volumetric flask, rinse the dish with *water R* and dilute to 50.0 mL with the same solvent.

Acidity or alkalinity

Boil 2.5 g with 50 mL of *carbon dioxide-free water R* under reflux. Filter *in vacuo*. To 10 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*; not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to green. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R1*; not more than 0.3 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

♦ Water-soluble substances

Maximum 0.2 per cent.

To 10.0 g add 50 mL of *carbon dioxide-free water R*, heat to boiling and maintain boiling under a reflux condenser for 30 min. Allow to cool, filter through a medium-speed filter paper and dilute to 50.0 mL with *carbon dioxide-free water R*. Take 25.0 mL of the filtrate, evaporate to dryness and heat at 105 °C for 1 h. The residue weighs a maximum of 10 mg.♦

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Aluminium

Maximum 2.0 per cent.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution To 5.0 mL of solution S2 add 10 mL of a 25.34 g/L solution of *caesium chloride R*, 10.0 mL of *hydrochloric acid R* and dilute to 100.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks, each containing 10.0 mL of *hydrochloric acid R* and 10 mL of a 25.34 g/L solution of *caesium chloride R*, introduce respectively 5.0 mL, 10.0 mL, 15.0 mL and 20.0 mL of *aluminium standard solution (100 ppm Al) R* and dilute to 100.0 mL with *water R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Nitrous oxide-acetylene flame.

Calcium

Maximum 0.9 per cent.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution To 5.0 mL of solution S2 add 10.0 mL of *hydrochloric acid R*, 10 mL of *lanthanum chloride solution R* and dilute to 100.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks, each containing 10.0 mL of *hydrochloric acid R* and 10 mL of *lanthanum chloride solution R*, introduce respectively 1.0 mL, 2.0 mL, 3.0 mL and 5.0 mL of *calcium standard solution (100 ppm Ca) R1* and dilute to 100.0 mL with *water R*.

Source Calcium hollow-cathode lamp.

Wavelength 422.7 nm.

Atomisation device Nitrous oxide-acetylene flame.

Iron

Maximum 0.25 per cent.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution To 2.5 mL of solution S1, add 50.0 mL of *0.5 M hydrochloric acid* and dilute to 100.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks, each containing 50.0 mL of *0.5 M hydrochloric acid*, introduce respectively 2.0 mL, 2.5 mL, 3.0 mL and 4.0 mL of *iron standard solution (250 ppm Fe) R* and dilute to 100.0 mL with *water R*.

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Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Correction Deuterium lamp.

Lead

Maximum 10 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Use solution S1.

Reference solutions Into 4 identical volumetric flasks, each containing 50.0 mL of *0.5 M hydrochloric acid*, introduce respectively 5.0 mL, 7.5 mL, 10.0 mL and 12.5 mL of *lead standard solution (10 ppm Pb) R1* and dilute to 100.0 mL with *water R*.

Source Lead hollow-cathode lamp.

Wavelength 217.0 nm.

Atomisation device Air-acetylene flame.

Magnesium

17.0 per cent to 19.5 per cent.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 0.5 mL of solution S2 to 100.0 mL with *water R*. To 4.0 mL of the solution, add 10.0 mL of *hydrochloric acid R*, 10 mL of *lanthanum chloride solution R* and dilute to 100.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks, each containing 10.0 mL of *hydrochloric acid R* and 10 mL of *lanthanum chloride solution R*, introduce respectively 2.5 mL, 3.0 mL, 4.0 mL and 5.0 mL of *magnesium standard solution (10 ppm Mg) R1* and dilute to 100.0 mL with *water R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285.2 nm.

Atomisation device Air-acetylene flame.

Loss on ignition

Maximum 7.0 per cent, determined on 1.00 g by ignition to constant weight at 1050-1100 °C.

♦ Microbial contamination

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If intended for cutaneous administration:

— TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

If intended for oral administration:

— TAMC: acceptance criterion 10^3 CFU/g (2.6.12);

— TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

LABELLING

The label states, where applicable, that the substance is suitable for oral or cutaneous administration.♦

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for talc used as antisticking agent or glidant in tablets and capsules or as antiadhesive in coated and film-coated tablets.

Particle-size distribution (2.9.31)

Specific surface area (2.9.26)◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

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Purified Water

General Notices

(Ph. Eur. monograph 0008)

H_2O 18.02

Ph Eur

DEFINITION

Water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised.

PURIFIED WATER IN BULK

PRODUCTION

Purified water in bulk is prepared by distillation, by ion exchange, by reverse osmosis or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

Purified water in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Microbiological monitoring

During production and subsequent storage, appropriate measures are taken to ensure that the microbial count is adequately controlled and monitored. Appropriate alert and action levels are set so as to detect adverse trends. Under normal conditions, an appropriate action level is a microbial count of 100 CFU/mL, determined by filtration through a membrane with a nominal pore size not greater than 0.45 µm, using R2A agar and incubating at 30-35 °C for not less than 5 days. The size of the sample is to be chosen in relation to the expected result.

R2A agar

Yeast extract	0.5 g
Proteose peptone	0.5 g
Casein hydrolysate	0.5 g
Glucose	0.5 g
Starch	0.5 g
Dipotassium hydrogen phosphate	0.3 g

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Magnesium sulfate, anhydrous	0.024 g
Sodium pyruvate	0.3 g
Agar	15.0 g
Purified water	to 1000 mL

Adjust the pH so that after sterilisation it is 7.2 ± 0.2. Sterilise by heating in an autoclave at 121 °C for 15 min.

Growth promotion of R2A agar

— *Preparation of test strains*. Use standardised stable suspensions of test strains or prepare them as stated in Table 0008.-1. Seed lot culture maintenance techniques (seed-lot systems) are used so that the viable micro-organisms used for inoculation are not more than 5 passages removed from the original master seed-lot. Grow each of the bacterial strains separately as described in Table 0008.-1. Use buffered sodium chloride-peptone solution pH 7.0 or phosphate buffer solution pH 7.2 to make test suspensions. Use the suspensions within 2 h, or within 24 h if stored at 2-8 °C. As an alternative to preparing and then diluting a fresh suspension of vegetative cells of *Bacillus subtilis*, a stable spore suspension is prepared and then an appropriate volume of the spore suspension is used for test inoculation. The stable spore suspension may be maintained at 2-8 °C for a validated period of time.

— *Growth promotion*. Test each batch of ready-prepared medium and each batch of medium, prepared either from dehydrated medium or from the ingredients described. Inoculate plates of R2A agar separately with a small number (not more than 100 CFU) of the micro-organisms indicated in Table 0008.-1. Incubate under the conditions described in the table. Growth obtained must not differ by a factor greater than 2 from the calculated value for a standardised inoculum. For a freshly prepared inoculum, growth of the micro-organisms must be comparable to that obtained with a previously tested and approved batch of medium.

Table 0008.-1. – *Growth promotion of R2A agar*

Micro-organism	**Preparation of the test strain**	**Growth promotion**
Pseudomonas aeruginosa such as: ATCC 9027 NCIMB 8626 CIP 82.118 NBRC 13275	Casein soyabean digest agar or casein soyabean digest broth 30-35 °C 18-24 h	R2A agar ≤ 100 CFU 30-35 °C ≤ 3 days
Bacillus subtilis such as: ATCC 6633 NCIMB 8054 CIP 52.62 NBRC 3134	Casein soyabean digest agar or casein soyabean digest broth 30-35 °C 18-24 h	R2A agar ≤ 100 CFU 30-35 °C ≤ 3 days

Total organic carbon or oxidisable substances

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Carry out the test for total organic carbon (2.2.44) with a limit of 0.5 mg/L or alternatively the following test for oxidisable substances: to 100 mL add 10 mL of *dilute sulfuric acid R* and 0.1 mL of *0.02 M potassium permanganate* and boil for 5 min; the solution remains faintly pink.

Conductivity

Determine the conductivity off-line or in-line under the following conditions.

EQUIPMENT

Conductivity cell:

— electrodes of a suitable material such as stainless steel;

— cell constant: the cell constant is generally certified by the supplier and is subsequently verified at suitable intervals using a certified reference solution with a conductivity less than 1500 $\mu S \cdot cm^{-1}$ or by comparison with a cell having a certified cell constant; the cell constant is confirmed if the value found is within 2 per cent of the certified value, otherwise re-calibration must be performed.

Conductometer Accuracy of 0.1 $\mu S \cdot cm^{-1}$ or better at the lowest range.

System calibration (conductivity cell and conductometer):

— against one or more suitable certified reference solutions;

— accuracy: within 3 per cent of the measured conductivity plus 0.1 $\mu S \cdot cm^{-1}$.

Conductometer calibration Calibration is carried out for each range of measurement to be used, after disconnection of the conductivity cell, using certified precision resistors or equivalent devices with an uncertainty not greater than 0.1 per cent of the certified value.

If in-line conductivity cells cannot be dismantled, system calibration may be performed against a calibrated conductivity-measuring instrument with a conductivity cell placed close to the cell to be calibrated in the water flow.

Temperature measurement Tolerance ± 2 °C.

PROCEDURE

Measure the conductivity without temperature compensation, recording simultaneously the temperature. Temperature-compensated measurement may be performed after suitable validation.

The water to be examined meets the requirements if the measured conductivity at the recorded temperature is not greater than the value in Table 0008.-2.

Table 0008.-2. – *Temperature and conductivity requirements*

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Temperature (°C)	Conductivity ($\mu S \cdot cm^{-1}$)
0	2.4
10	3.6
20	4.3
25	5.1
30	5.4
40	6.5
50	7.1
60	8.1
70	9.1
75	9.7
80	9.7
90	9.7
100	10.2

For temperatures not listed in Table 0008.-2, calculate the maximal permitted conductivity by interpolation between the next lower and next higher data points in the table.

Elemental impurities

If purified water in bulk does not meet the requirement for conductivity prescribed for *Water for injections (0169)* in bulk, a risk assessment according to general chapter *5.20. Elemental impurities* is carried out. The risk assessment should consider the role of water in the manufacturing process, in particular when water is used in a process but is no longer present in the final product.

CHARACTERS

Appearance

Clear and colourless liquid.

TESTS

Nitrates

Maximum 0.2 ppm.

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Place 5 mL in a test-tube immersed in iced water, add 0.4 mL of a 100 g/L solution of *potassium chloride R*, 0.1 mL of *diphenylamine solution R* and, dropwise with shaking, 5 mL of *nitrogen-free sulfuric acid R*. Transfer the tube to a water-bath at 50 °C. After 15 min, any blue colour in the solution is not more intense than that in a reference solution prepared at the same time in the same manner using a mixture of 4.5 mL of *nitrate-free water R* and 0.5 mL of *nitrate standard solution (2 ppm NO_3) R*.

Aluminium (*2.4.17*)

Maximum 10 ppb, if intended for use in the manufacture of dialysis solutions.

Prescribed solution To 400 mL of the water to be examined add 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *distilled water R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *distilled water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *distilled water R*.

Bacterial endotoxins (*2.6.14*)

Less than 0.25 IU/mL, if intended for use in the manufacture of dialysis solutions without a further appropriate procedure for removal of bacterial endotoxins.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

PURIFIED WATER IN CONTAINERS

DEFINITION

Purified water in bulk that has been filled and stored in conditions designed to assure the required microbiological quality. It is free from any added substances.

CHARACTERS

Appearance

Clear and colourless liquid.

TESTS

It complies with the tests prescribed in the section on Purified water in bulk and with the following additional tests.

Acidity or alkalinity

To 10 mL, freshly boiled and cooled in a borosilicate glass flask, add 0.05 mL of *methyl red solution R*. The solution is not coloured red.

To 10 mL add 0.1 mL of *bromothymol blue solution R1*. The solution is not coloured blue.

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Oxidisable substances

To 100 mL add 10 mL of *dilute sulfuric acid R* and 0.1 mL of *0.02 M potassium permanganate* and boil for 5 min. The solution remains faintly pink.

Chlorides

To 10 mL add 1 mL of *dilute nitric acid R* and 0.2 mL of *silver nitrate solution R2*. The solution shows no change in appearance for at least 15 min.

Sulfates

To 10 mL add 0.1 mL of *dilute hydrochloric acid R* and 0.1 mL of *barium chloride solution R1*. The solution shows no change in appearance for at least 1 h.

Ammonium

Maximum 0.2 ppm.

To 20 mL add 1 mL of *alkaline potassium tetraiodomercurate solution R*. After 5 min, examine the solution down the vertical axis of the tube. The solution is not more intensely coloured than a standard prepared at the same time by adding 1 mL of *alkaline potassium tetraiodomercurate solution R* to a mixture of 4 mL of *ammonium standard solution (1 ppm NH_4) R* and 16 mL of *ammonium-free water R*.

Calcium and magnesium

To 100 mL add 2 mL of *ammonium chloride buffer solution pH 10.0 R*, 50 mg of *mordant black 11 triturate R* and 0.5 mL of *0.01 M sodium edetate*. A pure blue colour is produced.

Residue on evaporation

Maximum 0.001 per cent.

Evaporate 100 mL to dryness on a water-bath and dry in an oven at 100-105 °C. The residue weighs a maximum of 1 mg.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/mL (*2.6.12*). Use casein soya bean digest agar.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

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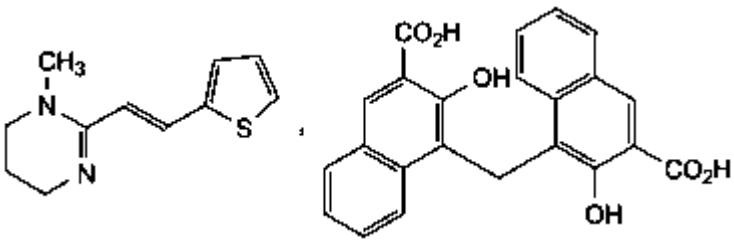
Pyrantel Embonate

General Notices

(Ph. Eur. monograph 1680)



$C_{34}H_{30}N_2O_6S$ 594.7 *22204-24-6*

Action and use

Anthelminthic.

Ph Eur

DEFINITION

1-Methyl-2-[(*E*)-2-(thiophen-2-yl)eth-1-en-1-yl]-1,4,5,6-tetrahydropyrimidine hydrogen 4,4′-methylenebis(3-hydroxynaphthalene-2-carboxylate).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow or yellow powder.

Solubility

Practically insoluble in water, soluble in dimethyl sulfoxide, practically insoluble in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *pyrantel embonate CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use and protect from light.*

Solvent mixture Mix 5 volumes of *glacial acetic acid R* and 5 volumes of *water for chromatography R*, then add 2 volumes of *diethylamine R* with cooling.

Test solution (a) Dissolve 0.800 g of the substance to be examined in 7 mL of the solvent mixture and dilute to 100.0 mL with *acetonitrile R*.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *pyrantel impurity A CRS* in the solvent mixture, add 2.5 mL of test solution (b) and dilute to 50 mL with the solvent mixture. Dilute 2 mL of this solution to 100 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (b) to 200.0 mL with the mobile phase.

Reference solution (c) Dissolve 8.0 mg of *pyrantel impurity D CRS* in *acetonitrile R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *acetonitrile R*.

Reference solution (d) Dissolve 8.0 mg of *pyrantel impurity C CRS* in *acetonitrile R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Solvent mixture, *acetonitrile for chromatography R* (72:928 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 288 nm and, for impurity D, at 238 nm.

Injection 20 µL of test solution (b) and reference solutions (a), (b) and (d); for impurity D, 50 µL of test solution (a) and reference solution (c).

Run time 4 times the retention time of pyrantel.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

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Relative retention With reference to pyrantel (retention time = about 11 min): impurity C = about 0.3; embonic acid = about 0.5; impurity A = about 1.3; impurity D = about 2.2.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to pyrantel and impurity A.

Calculation of percentage contents:

— for impurity D, use the concentration of impurity D in reference solution (c);

— for impurity C, use the concentration of impurity C in reference solution (d);

— for impurities other than C and D, use the concentration of pyrantel embonate in reference solution (b).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *impurity C*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than C and D (excluding embonic acid)*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 360 ppm.

To 0.46 g add 10 mL of *dilute nitric acid R* and 30 mL of *water R*. Heat on a water-bath for 5 min. Cool, dilute to 50 mL with *water R*, mix well and filter.

Sulfates (2.4.13)

Maximum 0.1 per cent.

To 0.50 g add 2.5 mL of *dilute nitric acid R* and dilute to 50 mL with *distilled water R*. Heat on a water-bath for 5 min, shake for 2 min, cool and filter.

Iron (2.4.9)

Maximum 75 ppm.

Ignite 0.66 g at 800 ± 50 °C for 2 h. Dissolve the residue in 2.5 mL of *dilute hydrochloric acid R* with gentle heating for 10 min. Cool and dilute to 50 mL with *water R*.

Loss on drying (2.2.32)

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Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.450 g add 10 mL of *acetic anhydride R* and 50 mL of *glacial acetic acid R*, heat at 50 °C and stir for 10 min. Allow to cool (a clear solution is not obtained). Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 59.47 mg of $C_{34}H_{30}N_2O_6S$.

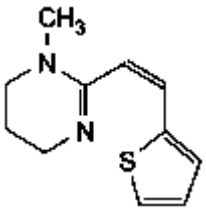
STORAGE

Protected from light.

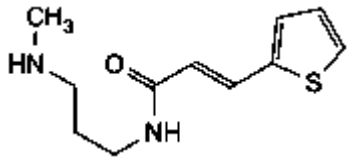
IMPURITIES

Specified impurities C, D.

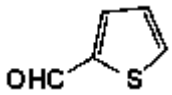
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



A. 1-methyl-2-[(*Z*)-2-(thiophen-2-yl)eth-1-en-1-yl]-1,4,5,6-tetrahydropyrimidine,



B. (*E*)-*N*-[3-(methylamino)propyl]-3-(thiophen-2-yl)prop-2-enamide,



C. thiophene-2-carbaldehyde,

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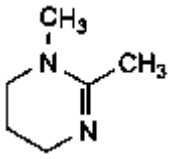

D. 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine.

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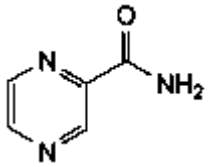
Pyrazinamide

General Notices

(Ph. Eur. monograph 0859)



$C_5H_5N_3O$ 123.1 *98-96-4*

Action and use

Antituberculosis drug.

Preparations

Pyrazinamide Oral Suspension

Pyrazinamide Tablets

Ph Eur

DEFINITION

Pyrazine-2-carboxamide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

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IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 188 °C to 191 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution (a) Dissolve 50.0 mg in *water R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *water R*.

Test solution (c) Dilute 2.0 mL of test solution (a) to 100.0 mL with *water R*.

Spectral range 290-350 nm for test solution (b); 230-290 nm for test solution (c).

Absorption maxima At 310 nm for test solution (b); at 268 nm for test solution (c).

Specific absorbance at the absorption maximum at 268 nm 640 to 680 for test solution (c).

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *pyrazinamide CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *ethanol (96 per cent) R*, evaporate to dryness and record new spectra using the residues.

D. Dissolve 0.1 g in 5 mL of *water R*. Add 1 mL of ferrous sulfate solution R2. The solution becomes orange. Add 1 mL of *dilute sodium hydroxide solution R*. The solution becomes dark blue.

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 25 mL of solution S add 0.05 mL of *phenolphthalein solution R1* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is red. Add 1.0 mL of *0.01 M hydrochloric acid*. The solution is colourless. Add 0.15 mL of *methyl red solution R*. The solution is red.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

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Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent. Dilute 5.0 mL of the solution to 25.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 10 mg of *pyrazine-2-carbonitrile R* (impurity B) in *water R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *water R*. To 5.0 mL of this solution add 5.0 mL of the test solution and dilute to 25.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Dissolve 6.80 g of *potassium dihydrogen phosphate R* in 800 mL of *water R*, add 1.84 g of *sodium hydroxide R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*; add 10.0 mL of *acetonitrile R* and 1.0 mL of *tetrahydrofuran R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 40 µL.

Run time 4 times the retention time of pyrazinamide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to pyrazinamide (retention time = about 5 min): impurity B = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to pyrazinamide and impurity B.

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 2.00 g.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

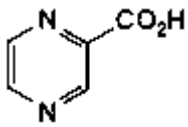
Dissolve 0.100 g in 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 12.31 mg of $C_5H_5N_3O$.

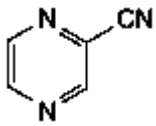
IMPURITIES

Specified impurities B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



A. pyrazine-2-carboxylic acid,



B. pyrazine-2-carbonitrile.

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Pyrazinamide Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Antituberculosis drug.

DEFINITION

Pyrazinamide Oral Suspension is a suspension containing Pyrazinamide in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of pyrazinamide, $C_5H_5N_3O$

95.0 to 105.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. Shake a quantity of the oral suspension containing 0.5 g of Pyrazinamide with 20 mL of *methanol* for 15 minutes, filter (Whatman GF/C is suitable) and evaporate the filtrate to dryness under a stream of nitrogen. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pyrazinamide (*RS 438*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.0, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions, using 900 mL of *water* as the dissolution medium and rotating the paddle at 50 revolutions per minute. Use a volume of the oral suspension containing one dose.

Related substances

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Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the oral suspension containing 0.1 g of Pyrazinamide with 50 mL of a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane*, filter, evaporate to dryness and dissolve the residue in sufficient of the same solvent mixture to produce 10 mL.

(2) Dilute 1 volume of solution (1) to 500 volumes with a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane*.

(3) Dissolve 10 mg of *nicotinic acid EPCRS* in a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane*, add 1 mL of solution (1) and dilute to 10 mL with the same solvent mixture.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, allow it to dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense that the spot in the chromatogram obtained with solution (2) (0.2%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the oral suspension containing 50 mg of Pyrazinamide add sufficient *absolute ethanol* to produce 50 mL, shake and centrifuge. Dilute 2 volumes of the solution to 10 volumes with the mobile phase and further dilute 1 volume to 10 volumes with the mobile phase.

(2) 0.002% w/v of *pyrazinamide BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 10 µL of each solution.

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MOBILE PHASE

5 volumes of *absolute ethanol* and 95 volumes of *hexane*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_5H_5N_3O$, weight in volume, using the declared content of $C_5H_5N_3O$ in *pyrazinamide BPCRS*.

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Pyrazinamide Tablets

General Notices

Action and use

Antituberculosis drug.

DEFINITION

Pyrazinamide Tablets contain Pyrazinamide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pyrazinamide, $C_5H_5N_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.25 g of Pyrazinamide with 20 mL of *absolute ethanol*, filter, evaporate the filtrate to dryness and dry the residue at 105° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pyrazinamide (*RS 306*).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.10 g of Pyrazinamide with 50 mL of a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*, filter, evaporate to dryness and dissolve the residue in sufficient of the same solvent mixture to produce 10 mL.
(2) Dilute 1 volume of solution (1) to 500 volumes with a mixture of 1 volume of *methanol* and 9 volumes of *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 10 cm.
(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

LIMITS

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Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.1 g of Pyrazinamide add 200 mL of *water*, allow to stand for 10 minutes, swirling occasionally, mix with the aid of ultrasound for 10 minutes and dilute to 500 mL with *water*. Filter and discard the first 20 mL of filtrate. Dilute 5 mL of the filtrate to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 268 nm, Appendix II B. Calculate the content of $C_5H_5N_3O$ taking 650 as the value of A(1%, 1 cm) at the maximum at 268 nm.

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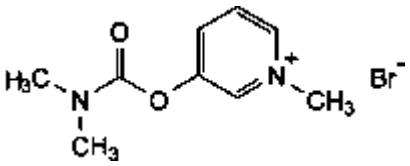
Pyridostigmine Bromide

General Notices

(Ph. Eur. monograph 1255)



$C_9H_{13}BrN_2O_2$ 261.1 *101-26-8*

Action and use

Cholinesterase inhibitor.

Preparation

Pyridostigmine Tablets

Ph Eur

DEFINITION

3-[(Dimethylcarbamoyl)oxy]-1-methylpyridinium bromide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline, deliquescent powder.

Solubility

Very soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *pyridostigmine bromide CRS*.

B. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 40 mL of solution S add a few drops of *methyl red solution R*. To 20 mL of this solution add 0.2 mL of *0.02 M sodium hydroxide*. The solution is yellow. To the other 20 mL add 0.2 mL of *0.02 M hydrochloric acid*. The solution is red.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase at about 40 °C. Allow to cool and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 4 mg of *pyridostigmine bromide CRS*, 4 mg of *pyridostigmine impurity A CRS* and 4 mg of *pyridostigmine impurity B CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase Mix 30 volumes of *acetonitrile R* and 70 volumes of a 4.33 g/L solution of *sodium dodecyl sulfate R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate 1.1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

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Run time Twice the retention time of pyridostigmine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B.

Relative retention With reference to pyridostigmine (retention time = about 32 min): impurity B = about 0.7; impurity A = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity A and pyridostigmine.

Limits:

— *impurities A, B*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent); at most one such peak has an area greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peak due to the bromide ion.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.230 g in 10 mL of *anhydrous acetic acid R*. Add 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 26.11 mg of $C_9H_{13}BrN_2O_2$.

STORAGE

In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container, protected from light.

IMPURITIES

Specified impurities *A, B.*

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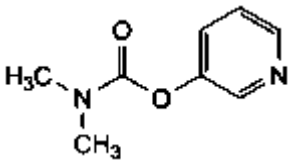
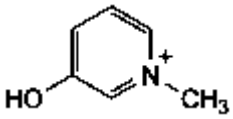


A. pyridin-3-yl dimethylcarbamate,



B. 3-hydroxy-1-methylpyridinium.

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Pyridostigmine Tablets

General Notices

Action and use

Cholinesterase inhibitor.

DEFINITION

Pyridostigmine Tablets contain Pyridostigmine Bromide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pyridostigmine bromide, $C_9H_{13}BrN_2O_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Triturate a quantity of the powdered tablets containing 0.1 g of Pyridostigmine Bromide with two 5 mL quantities of *water* and filter. Dilute the filtrate with *water* to contain 0.005% w/v of Pyridostigmine Bromide. The *light absorption* of the resulting solution, Appendix II B, exhibits a maximum at 270 nm. Reserve the filtrate for use in tests B and C.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute 1 volume of the filtrate obtained in test A to 10 volumes with *methanol*.

(2) 0.1% w/v of *pyridostigmine bromide EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 20 cm.

(e) After removal of the plate, dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

5 volumes of *water*, 10 volumes of *formic acid,* 35 volumes of *methanol* and 50 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. The filtrate obtained in test A yields the reactions characteristic of *bromides*, Appendix VI.

TESTS

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 0.1 g of Pyridostigmine Bromide with 100 mL of a mixture of 30 volumes of *acetonitrile* and 70 volumes of *water* for 30 minutes and filter through a glass fibre filter (Whatman GF/C is suitable).

(2) Dilute 6 volumes of solution (1) to 100 volumes with a mixture of 30 volumes of *acetonitrile* and 70 volumes of *water*.

(3) Dilute 1 volume of solution (1) to 250 volumes with a mixture of 30 volumes of *acetonitrile* and 70 volumes of *water*.

(4) 0.0005% w/v each of *pyridostigmine impurity A EPCRS* and *pyridostigmine bromide EPCRS* in the mobile phase.

(5) Dilute 1 volume of solution (3) to 10 volumes with a mixture of 30 volumes of *acetonitrile* and 70 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to continue for at least twice the retention time of the peak due to Pyridostigmine.

MOBILE PHASE

30 volumes of *acetonitrile* and 70 volumes of a 0.43% w/v solution of *sodium dodecyl sulfate*, previously adjusted to pH 2.0 with *orthophosphoric acid*.

Use the chromatogram obtained with solution (4) to identify the peak due to impurity A. When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to pyridostigmine (retention time = about 32 minutes) are: impurity B = about 0.75; impurity A = about 0.92.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to pyridostigmine impurity A and pyridostigmine bromide is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to pyridostigmine impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (6%);

the area of any peak corresponding to pyridostigmine impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.4%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.4%).

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Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.04%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing 0.15 g of Pyridostigmine Bromide with 50 mL of *water* for 30 minutes, filter, wash the residue with *water* and add sufficient *water* to produce 250 mL. Dilute 5 mL to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 270 nm, Appendix II B. Calculate the content of $C_9H_{13}BrN_2O_2$ taking 186 as the value of A(1%, 1 cm) at the maximum at 270 nm.

STORAGE

Pyridostigmine Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed under Pyridostigmine Bromide.

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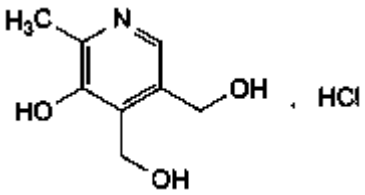
Pyridoxine Hydrochloride

General Notices

(Ph. Eur. monograph 0245)



$C_8H_{12}ClNO_3$ 205.6 *58-56-0*

Action and use

Vitamin B6.

Preparations

Pyridoxine Tablets

Vitamins B and C Injection

When vitamin B_6 is prescribed or demanded, Pyridoxine Hydrochloride shall be dispensed or supplied.

Ph Eur

DEFINITION

(5-Hydroxy-6-methylpyridine-3,4-diyl)dimethanol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

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mp

About 205 °C, with decomposition.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Solution A Dilute 1.0 mL of solution S (see Tests) to 50.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Solution B Dilute 1.0 mL of solution A to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Solution C Dilute 1.0 mL of solution A to 100.0 mL with the potassium dihydrogen phosphate 0.025 M + disodium hydrogen phosphate 0.025 M solution described in general chapter *2.2.3*.

Spectral ranges 250-350 nm for solution B; 220-350 nm for solution C.

Absorption maxima 288-296 nm for solution B; 248-256 nm and 320-327 nm for solution C.

Specific absorbances at the absorption maxima:

— 425 to 445 for solution B at 288-296 nm;

— 175 to 195 for solution C at 248-256 nm;

— 345 to 365 for solution C at 320-327 nm.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pyridoxine hydrochloride CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 10 mL with *water R*.

Reference solution Dissolve 0.10 g of *pyridoxine hydrochloride CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methylene chloride R*, *tetrahydrofuran R*, *acetone R* (9:13:13:65 *V/V/V/V*).

Application 2 µL.

Development In an unsaturated tank, over a path of 15 cm.

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Drying In air.

Detection Spray with a 50 g/L solution of *sodium carbonate R* in a mixture of 30 volumes of *ethanol (96 per cent) R* and 70 volumes of *water R*; dry in a current of air, spray with a 1 g/L solution of *dichloroquinonechlorimide R* in *ethanol (96 per cent) R* and examine immediately.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Solution S gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

2.4 to 3.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 2.5 mg of *pyridoxine impurity A CRS* and 2.5 mg of *4-deoxypyridoxine hydrochloride R* (impurity B) in *water R* and dilute to 10 mL with the same solvent. Dilute 2 mL of the solution to 10 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 2.72 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

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Injection 5 µL.

Run time 2.5 times the retention time of pyridoxine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to pyridoxine (retention time = about 12 min): impurity A = about 1.7; impurity B = about 1.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for each impurity, use the concentration of pyridoxine hydrochloride in reference solution (a).

Limits:

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.150 g in 5 mL of *anhydrous formic acid R*. Add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 20.56 mg of $C_8H_{12}ClNO_3$.

STORAGE

Protected from light.

IMPURITIES

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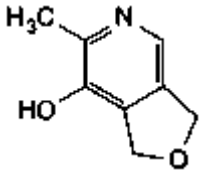
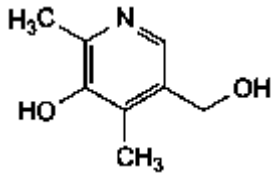
Specified impurities B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



A. 6-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-7-ol,



B. 5-(hydroxymethyl)-2,4-dimethylpyridin-3-ol.

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Pyridoxine Tablets

General Notices

Action and use

Vitamin B_6.

DEFINITION

Pyridoxine Tablets contain Pyridoxine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pyridoxine hydrochloride, $C_8H_{11}NO_3$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Pyridoxine Hydrochloride with 50 mL of 0.025M *standard phosphate buffer* for 15 minutes, dilute to 100 mL with the same solvent and filter. Dilute 5 mL of the filtrate to 100 mL with the same solvent. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 254 nm and 324 nm.
B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 290 nm, Appendix II B using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *pyridoxine hydrochloride BPCRS* in dissolution medium, at the maximum at 290 nm, Appendix II B using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of pyridoxine hydrochloride, $C_8H_{11}NO_3$,HCl in the medium using the declared content of $C_8H_{11}NO_3$,HCl in *pyridoxine hydrochloride BPCRS.*

LIMITS

The amount of pyridoxine hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Pyridoxine Hydrochloride with 15 mL of *water*, dilute to 20 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with *water*, dilute 1 volume of this solution to 5 volumes with *water*.
(3) 0.005% w/v each of *pyridoxine impurity A EPCRS* and *4-deoxypyridoxine hydrochloride* (impurity B).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography end-capped* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 210 nm.
(f) Inject 5 µL of each solution.
(g) Allow the chromatography to proceed for 3 times the retention time of pyridoxine.

MOBILE PHASE

0.272% w/v of *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *dilute orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to pyridoxine (retention time about 5 minutes) are: impurity A, about 1.7; impurity B, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

in the chromatogram obtained by solution (2), the *signal to noise ratio* of the principal peak is at least 20.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

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Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Pyridoxine Hydrochloride with 15 mL of *water*, dilute to 20 mL with *water* and filter. Dilute 1 volume of the filtrate to 25 volumes with *water*.

(2) 0.01% w/v of *pyridoxine hydrochloride BPCRS* in *water*.

(3) 0.005% w/v each of *pyridoxine impurity A EPCRS* and *4-deoxypyridoxine hydrochloride* (impurity B) in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used. Record the chromatograms for twice the retention time of Pyridoxine.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}NO_3$,HCl in the tablets using the declared content of $C_8H_{11}NO_3$,HCl in *pyridoxine hydrochloride BPCRS.*

STORAGE

Pyridoxine Tablets should be protected from light and stored at a temperature not exceeding 30°. When vitamin B_6 tablets are prescribed or demanded, Pyridoxine Tablets shall be dispensed or supplied.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Pyridoxine Hydrochloride.

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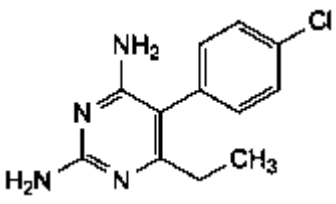
Pyrimethamine

General Notices

(Ph. Eur. monograph 0288)



$C_{12}H_{13}ClN_4$ 248.7 *58-14-0*

Action and use

Dihydrofolate reductase inhibitor; antiprotozoal (malaria).

Preparation

Pyrimethamine Tablets

Ph Eur

DEFINITION

5-(4-Chlorophenyl)-6-ethylpyrimidine-2,4-diamine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

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Second identification: A, C.

A. Melting point (2.2.14): 239 °C to 243 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *pyrimethamine CRS*.

C. Thin-layer chromatography (2.2.27).

Solvent mixture *methanol R*, *methylene chloride R* (10:90 *V/V*).

Test solution Dissolve 0.1 g of the substance to be examined in the solvent mixture and dilute to 100 mL with the solvent mixture.

Reference solution Dissolve 0.1 g of *pyrimethamine CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methylene chloride R*, *propanol R*, *glacial acetic acid R*, *toluene R* (4:8:12:76 *V/V/V/V*).

Application 20 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Shake 1.0 g with 50 mL of *carbon dioxide-free water R* for 2 min and filter.

Appearance of solution

Prepare the solution immediately before use Dissolve 0.25 g in a mixture of 1 volume of *methanol R* and 3 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents. The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink. Add 0.4 mL of *0.01 M hydrochloric acid* and 0.05 mL of *methyl red solution R*. The solution is red or orange.

Related substances

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Liquid chromatography (2.2.29).

Solvent mixture Mobile phase A, mobile phase B (50:50 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in 4 mL of the solvent mixture using sonication and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of the substance to be examined and 10 mg of *pyrimethamine impurity B CRS* in 50 mL of the solvent mixture using sonication and dilute to 100 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 2.72 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 8.0 with *ammonia R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	65	35
6 - 20	65 → 40	35 → 60
20 - 35	40 → 55	60 → 45

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to pyrimethamine (retention time = about 15 min): impurity B = about 0.8.

System suitability Reference solution (a):

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— *resolution*: minimum 5.0 between the peaks due to impurity B and pyrimethamine.

Calculation of percentage contents:

— for each impurity, use the concentration of pyrimethamine in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Sulfates (*2.4.13*)

Maximum 80 ppm, determined on solution S. Prepare the standard using a mixture of 2.5 mL of *sulfate standard solution (10 ppm SO_4) R* and 12.5 mL of *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 25 mL of *anhydrous acetic acid R* with gentle heating and allow to cool. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 24.87 mg of $C_{12}H_{13}ClN_4$.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.

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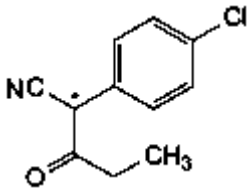
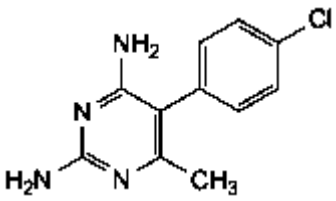
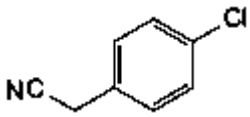


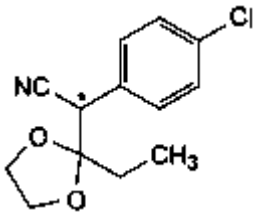
A. (2Ξ)-2-(4-chlorophenyl)-3-oxopentanenitrile,



B. 5-(4-chlorophenyl)-6-methylpyrimidine-2,4-diamine,



C. (4-chlorophenyl)acetonitrile,



D. (Ξ)-(4-chlorophenyl)(2-ethyl-1,3-dioxolan-2-yl)acetonitrile.

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Pyrimethamine Tablets

General Notices

Action and use

Dihydrofolate reductase inhibitor; antiprotozoal (malaria).

DEFINITION

Pyrimethamine Tablets contain Pyrimethamine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pyrimethamine, $C_{12}H_{13}ClN_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Pyrimethamine with 50 mL of *ethanol (96%)* for 20 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of pyrimethamine (*RS 309*).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and dilute with the dissolution medium, if necessary, to produce a solution expected to contain 0.0028% w/v of Pyrimethamine and measure the *absorbance* at the maximum at 273 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0028% w/v solution of *pyrimethamine BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of pyrimethamine, $C_{12}H_{13}ClN_4$, in the medium from the absorbances obtained and using the declared content of $C_{12}H_{13}ClN_4$, in *pyrimethamine BPCRS*.

LIMITS

The amount of pyrimethamine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solvent A Equal volumes of 0.17M *acetic acid* and *methanol*.

(1) Swirl a quantity of the tablets containing 0.25 g of Pyrimethamine with 150 mL of solvent A until disintegrated. Mix with the aid of ultrasound and add sufficient solvent A to produce 200 mL. Filter (Whatman GMF is suitable) and dilute 1 volume of the filtrate to 10 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase. Further dilute 1 volume to 10 volumes with mobile phase.

(3) 0.125% w/v of *pyrimethamine BPCRS* in 5.8M *sulfuric acid*. Boil 1 volume of the solution until reduced to approximately 0.5 volumes (*generation of impurities 1, 2 & 3*). The resulting solution should be clear and slightly yellow. Allow to cool and dilute 1 volume to 10 volumes with mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography (hybrid material)* (3.5 µm) (Zorbax Eclipse XDB-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 30 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of pyrimethamine.

MOBILE PHASE

45 volumes of methanol and 55 volumes of 0.005M *ammonium hydrogen carbonate*, adjusted to pH 9.3 with 0.74M *ammonia*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to pyrimethamine (retention time about 12 minutes) are; impurity A, about 0.1; impurity 1, about 0.3; impurity C, about 0.4; impurity 2, about 0.45; impurity B, about 0.5; impurity 3, about 0.6 and impurity D, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 1 and impurity 2 is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the area of all *secondary peaks* is not greater 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Use *solvent A* as prepared under Related Substances.

(1) Mix with the aid of ultrasound, a quantity of the powdered tablets containing 0.25 g of Pyrimethamine in 150 mL of solvent A and dilute with solvent A to produce 200 mL. Filter (Whatman GMF is suitable) and dilute 1 volume of the filtrate to 10 volumes with the mobile phase.
(2) 0.0125% w/v of *pyrimethamine BPCRS* in mobile phase.
(3) 0.125% w/v of *pyrimethamine BPCRS* in 5.8M *sulfuric acid*. Boil 1 volume of the solution until reduced to approximately 0.5 volumes (*generation of impurities 1, 2 & 3*). The resulting solution should be clear and slightly yellow. Allow to cool and dilute 1 volume to 10 volumes with mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

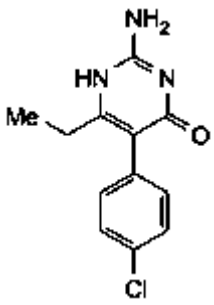
The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity 1 and impurity 2 is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of pyrimethamine, $C_{12}H_{13}ClN_4$, in the tablets using the declared content of $C_{12}H_{13}ClN_4$, in *pyrimethamine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Pyrimethamine* and:



1. 2-amino-5-(4-chlorophenyl)-6-ethyl-1,4-dihydropyrimidin-4-one

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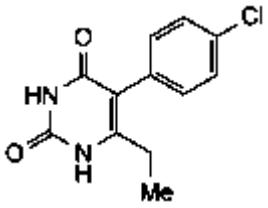
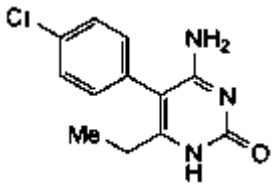


2. 5-(4-chlorophenyl)-6-ethyl-1,2,3,4-tetrahydropyrimidin-2,4-dione



3. 4-amino-5-(4-chlorophenyl)-6-ethyl-1,2-dihydropyrimidin-2-one

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Pyroxylin

General Notices

Cellulose Nitrate

Preparation

Flexible Collodion

DEFINITION

Pyroxylin is a nitrated cellulose obtained by the action of a mixture of nitric and sulfuric acids on wood pulp or cotton linters that have been freed from fatty matter. It must be damped with not less than 25% by weight of Isopropyl Alcohol or of Industrial Methylated Spirit.

CAUTION *Compliance is required with the provisions of relevant legislation relating to the storage of, use of and containers used for Pyroxylin*.

In the following tests, particular care should be exercised when drying pyroxylin. The material so obtained is explosive and sensitive to ignition by impact or friction and it should be handled as carefully as possible.

CHARACTERISTICS

White or almost white, cuboid granules or fibrous material, the latter resembling absorbent cotton but harsher to the touch and more powdery. Both the granules and the fibrous material appear moist. Highly flammable.

Soluble in *glacial acetic acid* and in *acetone*.

IDENTIFICATION

Add *water* to a solution in *acetone*. A white, viscid mass is readily precipitated.

TESTS

Clarity and colour of solution

A 10% w/v solution dissolves at 20° in a mixture of 1 volume of *ethanol (90%)* and 3 volumes of *ether* to produce an almost clear and colourless to pale straw-coloured solution.

Kinematic viscosity

1160 to 2900 mm^2s^{-1} when determined in the following manner. To 20 g, previously dried to constant weight by heating on a water-bath at 80° and allowing to cool in a desiccator over *silica gel*, add 200 mL of a mixture of 19 volumes of *acetone* and 1 volume of *water*. Shake

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vigorously to prevent the formation of aggregates of partly solvated pyroxylin and rotate suitably to obtain a homogeneous solution. Measure the viscosity of the solution within 48 hours using a falling sphere viscometer complying with British Standard 188: 1977 (Methods for the determination of viscosity of liquids). Fill the fall tube with the solution being examined to about 10 mm above the 220-mm mark, place vertically in the bath and allow to stand for air bubbles to clear and for temperature equilibrium to be attained. Clean the sphere, immerse it in a portion of the liquid being examined maintained at a temperature of 19.9° to 20.1° and when it is at this temperature introduce it, without wiping, into the delivery tube. Observe the time for the lowest part of the sphere to pass through the planes of the tops of the 175-mm mark and the 25-mm mark, using a telescope or other suitable device to avoid errors due to parallax. The average of three readings concordant to within 0.5% is taken as the time of fall. Calculate the kinematic viscosity (v) in square millimetres per second (mm^2s^{-1}) from the expression:

$$\nu = \frac{d^2 g(\delta - \rho)}{0.18 v \rho} \times 0.867$$

where d = the diameter of the sphere in cm,

δ = density of the sphere in g cm^{-3},

ρ = density of the liquid being tested in g cm^{-3},

v = velocity of fall in cm s^{-1},

g = local acceleration due to gravity in cm s^{-2}.

Nitrogen

11.7 to 12.2%, calculated with reference to the material dried to constant weight by heating on a water-bath at 80° and allowing to cool in a desiccator over silica gel, when determined by the following method. Transfer 0.4 g of the dried substance to a 750 mL round-bottomed flask using 60 mL of *water*, add 20 mL of *hydrogen peroxide solution (20 vol)* and then add slowly, with shaking, 50 mL of a 30% w/w solution of *potassium hydroxide* and 5 mL of *ethanol (96%)*. Agitate slowly for 3 hours or until the substance being examined has dissolved. Add 3 g of *Devarda's alloy* and immediately connect the flask to the spray trap of an ammonia-distillation apparatus, the receiver of which contains 50 mL of *0.1M hydrochloric acid VS* and 0.15 mL of *methyl red solution*. Allow the reaction to proceed until no further evolution of gas occurs and then heat the contents of the flask to boiling and distil carefully until 30 mL remains in the round-bottomed flask. Rinse the delivery tube into the receiver with *water* and titrate the combined distillate and rinsings with *0.1M sodium hydroxide VS*. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of acid required to neutralise the ammonia formed. Each mL of *0.1M hydrochloric acid VS* is equivalent to 1.401 mg of nitrogen.

STORAGE

Pyroxylin should be loosely packed, protected from light and stored at a temperature not exceeding 15°, remote from fire. The container should be suitably designed to disrupt should the internal pressure reach or exceed 1400 kPa. The amount of damping fluid must not be allowed to fall below 25% w/w; should this happen, the material should be either rewetted or used immediately for the preparation of Collodion.

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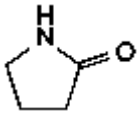
Pyrrolidone

General Notices

(Ph. Eur. monograph 2180)



C_4H_7NO 85.1 *616-45-5*

Ph Eur

DEFINITION

Pyrrolidin-2-one.

CHARACTERS

Appearance

Clear, colourless or slightly greyish liquid, or white or almost white crystals, or colourless crystal needles.

Solubility

Miscible with water, with ethanol (96 per cent) and with most common organic solvents.

mp

About 25 °C; the molten substance remains liquid at temperatures below the melting point.

bp

About 245 °C.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *pyrrolidone CRS*.

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B. Relative density (2.2.5): 1.112 to 1.115.

C. Refractive index (2.2.6): 1.487 to 1.490.

TESTS

Use the molten substance for all tests.

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than intensity 7 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

Alkalinity

To 100 mL of water R add 1.0 mL of bromothymol blue solution R1 and adjust to a green colour with 0.02 M potassium hydroxide or 0.02 M hydrochloric acid. To 50 mL of this solution add 20 mL of the substance to be examined and titrate with 0.02 M hydrochloric acid to the initial colour. Not more than 8.0 mL of 0.02 M hydrochloric acid is required.

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution The substance to be examined.

Reference solution (a) Dissolve 1 mL of the substance to be examined and 1 mL of N-methylpyrrolidone R (impurity C) in methylene chloride R and dilute to 20 mL with the same solvent.

Reference solution (b) Dissolve 1.1 g of the substance to be examined in methylene chloride R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 20.0 mL with methylene chloride R.

Reference solution (c) Dissolve 1 mL of butyrolactone R (impurity B) and 1 mL of butane-1,4-diol R (impurity A) in methylene chloride R and dilute to 20 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: methylpolysiloxane R (film thickness 5 µm).

Carrier gas nitrogen for chromatography R.

Flow rate 1.3 mL/min.

Split ratio 1:80.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 18.75	100 → 250
	18.75 - 30	250
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 0.1 µL.

Relative retention With reference to pyrrolidone (retention time = about 13 min): impurity B = about 0.73; impurity A = about 0.76; impurity C = about 0.97.

Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity C and pyrrolidone.

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurities A, C*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.7 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

STORAGE

Protected from light.

IMPURITIES

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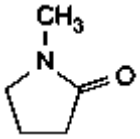
Specified impurities *A, B, C.*

A. butane-1,4-diol,

B. dihydrofuran-2(3*H*)-one (γ-butyrolactone),



C. 1-methylpyrrolidin-2-one (*N*-methylpyrrolidone).

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Quinine Sulfate Tablets

General Notices

Quinine Sulphate Tablets

Action and use

Antiprotozoal (malaria).

DEFINITION

Quinine Sulfate Tablets contain Quinine Sulfate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of quinine sulfate, $(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of *diethylamine*, 20 volumes of *acetone* and 80 volumes of *toluene* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) remove any coating from the tablets and extract a quantity of the powdered tablet cores containing 0.1 g of Quinine Sulfate with 10 mL of a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*) and filter. Solution (2) contains 1.0% w/v of *quinine sulfate BPCRS* in a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*). Solution (3) contains 1.0% w/v each of *quinidine sulfate BPCRS* and *quinine sulfate BPCRS*. After removal of the plate, allow it to dry in air and spray with 0.05M *ethanolic sulfuric acid* and then with *dilute potassium iodobismuthate solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

B. Extract a quantity of the powdered tablets containing 0.25 g of Quinine Sulfate with 25 mL of a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*) and filter. Evaporate the filtrate to dryness and wash the residue with 10 mL of *ether*. Filter and wash the residue with 10 mL of *ether*. Dry the residue at 60° at a pressure not exceeding 15 Pa for 2 hours. The pH of a 1% w/v suspension of the residue is 5.7 to 6.6, Appendix V L.

C. Extract a quantity of the powdered tablets containing 0.1 g of Quinine Sulfate with 20 mL of *water* and filter. The filtrate yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Dissolution

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Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *0.1M hydrochloric acid* and rotating the basket at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium. Measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted if necessary, at the maximum at 348 nm, Appendix II B. Calculate the total content of quinine sulfate, $(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$, in the medium taking 136 as the value of A(1%, 1 cm) at the maximum at 348 nm.

Other cinchona alkaloids

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) remove any coating from the tablets and mix a quantity of the powdered tablet cores containing 50 mg of Quinine Sulfate with 20 mL of the mobile phase. Heat gently to dissolve the powder as completely as possible, cool, dilute to 25 mL with the mobile phase and filter, discarding the first few mL of the filtrate. For solution (2) dissolve 20 mg of *quinine sulfate BPCRS*, with gentle heating if necessary, in 5 mL of the mobile phase and dilute to 10 mL with the mobile phase. Prepare solution (3) in the same manner as solution (2) using *quinidine sulfate BPCRS* in place of *quinine sulfate BPCRS*. Solution (4) is a mixture of equal volumes of solution (2) and solution (3). For solution (5) dilute 1 volume of solution (2) to 10 volumes with the mobile phase and dilute 1 volume of the resulting solution to 50 volumes with the mobile phase. Solution (6) contains 0.10% w/v of *thiourea* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 3.0 g of *hexylamine* in 700 mL of *water*, adjusting the pH to 2.8 with 1M *orthophosphoric acid*, adding 60 mL of *acetonitrile* and diluting to 1000 mL with *water* and (c) a detection wavelength of 250 nm for recording the chromatogram obtained with solution (6) and 316 nm for the other solutions.

Inject 10 µL of each of solutions (3) and (6). If necessary adjust the concentration of *acetonitrile* in the mobile phase so that in the chromatogram obtained with solution (3) the *capacity factor* of the peak due to quinidine is 3.5 to 4.5, V_0 being calculated from the peak due to thiourea in the chromatogram obtained with solution (6). Inject 10 µL of each of solutions (2), (3), (4) and (5). The chromatogram obtained with solution (2) shows a principal peak due to quinine and a peak due to dihydroquinine, with a retention time relative to quinine of about 1.4. The chromatogram obtained with solution (3) shows a principal peak due to quinidine and a peak due to dihydroquinidine, with a retention time relative to quinidine of about 1.2. The chromatogram obtained with solution (4) shows four peaks due to quinine, dihydroquinine, quinidine and dihydroquinidine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatogram obtained with solutions (2) and (3).

The test is not valid unless (a) in the chromatogram obtained with solution (4) the *resolution factor* between the peaks due to quinine and quinidine is at least 1.5 and the *resolution factor* between the peaks due to dihydroquinidine and quinine is at least 1.0 and (b) the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (5) is at least 5.

Inject 10 µL of solution (1) and record the chromatogram for 2.5 times the retention time of the principal peak. Calculate the percentage content of related substances by *normalisation*, disregarding any peaks the areas of which are less than that of the peak in the chromatogram obtained with solution (5) (0.2%). The content of dihydroquinine is not greater than 10%, the content of any related substance eluted before quinine is not greater than 5% and the content of any other related substance is not greater than 2.5%.

ASSAY

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Weigh and powder 20 tablets and dissolve as completely as possible, using heat, a quantity of the powdered tablets containing 0.4 g of Quinine Sulfate in 40 mL of *acetic anhydride*. Carry out Method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 26.10 mg of $(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$.

STORAGE

Quinine Sulfate Tablets that are not sugar-coated should be protected from light.

300 mg of Quinine Sulfate is approximately equivalent to 248.6 mg of anhydrous quinine.

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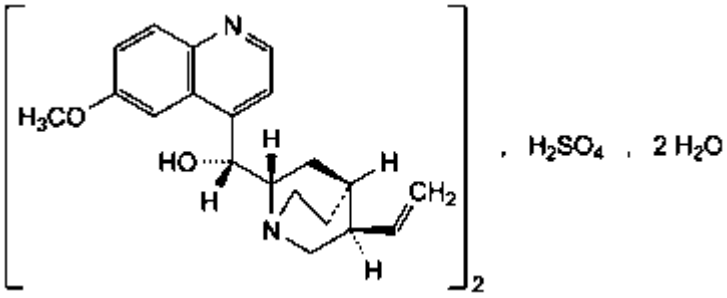
Quinine Sulfate

General Notices

Quinine Sulphate

(Ph. Eur. monograph 0019)



$C_{40}H_{50}N_4O_8S,2H_2O$ 783 *6119-70-6*

Action and use

Antiprotozoal (malaria).

Preparation

Quinine Sulfate Tablets

Ph Eur

DEFINITION

Alkaloid monosulfates, expressed as bis[(*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol] sulfate dihydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or fine, colourless needles.

Solubility

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Slightly soluble in water, sparingly soluble in boiling water and in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.10 g of *quinine sulfate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *diethylamine R*, *ether R*, *toluene R* (10:24:40 *V/V/V*).

Application 5 µL.

Development Twice over a path of 15 cm; dry in a current of air for 15 min between the 2 developments.

Drying At 105 °C for 30 min and allow to cool.

Detection Spray with *iodoplatinate reagent R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve about 5 mg in 5 mL of *water R*. Add 0.2 mL of *bromine water R* and 1 mL of *dilute ammonia R2*. A green colour develops.

C. Dissolve 0.1 g in 3 mL of *dilute sulfuric acid R* and dilute to 100 mL with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on the addition of 1 mL of *hydrochloric acid R*.

D. Dissolve about 45 mg in 5 mL of *dilute hydrochloric acid R*. The solution gives reaction (a) of sulfates (2.3.1).

E. pH (see Tests).

TESTS

Solution S

Dissolve 0.500 g in *0.1 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, *Method II*).

pH (2.2.3)

5.7 to 6.6 for a 10 g/L suspension in *water R*.

Specific optical rotation (2.2.7)

-237 to -245 (dried substance), determined on solution S.

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Other cinchona alkaloids

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 20 mg of the substance to be examined in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (a) Dissolve 20 mg of *quinine sulfate CRS* in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (b) Dissolve 20 mg of *quinidine sulfate CRS* (impurity A) in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (c) To 1 mL of reference solution (a) add 1 mL of reference solution (b).

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (e) Dissolve 10 mg of *thiourea R* in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.15-0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase Dissolve 6.8 g of *potassium dihydrogen phosphate R* and 3.0 g of *hexylamine R* in 700 mL of *water R*, adjust to pH 2.8 with *dilute phosphoric acid R*, add 60 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 250 nm for reference solution (e) and at 316 nm for the other solutions.

Injection 10 µL.

Run time 2.5 times the retention time of quinine.

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peaks due to quinine and impurity C; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurity A and dihydroquinidine; the chromatogram obtained with reference solution (c) shows 4 peaks due to impurity A, quinine, dihydroquinidine and impurity C which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with reference solutions (a) and (b).

Relative retention With reference to quinine: impurity C = about 1.4.

Relative retention With reference to impurity A: dihydroquinidine = about 1.5.

System suitability:

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— *resolution*: minimum 3.0 between the peaks due to quinine and impurity A and minimum 2.0 between the peaks due to dihydroquinidine and quinine in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 4 for the principal peak in the chromatogram obtained with reference solution (d);

— *mass distribution ratio*: 3.5 to 4.5 for the peak due to impurity A in the chromatogram obtained with reference solution (b), t_R, being calculated from the peak due to thiourea in the chromatogram obtained with reference solution (e); if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

— *impurity C*: maximum 10 per cent;

— *any impurity eluted before quinine*: for each impurity, maximum 5 per cent;

— *any other impurity*: for each impurity, maximum 2.5 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent).

Loss on drying (*2.2.32*)

3.0 per cent to 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

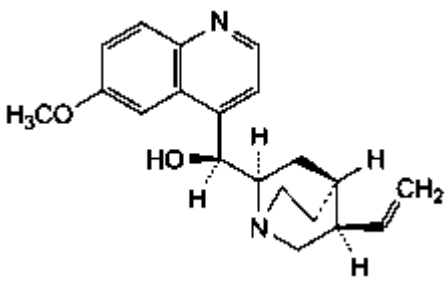
Dissolve 0.300 g in a mixture of 10 mL of *chloroform R* and 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 24.90 mg of $C_{40}H_{50}N_4O_8S$.

STORAGE

Protected from light.

IMPURITIES



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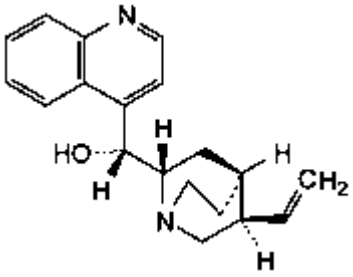
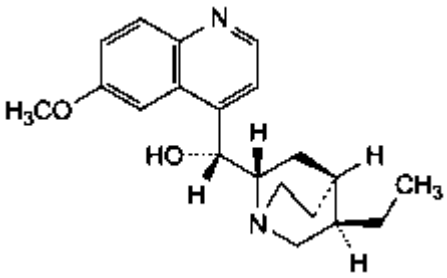
A. (*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine),



B. (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](quinolin-4-yl)methanol (cinchonidine),



C. (*R*)-[(2*S*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (dihydroquinine).

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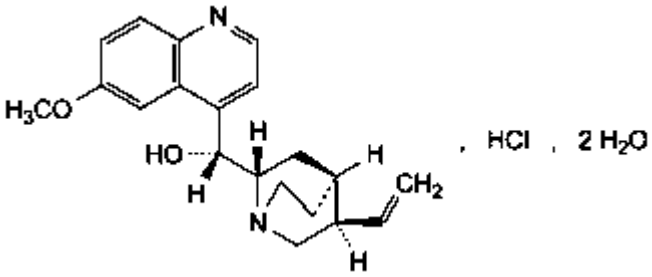
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Quinine Hydrochloride Dihydrate

General Notices

(Ph. Eur. monograph 0018)



$C_{20}H_{24}N_2O_2,HCl,2H_2O$ 396.9 *6119-47-7*

Action and use

Antiprotozoal (malaria).

Ph Eur

DEFINITION

Alkaloid monohydrochlorides, expressed as (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol hydrochloride dihydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white or colourless, fine, silky needles, often in clusters.

Solubility

Soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

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A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.10 g of quinine sulfate CRS in methanol R and dilute to 10 mL with the same solvent.

Plate TLC silica gel G plate R.

Mobile phase diethylamine R, ether R, toluene R (10:24:40 *V/V/V*).

Application 5 µL.

Development Twice over a path of 15 cm; dry in a current of air for 15 min between the 2 developments.

Drying At 105 °C for 30 min and allow to cool.

Detection Spray with iodoplatinate reagent R.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve about 10 mg in water R and dilute to 10 mL with the same solvent. To 5 mL of this solution add 0.2 mL of bromine water R and 1 mL of dilute ammonia R2. A green colour develops.

C. Dissolve 0.1 g in 3 mL of dilute sulfuric acid R and dilute to 100 mL with water R. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on the addition of 1 mL of hydrochloric acid R.

D. It gives reaction (a) of chlorides (2.3.1).

E. pH (see Tests).

TESTS

Solution S

Dissolve 1.0 g in carbon dioxide-free water R prepared from distilled water R and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

pH (2.2.3)

6.0 to 6.8.

Dilute 10 mL of solution S to 20 mL with carbon dioxide-free water R.

Specific optical rotation (2.2.7)

-258 to -245 (dried substance).

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Dissolve 0.500 g in *0.1 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Other cinchona alkaloids

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 20 mg of the substance to be examined in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (a) Dissolve 20 mg of *quinine sulfate CRS* in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (b) Dissolve 20 mg of *quinidine sulfate CRS* (impurity A) in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (c) To 1 mL of reference solution (a) add 1 mL of reference solution (b).

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (e) Dissolve 10 mg of *thiourea R* in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.15-0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase Dissolve 6.8 g of *potassium dihydrogen phosphate R* and 3.0 g of *hexylamine R* in 700 mL of *water R*, adjust to pH 2.8 with *dilute phosphoric acid R*, add 60 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 250 nm for reference solution (e) and at 316 nm for the other solutions.

Injection 10 µL.

Run time 2.5 times the retention time of quinine.

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peaks due to quinine and impurity C; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurity A and dihydroquinidine; the chromatogram obtained with reference solution (c) shows 4 peaks due to impurity A, quinine, dihydroquinidine and impurity C, which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with reference solutions (a) and (b).

Relative retention With reference to quinine: impurity C = about 1.4.

Relative retention With reference to impurity A: dihydroquinidine = about 1.5.

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System suitability:

— *resolution*: minimum 3.0 between the peaks due to quinine and impurity A and minimum 2.0 between the peaks due to dihydroquinidine and quinine in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 4 for the principal peak in the chromatogram obtained with reference solution (d);

— *mass distribution ratio*: 3.5 to 4.5 for the peak due to impurity A in the chromatogram obtained with reference solution (b), t_R, being calculated from the peak due to thiourea in the chromatogram obtained with reference solution (e); if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

— *impurity C*: maximum 10 per cent;

— *any impurity eluted before quinine*: for each impurity, maximum 5 per cent;

— *any other impurity*: for each impurity, maximum 2.5 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent).

Sulfates (*2.4.13*)

Maximum 500 ppm, determined on solution S.

Loss on drying (*2.2.32*)

6.0 per cent to 10.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 inflexion points.

1 mL of *0.1 M sodium hydroxide* is equivalent to 36.09 mg of $C_{20}H_{25}ClN_2O_2$

STORAGE

Protected from light.

IMPURITIES

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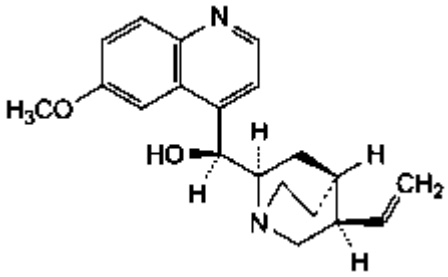
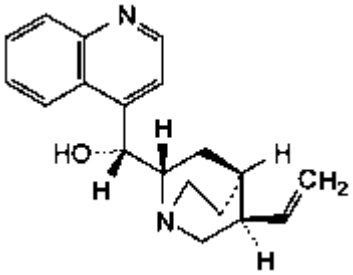
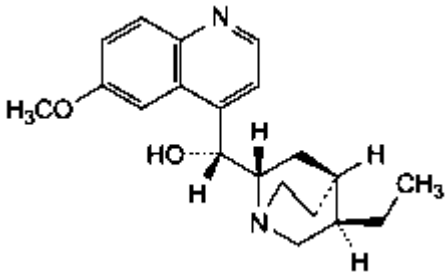


A. (*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine),



B. (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](quinolin-4-yl)methanol (cinchonidine),



C. (*R*)-[(2*S*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (dihydroquinine).

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Quinine Dihydrochloride Infusion

General Notices

Action and use

Antiprotozoal (malaria).

DEFINITION

Quinine Dihydrochloride Infusion is a sterile solution containing Quinine Dihydrochloride. It is prepared by diluting Quinine Dihydrochloride Sterile Concentrate with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations.

QUININE DIHYDROCHLORIDE STERILE CONCENTRATE

DEFINITION

Quinine Dihydrochloride Sterile Concentrate is a sterile solution of Quinine Hydrochloride in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of quinine dihydrochloride, $C_{20}H_{24}N_2O_2,2HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

An almost colourless to light yellow solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a volume of the concentrate containing 0.1 g of Quinine Dihydrochloride with 10 mL of a mixture of 1 volume of *ethanol (96%)* and 2 volumes of *chloroform* and filter.

(2) 1.0% w/v of *quinine sulfate BPCRS* in a mixture of 1 volume of *ethanol (96%)* and 2 volumes of *chloroform*.

(3) 1.0% w/v each of *quinidine sulfate BPCRS* and *quinine sulfate BPCRS* in a mixture of 1 volume of *ethanol (96%)* and 2 volumes of *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

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(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with 0.05M *ethanolic sulfuric acid* and then with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

10 volumes of *diethylamine*, 20 volumes of *acetone* and 80 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 1.5 to 3.0, Appendix V L.

Other cinchona alkaloids

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the concentrate being examined diluted, if necessary, with the mobile phase to produce a solution containing 0.2% w/v of Quinine Dihydrochloride.

(2) Dissolve 20 mg of *quinine sulfate BPCRS*, with gentle heating if necessary, in 5 mL of the mobile phase and dilute to 10 mL with the mobile phase.

(3) Prepare in the same manner as solution (2) but using *quinidine sulfate BPCRS* in place of *quinine sulfate BPCRS*.

(4) A mixture of equal volumes of solution (2) and solution (3).

(5) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase and dilute 1 volume of the resulting solution to 50 volumes with the mobile phase.

(6) 0.10% w/v of *thiourea* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 250 nm for recording the chromatogram obtained with solution (6) and 316 nm for the other solutions.

(f) Inject 10 µl of each solution.

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(g) Allow the chromatography to proceed for 2.5 times the retention time of the principal peak for solution (1).

MOBILE PHASE

Dissolve 6.8 g of *potassium dihydrogen orthophosphate* and 3.0 g of *hexylamine* in 700 mL of *water*, adjusting the pH to 2.8 with 1M *orthophosphoric acid*, adding 60 mL of *acetonitrile* and diluting to 1000 mL with *water*.

SYSTEM SUITABILITY

If necessary, adjust the concentration of *acetonitrile* in the mobile phase so that in the chromatogram obtained with solution (3) the *capacity factor* of the peak due to quinidine is 3.5 to 4.5, V_0 being calculated from the peak due to thiourea in the chromatogram obtained with solution (6). The chromatogram obtained with solution (2) shows a principal peak due to quinine and a peak due to dihydroquinine, with a retention time relative to quinine of about 1.4. The chromatogram obtained with solution (3) shows a principal peak due to quinidine and a peak, due to dihydroquinidine, with a retention time relative to quinidine of about 1.2. The chromatogram obtained with solution (4) shows four peaks due to quinine, dihydroquinine, quinidine and dihydroquinidine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with solutions (2) and (3).

The test is not valid unless:

in the chromatogram obtained with solution (4) the *resolution factor* between the peaks due to quinine and quinidine is at least 1.5 and the *resolution factor* between the peaks due to dihydroquinidine and quinine is at least 1.0;

in the chromatogram obtained with solution (5) the *signal-to-noise ratio* of the principal peak is at least 5.

LIMITS

In the chromatogram obtained with solution (1) calculate the percentage content of related substances by *normalization*:

the content of dihydroquinine is not greater than 10%;

the content of any related substance eluted before quinine is not greater than 5%;

the content of any other related substance is not greater than 2.5%.

Disregard any peaks the areas of which are less than that of the peak in the chromatogram obtained with solution (5) (0.2%).

ASSAY

To a volume containing 0.6 g of Quinine Dihydrochloride, add 20 mL of *water* and 5 mL of 5M *sodium hydroxide*, extract with three 25-mL quantities of *chloroform* and wash the combined extracts with 20 mL of *water*. Dry the chloroform extracts with *anhydrous sodium sulfate*, evaporate to dryness at a pressure of 2 kPa, dissolve the residue in 50 mL of *anhydrous acetic acid* and add 20 mL of *acetic anhydride*. Carry out method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 19.87 mg of $C_{20}H_{24}N_2O_2,2HCl$.

STORAGE

Quinine Dihydrochloride Sterile Concentrate should be protected from light.

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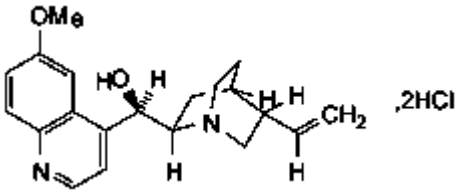
Quinine Dihydrochloride

General Notices



$C_{20}H_{24}N_2O_2,2HCl$ 397.3 *60-93-5*

Action and use

Antiprotozoal (malaria).

Preparation

Quinine Dihydrochloride Infusion

DEFINITION

Quinine Dihydrochloride is (8S,9R)-6′-methoxycinchonan-9-ol dihydrochloride. It contains not less than 99.0% and not more than 101.0% of alkaloid dihydrochlorides, calculated as $C_{20}H_{24}N_2O_2,2HCl$, with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder.

Very soluble in water; soluble in *ethanol (96%)*.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography* (*2.2.27*), Appendix III A, using the following solutions in *methanol*.

(1) 1.0% w/v of the substance being examined.

(2) 1.0% w/v of *quinine sulfate BPCRS*.

(3) 1.0% w/v each of *quinidine sulfate BPCRS* and *quinine sulfate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 4 µL of each solution.

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(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air for 15 minutes and repeat the development. Dry the plate at 105° for 30 minutes, allow to cool and spray with *iodoplatinate reagent*.

MOBILE PHASE

15 volumes of *diethylamine*, 36 volumes of *ether* and 60 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. Complies with the test for Acidity.

C. Yields reaction A characteristic of *chlorides*, (*2.3.1*) Appendix VI.

TESTS

Acidity

pH of a 3% w/v solution, 2.0 to 3.0, Appendix V L.

Specific optical rotation (*2.2.7*)

In a 3% w/v solution in 0.1M *hydrochloric acid*, -223 to -229 calculated with reference to the dried substance, Appendix V F.

Barium

To 15 mL of a 2.0% w/v solution add 1 mL of 1M *sulfuric acid*. The solution remains clear for at least 15 minutes.

Sulfate (*2.4.13*)

0.125 g complies with *the limit test for sulfates*, Appendix VII (0.12%).

Other cinchona alkaloids

Carry out the method for *liquid chromatography* (*2.2.29*) Appendix III D, using the *normalisation procedure* and the following solutions in the mobile phase.

(1) Dissolve 20 mg of the substance being examined, with gentle heating if necessary, in 5 mL and dilute to 10 mL.

(2) Prepare as for solution (1) but using *quinine sulfate BPCRS* in place of the substance being examined.

(3) Prepare as for solution (1) but using *quinidine sulfate BPCRS* in place of the substance being examined.

(4) Mix equal volumes of solutions (2) and (3).

(5) Dilute 1 volume of solution (2) to 10 volumes and dilute 1 volume of the resulting solution to 50 volumes.

(6) 0.10% w/v of *thiourea*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 250 nm for recording the chromatogram obtained with solution (6) and a detection wavelength of 316 nm for the other solutions.

(f) Inject 10 µL of each solution. Inject separately 10 µL of each of solutions (3) and (6).

(g) For solution (1) allow the chromatography to proceed for 2.5 times the retention time of the principal peak.

MOBILE PHASE

Dissolve 6.8 g of *potassium dihydrogen orthophosphate* and 3.0 g of *hexylamine* in 700 mL of *water*, adjust to pH 2.8 with 1M *orthophosphoric acid*, add 60 mL of *acetonitrile* and dilute to 1000 mL with *water*. If necessary adjust the concentration of acetonitrile in the mobile phase so that in the chromatogram obtained with solution (3) the *capacity factor* of the peak due to quinidine is 3.5 to 4.5, V_O being calculated from the peak due to thiourea in the chromatogram obtained with solution (6).

SYSTEM SUITABILITY

The test is not valid unless (a) in the chromatogram obtained with solution (4) the *resolution* between the peaks due to quinine and quinidine is at least 1.5 and the *resolution* between the peaks due to dihydroquinidine and quinine is at least 1.0 and (b) the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (5) is at least 5.

The chromatogram obtained with solution (2) shows a principal peak due to quinidine and a peak due to dihydroquinine with a retention time relative to quinine of about 1.4. The chromatogram obtained with solution (3) shows a principal peak due to quinidine and a peak due to dihydroquinidine, with a retention time relative to quinidine of about 1.2. The chromatogram obtained with solution (4) shows four peaks due to quinine, dihydroquinine, quinidine and dihydroquinidine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with solutions (2) and (3).

LIMITS

In the chromatogram obtained with solution (1):

the content of dihydroquinine is not greater than 10%;

the content of any related substance eluting before quinine is not more than 5%;

the content of any other related substance is not more than 2.5%.

Disregard any peak with an area less than that of the peak in the chromatogram obtained with solution (5).

Loss on drying (*2.2.32*)

When dried to constant weight at 105°, loses not more than 3.0% of its weight. Use 1 g.

Sulfated ash (*2.4.14*)

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Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.150 g in a mixture of 10 mL of *water* and 50 mL of *ethanol*. Titrate with *0.1*M *sodium hydroxide*, determining the end-point potentiometrically, Appendix VIII B.

Each mL of *0.1*M *sodium hydroxide* is equivalent to 39.73 mg of $C_{20}H_{24}N_2O_2$,2HCl.

STORAGE

Quinine Dihydrochloride should be protected from light.

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Quinine Bisulfate Tablets

General Notices

Quinine Bisulphate Tablets

Action and use

Antiprotozoal (malaria).

DEFINITION

Quinine Bisulfate Tablets contain Quinine Bisulfate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of quinine bisulfate, $C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of *diethylamine*, 20 volumes of *acetone* and 80 volumes of *toluene* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) remove any coating from the tablets and extract a quantity of the powdered tablet cores containing 0.1 g of Quinine Bisulfate with 10 mL of a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*) and filter. Solution (2) contains 1.0% w/v of *quinine sulfate BPCRS* in a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*). Solution (3) contains 1.0% w/v each of *quinidine sulfate BPCRS* and *quinine sulfate BPCRS*. After removal of the plate, allow it to dry in air and spray with 0.05M *ethanolic sulfuric acid* and then with *dilute potassium iodobismuthate solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

B. Shake a quantity of the powdered tablets containing 0.25 g of Quinine Bisulfate with 25 mL of a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*65%*) and filter. Evaporate the filtrate to dryness and wash the residue with 10 mL of *ether*. Filter, wash the residue with 10 mL of *ether* and dry at 60° at a pressure not exceeding 15 Pa for 2 hours. The pH of a 1% w/v solution is 2.8 to 3.4, Appendix V L.

C. Extract a quantity of the powdered tablets containing 0.5 g of Quinine Bisulfate with 10 mL of *water* and filter. The filtrate yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Dissolution

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Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *0.1M hydrochloric acid* and rotating the basket at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium. Measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted if necessary, at the maximum at 348 nm, Appendix II B. Calculate the total content of quinine bisulfate, $C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$, in the medium taking 99 as the value of A(1%, 1 cm) at the maximum at 348 nm.

Other cinchona alkaloids

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) remove any coating from the tablets and mix a quantity of the powdered tablet cores containing 50 mg of Quinine Bisulfate with 20 mL of the mobile phase. Heat gently to dissolve the powder as completely as possible, cool, dilute to 25 mL with the mobile phase and filter, discarding the first few mL of the filtrate. For solution (2) dissolve 20 mg of *quinine sulfate BPCRS*, with gentle heating if necessary, in 5 mL of the mobile phase and dilute to 10 mL with the mobile phase. Prepare solution (3) in the same manner as solution (2) using *quinidine sulfate BPCRS* in place of *quinine sulfate BPCRS*. Solution (4) is a mixture of equal volumes of solutions (2) and (3). For solution (5) dilute 1 volume of solution (2) to 10 volumes with the mobile phase and dilute 1 volume of the resulting solution to 50 volumes with the mobile phase. Solution (6) contains 0.10% w/v of *thiourea* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 3.0 g of *hexylamine* in 700 mL of *water*, adjusting the pH to 2.8 with 1M *orthophosphoric acid*, adding 60 mL of *acetonitrile* and diluting to 1000 mL with *water* and (c) a detection wavelength of 250 nm for recording the chromatogram obtained with solution (6) and 316 nm for the other solutions.

Inject separately 10 µL of each of solutions (3) and (6). If necessary adjust the concentration of *acetonitrile* in the mobile phase so that in the chromatogram obtained with solution (3) the *capacity factor* of the peak due to quinidine is 3.5 to 4.5, V_0 being calculated from the peak due to thiourea in the chromatogram obtained with solution (6). Inject 10 µL of each of solutions (2), (3), (4) and (5). The chromatogram obtained with solution (2) shows a principal peak due to quinine and a peak due to dihydroquinine with a retention time relative to quinine of about 1.4. The chromatogram obtained with solution (3) shows a principal peak due to quinidine and a peak due to dihydroquinidine, with a retention time relative to quinidine of about 1.2. The chromatogram obtained with solution (4) shows four peaks due to quinine, dihydroquinine, quinidine and dihydroquinidine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with solutions (2) and (3).

The test is not valid unless (a) in the chromatogram obtained with solution (4) the *resolution factor* between the peaks due to quinine and quinidine is at least 1.5 and the *resolution factor* between the peaks due to dihydroquinidine and quinine is at least 1.0 and (b) the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (5) is at least 5.

Inject 10 µL of solution (1) and allow the chromatography to proceed for 2.5 times the retention time of the principal peak. Calculate the percentage content of related substances by *normalisation*, disregarding any peaks the areas of which are less than that of the peak in the chromatogram obtained with solution (5) (0.2%). The content of dihydroquinine is not greater than 10%, the content of any related substance eluting before quinine is not greater than 5% and the content of any other related substance is not greater than 2.5%.

ASSAY

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Weigh and powder 20 tablets. Dissolve as completely as possible a quantity of the powdered tablets containing 0.6 g of Quinine Bisulfate in 40 mL of *acetic anhydride* using heat. Carry out Method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 54.86 mg of $C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$.

STORAGE

Quinine Bisulfate Tablets that are not sugar-coated should be protected from light.

300 mg of Quinine Bisulfate is approximately equivalent to 177.5 mg of anhydrous quinine.

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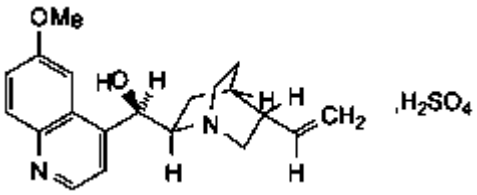
Quinine Bisulfate

General Notices

Quinine Bisulphate



$C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$ 548.6 *549-56-4*

Action and use

Antiprotozoal (malaria).

Preparation

Quinine Bisulfate Tablets

DEFINITION

Quinine Bisulfate is (8*S*,9*R*)-6′-methoxycinchonan-9-ol hydrogen sulfate heptahydrate. It contains not less than 98.5% and not more than 101.5% of alkaloid hydrogen sulfates, calculated as $C_{20}H_{24}N_2O_2,H_2SO_4$ with reference to the anhydrous substance.

CHARACTERISTICS

Colourless crystals or a white, crystalline powder; efflorescent in dry air.

Freely soluble in *water*; sparingly soluble in *ethanol (96%)*.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 15 volumes of *diethylamine*, 36 volumes of *ether* and 60 volumes of *toluene* as the mobile phase. Apply separately to the plate 4 µL of each of three solutions in *methanol* containing (1) 1.0% w/v of the substance being examined, (2) 1.0% w/v of *quinine sulfate BPCRS* and (3) 1.0% w/v each of *quinidine sulfate BPCRS* and *quinine sulfate BPCRS*. After removal of the plate, dry it in a current of air for 15 minutes and repeat the development. Dry the plate at 105° for 30 minutes, allow it to cool and spray with *iodoplatinate reagent*. The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

B. Complies with the test for Acidity.

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C. Yields the reactions characteristic of sulfates, Appendix VI.

TESTS

Acidity

pH of a 1% w/v solution, 2.8 to 3.4, Appendix V L.

Specific optical rotation

In a 3% w/v solution in 0.1M *hydrochloric acid*, -208 to -216, calculated with reference to the anhydrous substance, Appendix V F.

Other cinchona alkaloids

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve 20 mg of the substance being examined, with gentle heating if necessary, in 5 mL of the mobile phase and dilute to 10 mL with the mobile phase. Prepare solutions (2) and (3) in the same manner using *quinine sulfate BPCRS* and *quinidine sulfate BPCRS* respectively in place of the substance being examined. Solution (4) is a mixture of equal volumes of solutions (2) and (3). For solution (5) dilute 1 volume of solution (2) to 10 volumes with the mobile phase and dilute 1 volume of the resulting solution to 50 volumes with the mobile phase. Solution (6) contains 0.10% w/v of *thiourea* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 3.0 g of *hexylamine* in 700 mL of *water*, adjusting the pH to 2.8 with 1M *orthophosphoric acid*, adding 60 mL of *acetonitrile* and diluting to 1000 mL with *water* and (c) a detection wavelength of 250 nm for recording the chromatogram obtained with solution (6) and 316 nm for the other solutions.

Inject separately 10 µL of each of solutions (3) and (6). If necessary adjust the concentration of *acetonitrile* in the mobile phase so that in the chromatogram obtained with solution (3) the *capacity factor* of the peak due to quinidine is 3.5 to 4.5, V_O being calculated from the peak due to thiourea in the chromatogram obtained with solution (6). Inject 10 µL of each of solutions (2), (3), (4) and (5). The chromatogram obtained with solution (2) shows a principal peak due to quinidine and a peak due to dihydroquinine with a retention time relative to quinine of about 1.4. The chromatogram obtained with solution (3) shows a principal peak due to quinidine and a peak due to dihydroquinidine, with a retention time relative to quinidine of about 1.2. The chromatogram obtained with solution (4) shows four peaks due to quinine, dihydroquinine, quinidine and dihydroquinidine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with solutions (2) and (3).

The test is not valid unless (a) in the chromatogram obtained with solution (4) the *resolution factor* between the peaks due to quinine and quinidine is at least 1.5 and the *resolution factor* between the peaks due to dihydroquinidine and quinine is at least 1.0 and (b) the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (5) is at least 5.

Inject 10 µL of solution (1) and allow the chromatography to proceed for 2.5 times the retention time of the principal peak. Calculate the percentage content of related substances by *normalisation*, disregarding any peaks the areas of which are less than that of the peak in the chromatogram obtained with solution (5) (0.2%). The content of dihydroquinine is not greater than 10%, the content of any related substances eluting before quinine is not greater than 5% and the content of any other related substances is not greater than 2.5%.

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Sulfated ash

Not more than 0.1%, Appendix IX A.

Water

19.0 to 25.0% w/w, Appendix IX C. Use 0.2 g.

Titratable cation

75.3 to 79.6%, calculated with reference to the anhydrous substance, when determined by the following method. Add to the combined aqueous solutions reserved in the Assay 0.1 mL of *phenolphthalein solution R1* and titrate with *0.1M hydrochloric acid VS*. Each mL of *0.1M sodium hydroxide VS* is equivalent to 16.32 mg of $[C_{20}H_{26}N_2O_2]^{2+}$.

ASSAY

Dissolve 0.45 g in 15 mL of *water*. Add 25 mL of *0.1M sodium hydroxide VS* and extract with three 25 mL quantities of *chloroform*. Wash the combined chloroform extracts with 20 mL of *water*, combine the aqueous solutions and reserve for the test for Titratable cation. Dry the chloroform extracts with *anhydrous sodium sulfate*, evaporate to dryness at a pressure of 2 kPa and dissolve the residue in 50 mL of *anhydrous acetic acid*. Carry out method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 21.13 mg of $C_{20}H_{24}N_2O_2,H_2SO_4$.

STORAGE

Quinine Bisulfate should be protected from light.

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Quinidine Sulfate Tablets

General Notices

Quinidine Sulphate Tablets

Action and use

Class I antiarrhythmic.

DEFINITION

Quinidine Sulfate Tablets contain Quinidine Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of quinidine sulfate, $(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of *diethylamine*, 20 volumes of *acetone* and 80 volumes of *toluene* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 0.1 g of Quinidine Sulfate with 10 mL of a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*) and filter. Solution (2) contains 1.0% w/v of *quinidine sulfate BPCRS* in a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*). Solution (3) contains 1.0% w/v each of *quinidine sulfate BPCRS* and *quinine sulfate BPCRS*. After removal of the plate, allow it to dry in air and spray with 0.05M *ethanolic sulfuric acid* and then with *dilute potassium iodobismuthate solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

B. Shake a quantity of the powdered tablets containing 0.25 g of Quinidine Sulfate with 25 mL of a mixture of 2 volumes of *chloroform* and 1 volume of *ethanol* (*96%*) and filter. Evaporate the filtrate to dryness and wash the residue with 10 mL of *ether*. Filter, wash the residue with 10 mL of *ether* and dry the residue at 60° at a pressure not exceeding 15 Pa for 2 hours. The pH of a 1% w/v solution of the residue is 6.0 to 6.8, Appendix V L.

C. Extract a quantity of the powdered tablets containing 0.1 g of Quinidine Sulfate with 20 mL of *water* and filter. The filtrate yields the reactions characteristic of *sulfates*, Appendix VI.

Other cinchona alkaloids

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) mix a quantity of the powdered tablets containing 50 mg of Quinidine Sulfate with 20 mL of the mobile phase. Heat gently to dissolve the powder as completely

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as possible, cool, dilute to 25 mL with the mobile phase and filter, discarding the first few mL of filtrate. For solution (2) dissolve 20 mg of *quinine sulfate BPCRS*, with gentle heating if necessary, in 5 mL of the mobile phase and dilute to 10 mL with the mobile phase. Prepare solution (3) in the same manner as solution (2) but using *quinidine sulfate BPCRS* in place of *quinine sulfate BPCRS*. Solution (4) is a mixture of equal volumes of solutions (2) and (3). For solution (5) dilute 1 volume of solution (2) to 10 volumes with the mobile phase and dilute 1 volume of the resulting solution to 50 volumes with the mobile phase. Solution (6) contains 0.10% w/v of *thiourea* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS 5 µm is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 3.0 g of *hexylamine* in 700 mL of *water*, adjusting the pH to 2.8 with 1M *orthophosphoric acid*, adding 60 mL of *acetonitrile* and diluting to 1000 mL with *water* and (c) a detection wavelength of 250 nm for recording the chromatogram obtained with solution (6) and 316 nm for the other solutions.

Inject separately 10 µL of each of solutions (3) and (6). If necessary, adjust the concentration of *acetonitrile* in the mobile phase so that in the chromatogram obtained with solution (3) the *capacity factor* of the peak due to quinidine is 3.5 to 4.5, V_0 being calculated from the peak due to thiourea in the chromatogram obtained with solution (6). Inject 10 µL of each of solutions (2), (3), (4) and (5). The chromatogram obtained with solution (2) shows a principal peak due to quinine and a peak due to dihydroquinine with a retention time relative to quinine of about 1.4. The chromatogram obtained with solution (3) shows a principal peak due to quinidine and a peak due to dihydroquinidine, with a retention time relative to quinidine of about 1.2. The chromatogram obtained with solution (4) shows four peaks due to quinine, dihydroquinine, quinidine and dihydroquinidine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with solutions (2) and (3).

The test is not valid unless (a) in the chromatogram obtained with solution (4) the *resolution factor* between the peaks due to quinine and quinidine is at least 1.5 and the *resolution factor* between the peaks due to dihydroquinidine and quinine is at least 1.0 and (b) the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (5) is at least 5.

Inject 10 µL of solution (1) and allow the chromatography to proceed for 2.5 times the retention time of the principal peak. Calculate the percentage content of related substances by *normalisation*, disregarding any peaks the areas of which are less than that of the peak in the chromatogram obtained with solution (5) (0.2%). The content of dihydroquinidine is not greater than 15%, the content of any related substance eluting before quinidine is not greater than 5% and the content of any other related substance is not greater than 2.5%.

ASSAY

Weigh and powder 20 tablets. Dissolve as completely as possible using heat a quantity of the powdered tablets containing 0.4 g of Quinidine Sulfate in 40 mL of *acetic anhydride* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 26.10 mg of $(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$.

STORAGE

Quinidine Sulfate Tablets should be protected from light.

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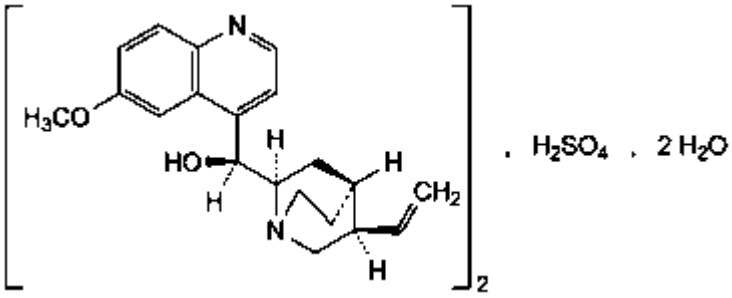
Quinidine Sulfate

General Notices

Quinidine Sulphate

(Ph. Eur. monograph 0017)



$C_{40}H_{50}N_4O_8S,2H_2O$ 783 *6591-63-5*

Action and use

Class I antiarrhythmic.

Preparation

Quinidine Sulfate Tablets

Ph Eur

DEFINITION

Alkaloid monosulfates, expressed as bis[(*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol] sulfate dihydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or silky, colourless needles.

Solubility

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Slightly soluble in water, soluble in boiling water and in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.10 g of *quinidine sulfate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *diethylamine R*, *ether R*, *toluene R* (10:24:40 *V/V/V*).

Application 5 µL.

Development Twice over a path of 15 cm; dry in a current of air for 15 min between the 2 developments.

Drying At 105 °C for 30 min and allow to cool.

Detection Spray with *iodoplatinate reagent R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve about 5 mg in 5 mL of *water R*. Add 0.2 mL of *bromine water R* and 1 mL of *dilute ammonia R2*. A green colour develops.

C. Dissolve 0.1 g in 3 mL of *dilute sulfuric acid R* and dilute to 100 mL with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on addition of 1 mL of *hydrochloric acid R*.

D. Dissolve about 50 mg in 5 mL of hot *water R*, cool, add 1 mL of *silver nitrate solution R1* and stir with a glass rod. After a few minutes, a white precipitate is formed that dissolves on the addition of *dilute nitric acid R*.

E. It gives reaction (a) of sulfates (2.3.1).

F. pH (see Tests).

TESTS

Solution S

Dissolve 0.500 g in *0.1 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, *Method II*).

pH (2.2.3)

6.0 to 6.8.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

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Specific optical rotation (2.2.7)

+ 275 to + 290 (dried substance), determined on solution S.

Other cinchona alkaloids

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 20 mg of the substance to be examined in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (a) Dissolve 20 mg of *quinine sulfate CRS* (impurity A) in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (b) Dissolve 20 mg of *quinidine sulfate CRS* in 5 mL of the mobile phase, with gentle heating if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (c) To 1 mL of reference solution (a) add 1 mL of reference solution (b).

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (e) Dissolve 10 mg of *thiourea R* in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.15-0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase Dissolve 6.8 g of *potassium dihydrogen phosphate R* and 3.0 g of *hexylamine R* in 700 mL of *water R*, adjust to pH 2.8 with *dilute phosphoric acid R*, add 60 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 250 nm for reference solution (e) and at 316 nm for the other solutions.

Injection 10 µL.

Run time 2.5 times the retention time of quinidine.

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurity A and dihydroquinine; use the chromatogram obtained with reference solution (b) to identify the peaks due to quinidine and impurity C; the chromatogram obtained with reference solution (c) shows 4 peaks due to quinidine, impurity A, impurity C and dihydroquinine which are identified by comparison of their retention times with those of the corresponding peaks in the chromatograms obtained with reference solutions (a) and (b).

Relative retention With reference to impurity A: dihydroquinine = about 1.4.

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Relative retention With reference to quinidine: impurity C = about 1.5.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to impurity A and quinidine and minimum 2.0 between the peaks due to impurities C and A in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 4 for the principal peak in the chromatogram obtained with reference solution (d);

— *mass distribution ratio*: 3.5 to 4.5 for the peak due to quinidine in the chromatogram obtained with reference solution (b), t_R, being calculated from the peak due to thiourea in the chromatogram obtained with reference solution (e); if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

— *impurity C*: maximum 15 per cent;

— *any impurity eluted before quinidine*: for each impurity, maximum 5 per cent;

— *any other impurity*: for each impurity, maximum 2.5 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent).

Boron

Maximum 5 ppm. *Avoid where possible the use of glassware.*

Test solution Dissolve 1.00 g in a mixture of 0.5 mL of *hydrochloric acid R* and 4.0 mL of *water R*.

Reference solution Dissolve 0.572 g of *boric acid R* in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *water R*. To 1.0 mL of this solution add 3.0 mL of *water R* and 0.5 mL of *hydrochloric acid R*.

Blank solution Add 0.5 mL of *hydrochloric acid R* to 4.0 mL of *water R*.

Add 3.0 mL of a 100 g/L solution of *2-ethylhexane-1,3-diol R* in *methylene chloride R* to the test solution, to the reference solution and to the blank solution, then shake for 1 min. Allow to stand for 6 min. To 1.0 mL of the lower layer, add 2.0 mL of a 3.75 g/L solution of *curcumin R* in *anhydrous acetic acid R* and 0.3 mL of *sulfuric acid R*. Mix and after 20 min add 25.0 mL of *ethanol (96 per cent) R*. Mix. The blank solution is yellow. Any red colour in the test solution is not more intense than that in the reference solution.

Loss on drying (*2.2.32*)

3.0 per cent to 5.0 per cent, determined on 1.000 g by drying in an oven at 130 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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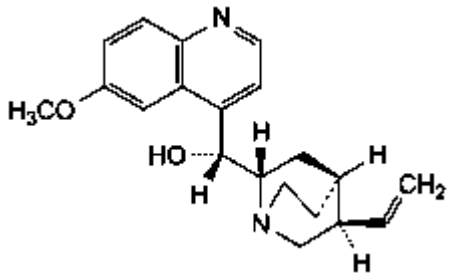
Dissolve 0.200 g in 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, using 0.15 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 24.90 mg of $C_{40}H_{50}N_4O_8S$.

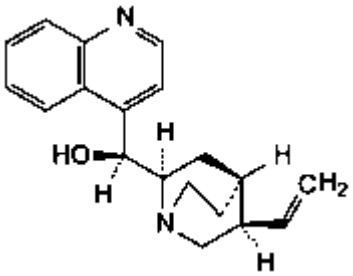
STORAGE

Protected from light.

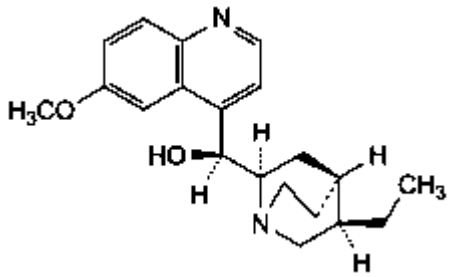
IMPURITIES



A. (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (quinine),



B. (*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](quinolin-4-yl)methanol (cinchonine),



C. (*S*)-[(2*R*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol (dihydroquinidine).

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Quinapril Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Quinapril Tablets contain Quinapril Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of quinapril, $C_{25}H_{30}N_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing the equivalent of 10 mg of quinapril with 4 mL of *methanol*. Centrifuge and use the supernatant liquid.

(2) 0.27% w/v of *quinapril hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 12 µL of each solution.

(d) Develop the plate to 6 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 6 volumes of *acetone* and 13 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the peak due to quinapril in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, expected to contain the equivalent of 0.00055% w/v of quinapril.

(2) 0.00060% w/v of *quinapril hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (4 cm × 6.0 mm) packed with *nitrile silica gel for chromatography* (3 µm) (Zorbax CN Reliance is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.2 volumes of *methanesulfonic acid*, 35 volumes of *acetonitrile R1*and 65 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the total content of quinapril, $C_{25}H_{30}N_2O_5$, in the medium from the chromatograms obtained and using the declared content of $C_{25}H_{30}N_2O_5$,HCl, in *quinapril hydrochloride BPCRS*. Each mg of $C_{25}H_{30}N_2O_5$,HCl is equivalent to 0.9233 mg of $C_{25}H_{30}N_2O_5$.

LIMITS

The amount of quinapril released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 40 volumes of *acetonitrile R1* and 60 volumes of a 0.288% w/v solution of *ammonium dihydrogen phosphate* previously adjusted to pH 6.5 with *dilute ammonia* (solvent A).

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 50 mg of quinapril in solvent A and dilute to 25 mL. Filter through a 0.45-µm PTFE filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.1% w/v of *quinapril for system suitability EPCRS*.

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(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.

(d) Use a column temperature of 30°.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 214 nm.

(g) Inject 10 µL of each solution.

(h) Allow the chromatography to proceed for 3 times the retention time of quinapril.

MOBILE PHASE

47 volumes of *acetonitrile R1* and 53 volumes of a 0.577% w/v solution of *sodium dodecyl sulfate* adjusted to pH 2.2 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to quinapril (retention time about 12 minutes) are: impurity A; about 0.1; impurity C; about 0.3; impurity D; about 0.4; impurity M; about 0.7; impurities G + H; about 0.9 and impurity E; about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and quinapril is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks due to impurities A, C, D and E using the chromatogram obtained with solution (3) and the chromatogram supplied with *quinapril for system suitability EPCRS*. Multiply the area of any peak corresponding to impurity E by a correction factor of 1.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (4) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

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the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a solution containing 35 volumes of *acetonitrile R1* and 65 volumes of *water* (solvent B).

Prepare a solution continuing 35 volumes of *acetonitrile R1* and 65 volumes of a 0.05M solution of *dipotassium hydrogen orthophosphate*, previously adjusted to pH 6.5 with *orthophosphoric acid* (solvent C).

(1) To 10 whole tablets add 300 mL of solvent B and mix with the aid of ultrasound. Shake for 15 minutes, dilute to 500 mL with solvent B and centrifuge. Dilute the supernatant liquid, if necessary, with sufficient solvent B to produce a solution containing the equivalent of 0.01% w/v of quinapril and filter.
(2) 0.108% w/v of *quinapril hydrochloride BPCRS* in solvent B. Dilute 1 volume to 10 volumes with solvent C.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{30}N_2O_5$ in the tablets using the declared content of $C_{25}H_{30}N_2O_5$,HCl, in *quinapril hydrochloride BPCRS*.
Each mg of $C_{25}H_{30}N_2O_5$,HCl is equivalent to 0.9233 mg of $C_{25}H_{30}N_2O_5$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of quinapril.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Quinapril Hydrochloride.

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a Williams Lea company

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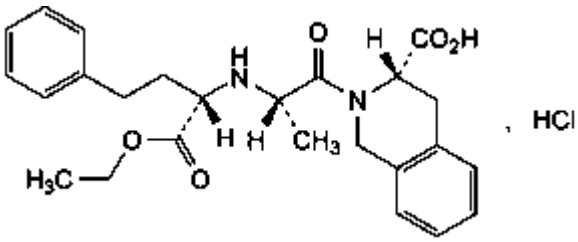
Quinapril Hydrochloride

General Notices

(Ph. Eur. monograph 1763)



$C_{25}H_{31}ClN_2O_5$ 475.0 *82586-55-8*

Action and use

Angiotensin converting enzyme inhibitor.

Preparation

Quinapril Tablets

Ph Eur

DEFINITION

(3*S*)-2-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or slightly pink, hygroscopic powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), very slightly soluble in acetone.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *quinapril hydrochloride CRS*.

B. Specific optical rotation (see Tests).

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Specific optical rotation (2.2.7)

+ 14.4 to + 16.6 (anhydrous substance).

Dissolve 0.500 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Diastereoisomers

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Solvent mixture Adjust 500 mL of the mobile phase to pH 6.5 with *concentrated ammonia R*.

Test solution Dissolve 100 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *quinapril for peak identification CRS* (containing impurities G, H and I) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase Mix 260 mL of *tetrahydrofuran R* (non-stabilised) with 740 mL of a freshly prepared solution containing 1.08 g/L of *sodium octanesulfonate R* and 2.88 g/L of *ammonium dihydrogen phosphate R*, previously adjusted to pH 4.5 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 3.5 times the retention time of quinapril.

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Identification of impurities Use the chromatogram supplied with *quinapril for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities G, H and I.

Relative retention With reference to quinapril (retention time = about 18 min): impurity G = about 0.9; impurity H = about 1.2; impurity I = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity G and quinapril;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity H and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to quinapril.

Limits:

— *impurities G, H, I*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mix 40 volumes of *acetonitrile R1* and 60 volumes of a 2.88 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 6.5 with *dilute ammonia R1*.

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *quinapril for system suitability CRS* (containing impurities A, C, D, E and G) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (c) In order to prepare impurity M *in situ*, dissolve 250 mg of the substance to be examined in *methylene chloride R* and dilute to 5.0 mL with the same solvent. Expose this solution to a source of ultraviolet light for 2.5 h and evaporate the solvent. Dissolve 40 mg of the remaining substance in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Temperature:

— *column*: 30 °C;

— *autosampler*: 5 °C.

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Mobile phase acetonitrile R1, 5.77 g/L solution of sodium dodecyl sulfate R adjusted to pH 2.2 with phosphoric acid R (48:52 *V/V*).

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL.

Run time 3 times the retention time of quinapril.

Identification of impurities Use the chromatogram supplied with quinapril for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C, D, E and G; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity M.

Relative retention With reference to quinapril (retention time = about 12 min): impurity A = about 0.1; impurity C = about 0.3; impurity D = about 0.4; impurity M = about 0.7; impurities G + H = about 0.9; impurity E = about 2.3.

System suitability Reference solution (b):

— resolution: minimum 1.5 between the peaks due to impurities C and D; minimum 1.5 between the peaks due to impurity G and quinapril.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 1.5;

— *impurities C, D*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities E, M*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to impurities G + H.

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 23.75 mg of $C_{25}H_{31}ClN_2O_5$.

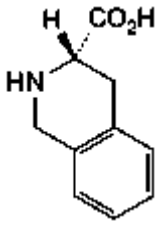
STORAGE

In an airtight container at a temperature of 2 °C to 8 °C.

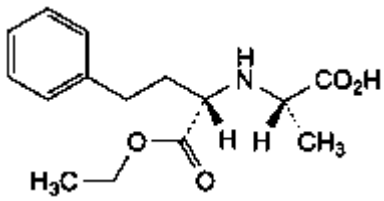
IMPURITIES

Specified impurities *A, C, D, E, G, H, I, M.*

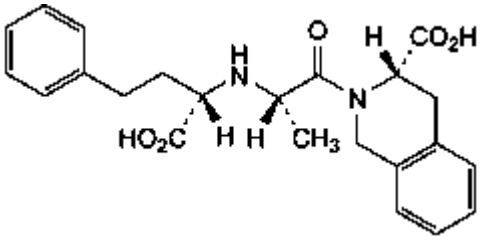
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, J.*



A. (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



B. (2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



C. (3*S*)-2-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

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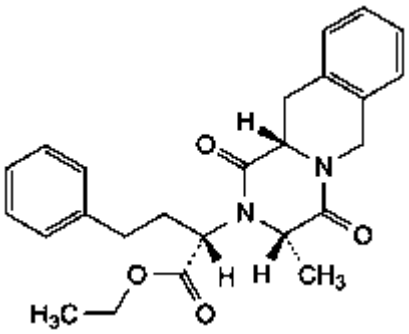
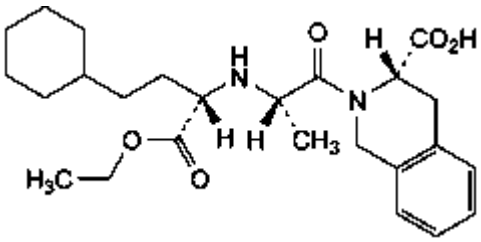
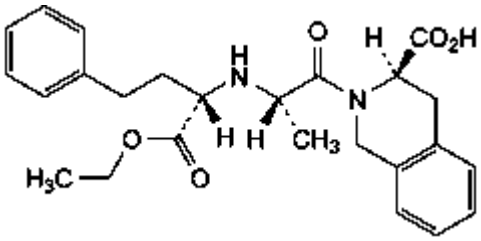


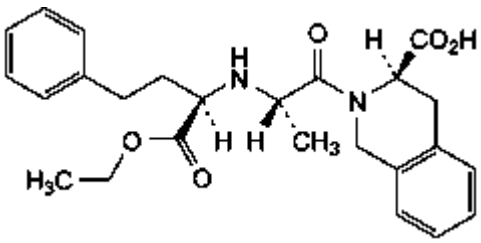
D. ethyl (2*S*)-2-[(3*S*,11a*S*)-3-methyl-1,4-dioxo-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl]-4-phenylbutanoate,



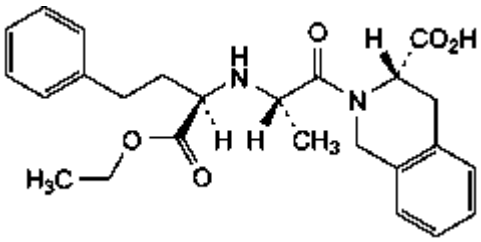
E. (3*S*)-2-[(2*S*)-2-[[(1*S*)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



G. (3*R*)-2-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



H. (3*R*)-2-[(2*S*)-2-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



I. (3*S*)-2-[(2*S*)-2-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

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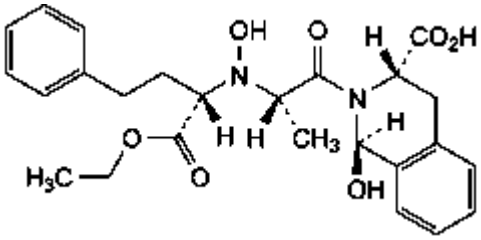
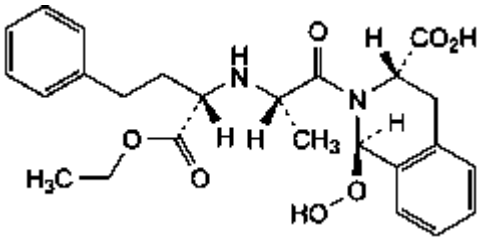


J. (1*R*,3*S*)-2-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl](hydroxy)amino]propanoyl]-1-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



M. (1*R*,3*S*)-2-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1-hydroperoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

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Quetiapine Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Quetiapine Tablets contain Quetiapine Fumarate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of quetiapine, $C_{21}H_{25}N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 40 mg of quetiapine with 10 mL of *acetonitrile*, filter and discard the filtrate. Extract the residue with 10 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of quetiapine fumarate (*RS 496*).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary to produce a solution containing the equivalent of 0.0028% w/v of quetiapine, at the maximum at 290 nm, Appendix II B using 0.01M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a solution of 0.0032% w/v of *quetiapine fumarate BPCRS* using 0.01M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the content of quetiapine, $C_{21}H_{25}N_3O_2S$, in the tablets from the absorbance obtained and using the declared content of $C_{46}H_{54}N_6O_8S_2$ in *quetiapine fumarate BPCRS*. Each mg of $C_{46}H_{54}N_6O_8S_2$ is equivalent to 0.8686 mg of $C_{21}H_{25}N_3O_2S$.

LIMITS

The amount of quetiapine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing the equivalent of 25 mg of quetiapine with 20 mL, dilute to 25 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of this solution to 5 volumes.
(3) 0.02% w/v of *quetiapine fumarate*, 0.004% w/v of *quetiapine impurity G BPCRS* and 0.004% w/v of *quetiapine impurity I BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5µm) (Hypersil Gold C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 30 µL of each solution.
(g) For solution (1), allow the run time to proceed for twice the retention time of quetiapine.

MOBILE PHASE

7 volumes of *acetonitrile*, 39 volumes of a 0.26% w/v solution of *diammonium hydrogen orthophosphate* in *water* and 54 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to quetiapine (retention time about 14 minutes) are: impurity H, about 0.5; impurity G, about 0.6 and impurity I, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to quetiapine and impurity I is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify any peaks due to impurity G using the chromatogram obtained with solution (3) and multiply the peak area by the correction factor of 0.7;

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of powdered tablets containing the equivalent of 50 mg of quetiapine with 200 mL, dilute to 250 mL and filter.

(2) 0.023% w/v of *quetiapine fumarate BPCRS*.

(3) 0.02% w/v of *quetiapine fumarate BPCRS* and 0.004% w/v of *quetiapine impurity I BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to quetiapine and impurity I is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{25}N_3O_2S$ in the tablets using the declared content of $C_{46}H_{54}N_6O_8S_2$ in *quetiapine fumarate BPCRS*. Each mg of $C_{46}H_{54}N_6O_8S_2$ is equivalent to 0.8686 mg of $C_{21}H_{25}N_3O_2S$.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities G, H and I listed under Quetiapine Fumarate.

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Quetiapine Prolonged-release Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Quetiapine Prolonged-release Tablets contain Quetiapine Fumarate. They are formulated so that the medicament is released over a period of several hours.

Quetiapine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of quetiapine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of quetiapine, $C_{21}H_{25}N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 40 mg of quetiapine with 10 mL of *acetonitrile*, filter and discard the filtrate. Extract the residue with 10 mL of *methanol*, filter and evaporate the filtrate to dryness. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of quetiapine fumarate (*RS 496*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing the equivalent of 12.5 mg of quetiapine with 20 mL, dilute to 25 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes, dilute 1 volume of this solution to 5 volumes.

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(3) 0.02% w/v of *quetiapine fumarate BPCRS*, 0.004% w/v of *quetiapine impurity G BPCRS*, and 0.004% w/v of *quetiapine impurity I BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5µm) (Hypersil Gold C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 30 µL of each solution.

(g) For solution (1), allow the run time to proceed for twice the retention time of quetiapine.

MOBILE PHASE

7 volumes of *acetonitrile*, 39 volumes of a 0.26% w/v solution of *diammonium hydrogen orthophosphate* in *water* and 54 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to quetiapine (retention time about 14 minutes) are: impurity H, about 0.5; impurity G, about 0.6 and impurity I, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to quetiapine and impurity I is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify any peaks due to impurity G using the chromatogram obtained with solution (3) and multiply the peak area by the correction factor of 0.7;

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of powdered tablets containing the equivalent of 50 mg of quetiapine with 200 mL, dilute to 250 mL and filter.

(2) 0.023% w/v of *quetiapine fumarate BPCRS*.

(3) 0.02% w/v *quetiapine fumarate BPCRS* and 0.004% w/v *quetiapine impurity I BPCRS*.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to quetiapine and impurity I is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{25}N_3O_2S$ in the tablets using the declared content of $C_{46}H_{54}N_6O_8S_2$ in *quetiapine fumarate BPCRS*. Each mg of $C_{46}H_{54}N_6O_8S_2$ is equivalent to 0.8686 mg of $C_{21}H_{25}N_3O_2S$.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities G, H and I listed under Quetiapine Fumarate.

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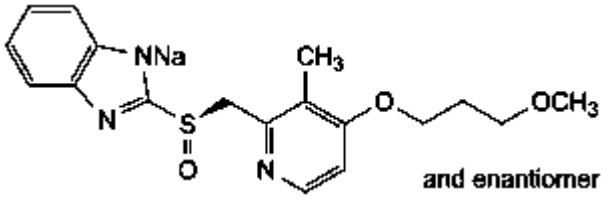
Rabeprazole Sodium

General Notices

(Ph. Eur. monograph 2868)



$C_{18}H_{20}N_3NaO_3S$ 381.4 *117976-90-6*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Ph Eur

DEFINITION

Sodium 2-[(*RS*)-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfinyl]benzimidazol-1-ide.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish-white, hygroscopic powder.

Solubility

Very soluble to freely soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Dissolve the substance to be examined in *methanol R*, evaporate to dryness and record the spectrum using the residue.

Comparison Repeat the operations using *rabeprazole sodium hydrate CRS*.

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B. Loss on drying (see Tests).

C. It gives reaction (a) of sodium (2.3.1).

TESTS

pH (2.2.3)

9.5 to 11.5.

Dissolve 0.100 g in carbon dioxide-free water R and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture methanol R, 0.1 M phosphate buffer solution pH 11.3 R (20:80 *V/V*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of rabeprazole for system suitability CRS (containing impurities A and H) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (c) Dissolve 20.0 mg of rabeprazole sodium hydrate CRS in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: mix 5 volumes of acetonitrile R and 95 volumes of a 4.35 g/L solution of dipotassium hydrogen phosphate R previously adjusted to pH 7.0 with phosphoric acid R;

— *mobile phase B*: methanol R;

— *mobile phase C*: acetonitrile R;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 2	100	0	0
2 - 7	100 → 85	0	0 → 15
7 - 27	85 → 30	0 → 40	15 → 30
27 - 32	30 → 15	40 → 55	30

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Autosampler Set at 6 °C.

Injection 5 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *rabeprazole for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and H.

Relative retention With reference to rabeprazole (retention time = about 19 min): impurity A = about 0.9; impurity H = about 0.98.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity H and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rabeprazole.

Calculation of percentage contents:

— for each impurity, use the concentration of rabeprazole sodium in reference solution (a).

Limits:

— *impurity A*: maximum 0.8 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

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Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{18}H_{20}N_3NaO_3S$ taking into account the assigned content of *rabeprazole sodium hydrate CRS*.

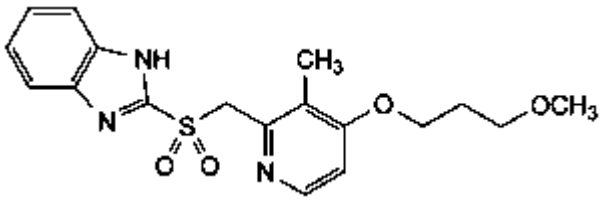
STORAGE

In an airtight container, protected from light.

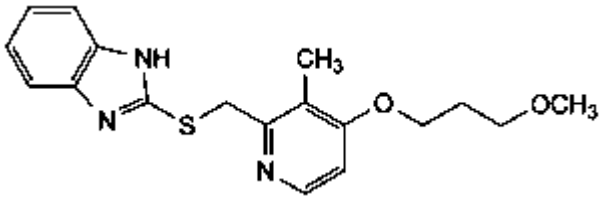
IMPURITIES

Specified impurities *A.*

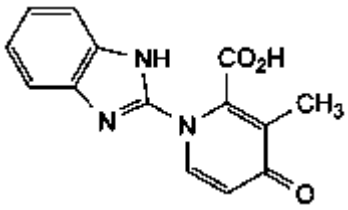
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, G, H, I, K.*



A. 2-[[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfonyl]-1*H*-benzimidazole,



B. 2-[[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfanyl]-1*H*-benzimidazole,



C. 1-(1*H*-benzimidazol-2-yl)-3-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid,

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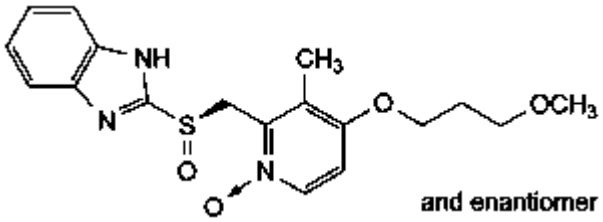
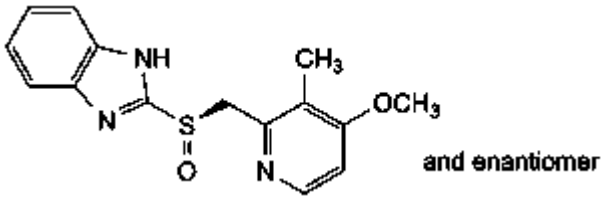
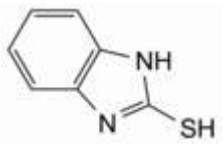


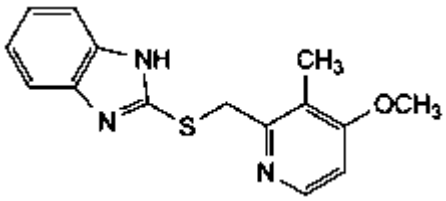
D. 2-[[(*RS*)-(1*H*-benzimidazol-2-yl)sulfinyl]methyl]-4-(3-methoxypropoxy)-3-methylpyridine 1-oxide,



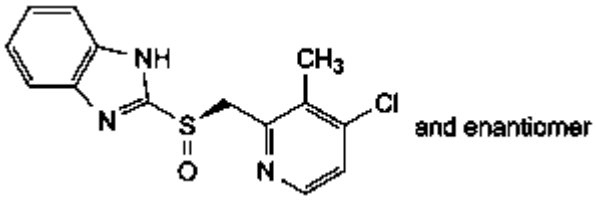
E. 2-[(*RS*)-[(4-methoxy-3-methylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole,



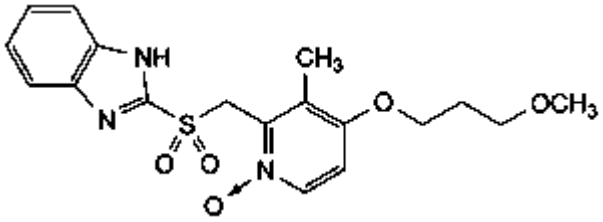
F. 1*H*-benzimidazole-2-thiol,



G. 2-[[(4-methoxy-3-methylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole,



H. 2-[(*RS*)-[(4-chloro-3-methylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole,



I. 2-[[(1*H*-benzimidazol-2-yl)sulfonyl]methyl]-4-(3-methoxypropoxy)-3-methylpyridine 1-oxide,

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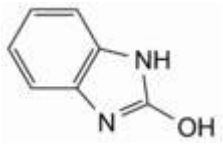

K. 1*H*-benzimidazol-2-ol.

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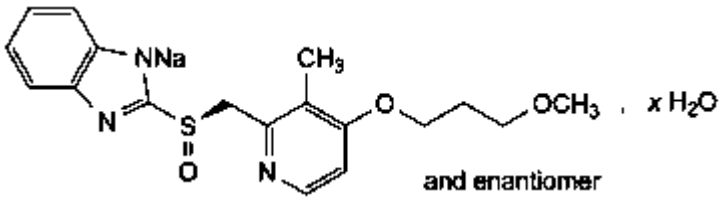
Rabeprazole Sodium Hydrate

General Notices

(Ph. Eur. monograph 2331)



$C_{18}H_{20}N_3NaO_3S,xH_2O$ 381.4 (anhydrous substance)

891191-56-3

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Ph Eur

DEFINITION

Sodium 2-[(*RS*)-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfinyl]benzimidazol-1-ide hydrate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or slightly yellowish-white, hygroscopic, amorphous or crystalline powder.

Solubility

Very soluble to freely soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *rabeprazole sodium hydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Water (see Tests).

C. It gives reaction (a) of sodium (2.3.1).

TESTS

pH (2.2.3)

9.5 to 11.5.

Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture *methanol R*, *0.1 M phosphate buffer solution pH 11.3 R* (20:80 *V/V*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *rabeprazole for system suitability CRS* (containing impurities A and H) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (c) Dissolve 20.0 mg of *rabeprazole sodium hydrate CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: mix 5 volumes of *acetonitrile R* and 95 volumes of a 4.35 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 7.0 with *phosphoric acid R*;

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— *mobile phase B*: *methanol R*;

— *mobile phase C*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 2	100	0	0
2 - 7	100 → 85	0	0 → 15
7 - 27	85 → 30	0 → 40	15 → 30
27 - 32	30 → 15	40 → 55	30

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Autosampler Set at 6 °C.

Injection 5 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *rabeprazole for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and H.

Relative retention With reference to rabeprazole (retention time = about 19 min): impurity A = about 0.9; impurity H = about 0.98.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity H and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rabeprazole.

Calculation of percentage contents:

— for each impurity, use the concentration of rabeprazole sodium hydrate in reference solution (a).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

1.5 per cent to 7.0 per cent, determined on 0.200 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{18}H_{20}N_3NaO_3S$ taking into account the assigned content of *rabeprazole sodium hydrate CRS*.

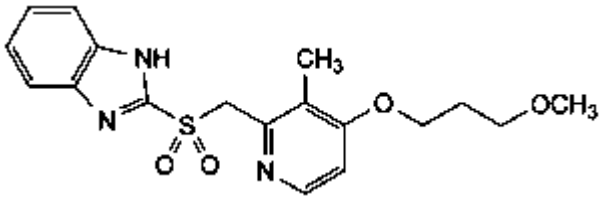
STORAGE

In an airtight container, protected from light.

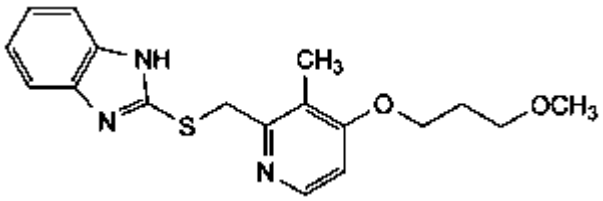
IMPURITIES

Specified impurities A.

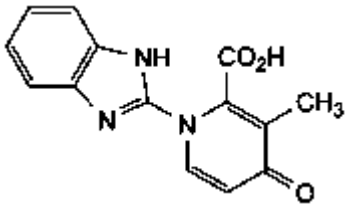
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, G, H, I, K.



A. 2-[[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfonyl]-1*H*-benzimidazole,



B. 2-[[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfanyl]-1*H*-benzimidazole,



C. 1-(1*H*-benzimidazol-2-yl)-3-methyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid,

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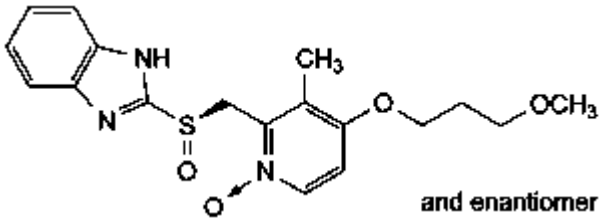
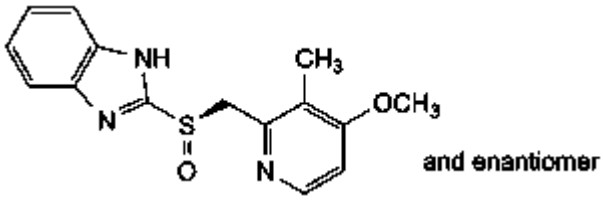
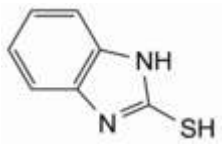


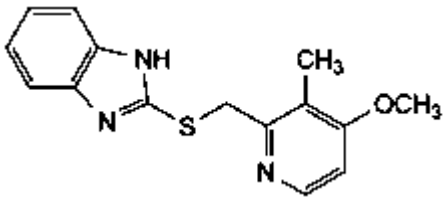
D. 2-[[(*RS*)-(1*H*-benzimidazol-2-yl)sulfinyl]methyl]-4-(3-methoxypropoxy)-3-methylpyridine 1-oxide,



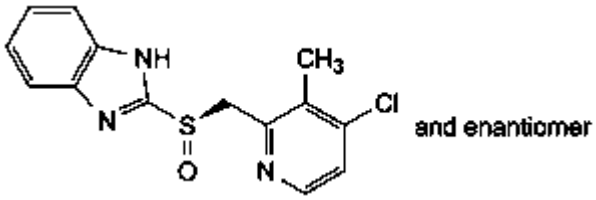
E. 2-[(*RS*)-[(4-methoxy-3-methylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole,



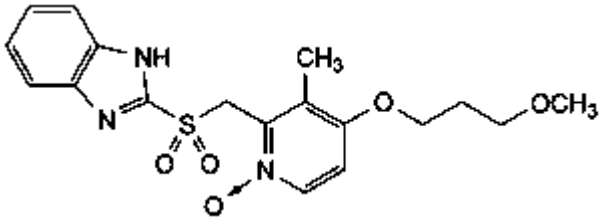
F. 1*H*-benzimidazole-2-thiol,



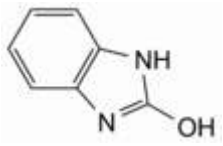
G. 2-[[(4-methoxy-3-methylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole,



H. 2-[(*RS*)-[(4-chloro-3-methylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole,



I. 2-[[(1*H*-benzimidazol-2-yl)sulfonyl]methyl]-4-(3-methoxypropoxy)-3-methylpyridine 1-oxide,



K. 1*H*-benzimidazol-2-ol.

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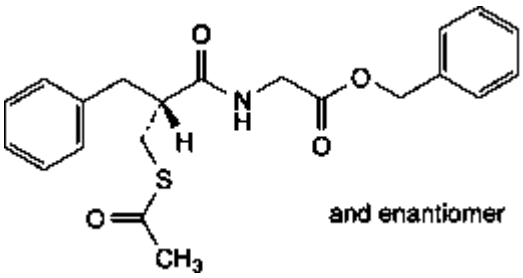
Racecadotril

General Notices

(Ph. Eur. monograph 2171)



$C_{21}H_{23}NO_4S$ 385.5 *81110-73-8*

Ph Eur

DEFINITION

Benzyl [[(2*RS*)-2-[(acetylsulfanyl)methyl]-3-phenylpropanoyl]amino]acetate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *racecadotril CRS*.

TESTS

Appearance of solution

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The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 5.0 g in 10 mL of acetone R.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase A, mobile phase B (50:50 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) *Prepare immediately before use*. Dissolve 10 mg of racecadotril impurity A CRS in 5.0 mL of the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of racecadotril impurity G CRS in the solvent mixture and dilute to 50 mL with the solvent mixture. To 5 mL of this solution add 1 mL of test solution (b) and dilute to 100 mL with the solvent mixture.

Reference solution (d) Dissolve 50.0 mg of racecadotril CRS in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 25.0 mL with the solvent mixture.

Reference solution (e) Dissolve 2 mg of racecadotril for peak identification CRS (containing impurities C, E and F) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of potassium dihydrogen phosphate R in water for chromatography R, adjust to pH 2.5 with phosphoric acid R and dilute to 1000 mL with water for chromatography R;

— *mobile phase B*: acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	60	40

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
5 - 25	60 → 20	40 → 80
25 - 35	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the solvent mixture, test solution (a) and reference solutions (a), (b), (c) and (e).

Identification of impurities Use the chromatogram supplied with *racecadotril for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities C, E and F.

Relative retention With reference to racecadotril (retention time = about 16 min): impurity A = about 0.2; impurity C = about 0.3; impurity E = about 0.5; impurity F = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity G and racecadotril.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.4; impurity E = 0.6; impurity F = 0.7;

— *impurities C, E, F*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

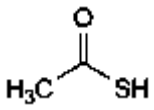
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{21}H_{23}NO_4S$ taking into account the assigned content of *racecadotril CRS*.

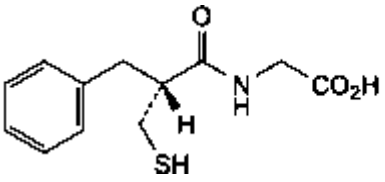
IMPURITIES

Specified impurities *A, C, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, G, H.*

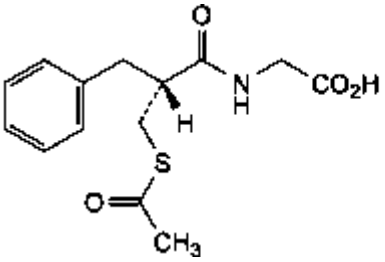


A. ethanethioic acid (thioacetic acid),



and enantiomer

B. [[(2*RS*)-2-benzyl-3-sulfanylpropanoyl]amino]acetic acid,



and enantiomer

C. [[(2*RS*)-2-[(acetylsulfanyl)methyl]-3-phenylpropanoyl]amino]acetic acid,

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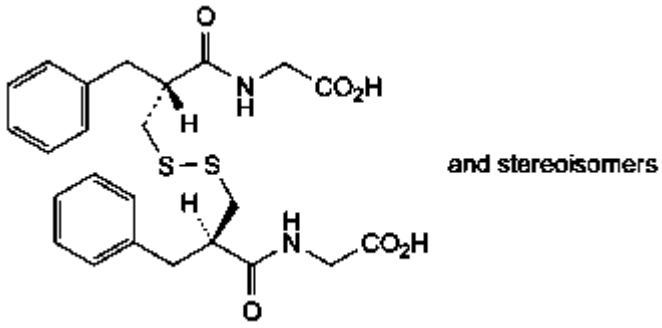
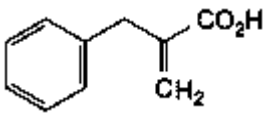
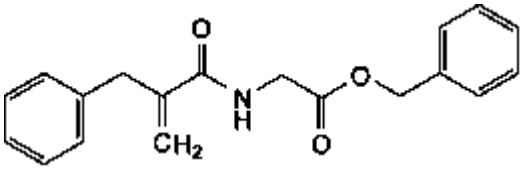


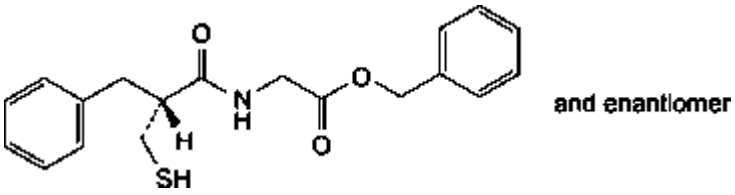
D. 5,10-dibenzyl-4,11-dioxo-7,8-dithia-3,12-diazatetradecanedioic acid,



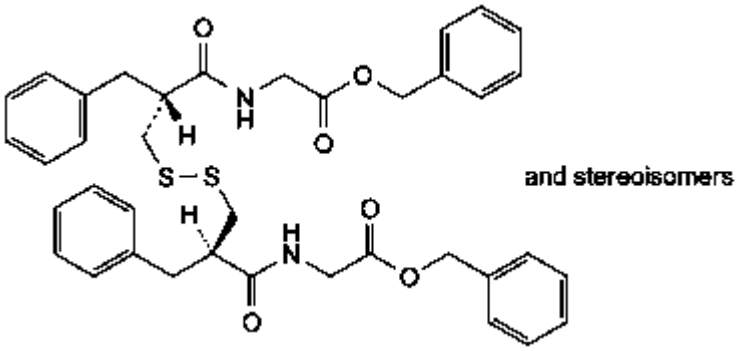
E. 2-benzylprop-2-enoic acid (2-benzylacrylic acid),



F. benzyl [(2-benzylprop-2-enoyl)amino]acetate,



G. benzyl [[(2*RS*)-2-benzyl-3-sulfanylpropanoyl]amino]acetate,



H. dibenzyl 5,10-dibenzyl-4,11-dioxo-7,8-dithia-3,12-diazatetradecanedioate.

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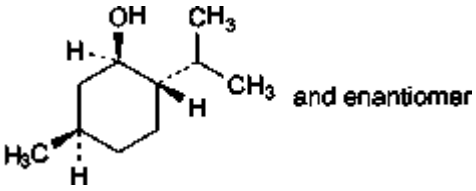
Racementhol

General Notices

(Racemic Menthol, Ph. Eur. monograph 0623)



$C_{10}H_{20}O$ 156.3 *89-78-1*

Preparation

Menthol and Benzoin Inhalation

Ph Eur

DEFINITION

Mixture of equal parts of (1*RS*,2*SR*,5*RS*)-5-methyl-2-(1-methylethyl)cyclohexanol.

CHARACTERS

Appearance

Free-flowing or agglomerated, crystalline powder or prismatic or acicular, colourless, shiny crystals.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and in light petroleum, freely soluble in fatty oils and in liquid paraffin, very slightly soluble in glycerol.

mp

About 34 °C.

IDENTIFICATION

First identification: A, C.

Second identification: B, D.

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A. Optical rotation (see Tests).

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 25 mg of *menthol CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ethyl acetate R*, *toluene R* (5:95 *V/V*).

Application 2 µL.

Development Over a path of 15 cm.

Drying In air, until the solvents have evaporated.

Detection Spray with *anisaldehyde solution R* and heat at 100-105 °C for 5-10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in position and approximate dimensions to the principal peak in the chromatogram obtained with reference solution (c).

D. Dissolve 0.20 g in 0.5 mL of *anhydrous pyridine R*. Add 3 mL of a 150 g/L solution of *dinitrobenzoyl chloride R* in *anhydrous pyridine R*. Heat on a water-bath for 10 min. Add 7.0 mL of *water R* in small quantities with stirring and allow to stand in iced water for 30 min. A precipitate is formed. Allow to stand and decant the supernatant. Wash the precipitate with 2 quantities, each of 5 mL, of iced *water R*, recrystallise from 10 mL of *acetone R*, wash with iced *acetone R* and dry at 75 °C at a pressure not exceeding 2.7 kPa for 30 min. The crystals melt (2.2.14) at 130 °C to 131 °C.

TESTS

Solution S

Dissolve 2.50 g in 10 mL of *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent. Add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

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Optical rotation (*2.2.7*)

-0.2° to + 0.2°, determined on solution S.

Related substances

Gas chromatography (*2.2.28*).

Test solution (a) Dissolve 0.20 g of the substance to be examined in *methylene chloride R* and dilute to 50.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methylene chloride R*.

Reference solution (a) Dissolve 40.0 mg of the substance to be examined and 40.0 mg of *isomenthol R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 0.10 mL of test solution (a) to 100.0 mL with *methylene chloride R*.

Reference solution (c) Dissolve 40.0 mg of *menthol CRS* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Column:

— *material*: glass;

— *size*: *l* = 2.0 m, Ø = 2 mm;

— *stationary phase*: diatomaceous earth for gas chromatography R impregnated with 15 per cent *m/m* of *macrogol 1500 R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 120 °C;

— *injection port*: 150 °C;

— *detector*: 200 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time Twice the retention time of menthol.

System suitability:

— *resolution*: minimum 1.4 between the peaks due to menthol and isomenthol in the chromatogram obtained with reference solution (a);

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— *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

Limits Test solution (a):

— *total*: not more than 1 per cent of the area of the principal peak;

— *disregard limit*: 0.05 per cent of the area of the principal peak.

Residue on evaporation

Maximum 0.05 per cent.

Evaporate 2.00 g on a water-bath and heat in an oven at 100-105 °C for 1 h. The residue weighs not more than 1.0 mg.

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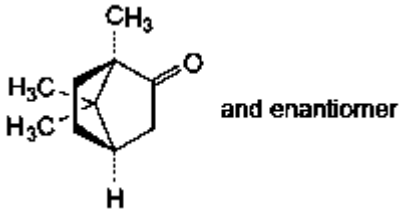
Racemic Camphor

General Notices

(Ph. Eur. monograph 0655)



$C_{10}H_{16}O$ 152.2 *76-22-2*

Action and use

Counter-irritant.

Preparations

Camphorated Opium Tincture

Concentrated Camphorated Opium Tincture

Concentrated Camphor Water

Ph Eur

DEFINITION

(1*RS*,4*RS*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one.

CHARACTERS

Appearance

White or almost white, crystalline powder or friable, crystalline masses, highly volatile even at room temperature.

Solubility

Slightly soluble in water, very soluble in ethanol (96 per cent) and in light petroleum, freely soluble in fatty oils, very slightly soluble in glycerol.

IDENTIFICATION

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First identification: A, C.

Second identification: A, B, D.

A. Optical rotation (see Tests).

B. Melting point (2.2.14): 172 °C to 180 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Mulls in *liquid paraffin R*.

Comparison *racemic camphor CRS*.

D. Dissolve 1.0 g in 30 mL of *methanol R*. Add 1.0 g of *hydroxylamine hydrochloride R* and 1.0 g of *anhydrous sodium acetate R*. Boil under a reflux condenser for 2 h. Allow to cool and add 100 mL of *water R*. A precipitate is formed. Filter, wash with 10 mL of *water R* and recrystallise from 10 mL of a mixture of 4 volumes of *ethanol (96 per cent) R* and 6 volumes of *water R*. The crystals, dried *in vacuo*, melt (2.2.14) at 118 °C to 121 °C.

TESTS

Carry out the weighings rapidly.

Solution S

Dissolve 2.50 g in 10 mL of *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

Dissolve 1.0 g in 10 mL of *ethanol (96 per cent) R* and add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Optical rotation (2.2.7)

-0.15° to + 0.15°, determined on solution S.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 50 mg of the substance to be examined in *hexane R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of the substance to be examined and 50 mg of *bornyl acetate R* in *hexane R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 200.0 mL with *hexane R*.

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Column:

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: diatomaceous earth for gas chromatography R impregnated with 10 per cent *m/m* of *macrogol 20 000 R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 130 °C;

— *injection port and detector*: 200 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time 3 times the retention time of camphor.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to camphor and bornyl acetate in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *any impurity*: for each impurity, not more than 2 per cent of the area of the principal peak;

— *total*: not more than 4 per cent of the area of the principal peak;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b).

Halogens

Maximum 100 ppm.

Dissolve 1.0 g in 10 mL of *2-propanol R* in a distillation flask. Add 1.5 mL of *dilute sodium hydroxide solution R* and 50 mg of *nickel-aluminium alloy R*. Heat on a water-bath until the *2-propanol R* has evaporated. Allow to cool and add 5 mL of *water R*. Mix and filter through a wet filter previously washed with *water R* until free from chlorides. Dilute the filtrate to 10.0 mL with *water R*. To 5.0 mL of this solution, add *nitric acid R* dropwise until the precipitate which forms is redissolved and dilute to 15 mL with *water R*. The solution complies with the limit test for chlorides (*2.4.4*).

Water

Dissolve 1 g in 10 mL of *light petroleum R*. The solution is clear (*2.2.1*).

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Residue on evaporation

Maximum 0.05 per cent.

Evaporate 2.0 g on a water-bath and dry at 100-105 °C for 1 h. The residue weighs not more than 1 mg.

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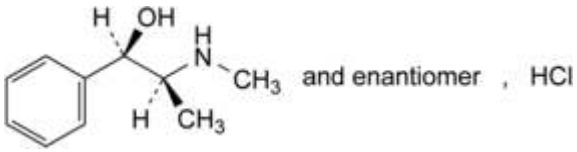
Racephedrine Hydrochloride

General Notices

(Racemic Ephedrine Hydrochloride, Ph. Eur. monograph 0715)



$C_{10}H_{16}ClNO$ 201.7 *134-71-4*

Action and use

Adrenoceptor agonist.

Ph Eur

DEFINITION

Racemic ephedrine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (1*RS*,2*SR*)-2-(methylamino)-1-phenylpropan-1-ol hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, freely soluble in water, soluble in ethanol (96 per cent).

It melts at about 188 °C.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *racemic ephedrine hydrochloride CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To 0.1 mL of solution S (see Tests) add 1 mL of *water R*, 0.2 mL of *copper sulfate solution R* and 1 mL of *strong sodium hydroxide solution R*. A violet colour is produced. Add 2 mL of *ether R* and shake. The ether layer is purple and the aqueous layer is blue.

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E. To 5 mL of solution S add 5 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 5.00 g in *distilled water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.1 mL of *0.01 M sodium hydroxide*; the solution is yellow. Add 0.2 mL of *0.01 M hydrochloric acid*; the solution is red.

Optical rotation (*2.2.7*)

+ 0.2° to -0.2°, determined on solution S.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a) Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 20 mg of *racemic ephedrine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1 mL of test solution (a) to 200 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 5 volumes of *chloroform R*, 15 volumes of *concentrated ammonia R* and 80 volumes of *2-propanol R*. Allow the plate to dry in air. Spray with *ninhydrin solution R* and heat at 110 °C for 5 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any spot of lighter colour than the background.

Sulfates (*2.4.13*)

15 mL of solution S complies with the limit test for sulfates (100 ppm).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.170 g in 30 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the two points of inflexion.

1 mL of *0.1 M sodium hydroxide* corresponds to 20.17 mg of $C_{10}H_{16}ClNO$.

STORAGE

Store protected from light.

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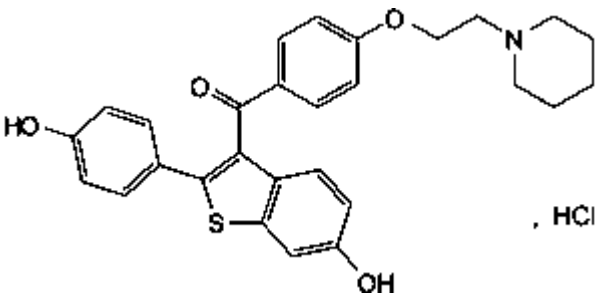
Raloxifene Hydrochloride

General Notices

(Ph. Eur. monograph 2375)



$C_{28}H_{28}ClNO_4S$ 510.0 *82640-04-8*

Action and use

Selective oestrogen receptor modulator.

Ph Eur

DEFINITION

[6-Hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl][4-[2-(piperidin-1-yl)ethoxy]phenyl]methanone hydrochloride.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Almost white or pale-yellow powder.

Solubility

Very slightly soluble or practically insoluble in water and in acetone, slightly soluble in ethanol (96 per cent *V/V*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *raloxifene hydrochloride CRS*.

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B. Dissolve 20 mg of the substance to be examined in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, mobile phase A (30:70 *V/V*).

Test solution Dissolve 30 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) In order to produce impurity C *in situ*, to 6 mg of the substance to be examined add 15 mL of *acetonitrile R*, 3 mL of *water R* and 5 mL of stabilised *strong hydrogen peroxide solution R*. Store at 30 °C for at least 6 h then dilute to 50.0 mL with mobile phase A. To 1.0 mL of this solution add 3 mg of the substance to be examined dissolved in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 3 mg of *raloxifene for peak identification CRS* (containing impurity A) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 9.0 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	75	25
9 - 40	75 → 50	25 → 50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

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Injection 10 µL.

Identification of impurity A Use the chromatogram supplied with *raloxifene for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to raloxifene (retention time = about 18 min): impurity A = about 0.7; impurity C = about 1.2.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to raloxifene and impurity C in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.8 for the principal peak in the chromatogram obtained with reference solution (a).

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*).

Buffer solution pH 2.5 7.2 g/L Solution of *potassium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *raloxifene hydrochloride CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) In order to produce impurity C *in situ*, to 6 mg of the substance to be examined add 15 mL of *acetonitrile R*, 3 mL of *water R* and 5 mL of stabilised *strong hydrogen peroxide solution R*. Store at 30 °C for at least 6 h, then dilute to 50.0 mL with buffer solution pH 2.5.

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Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase *acetonitrile R*, buffer solution pH 2.5 (33:67 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Run time Twice the retention time of raloxifene.

Relative retention With reference to raloxifene (retention time = about 3 min): impurity C = about 1.2.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to raloxifene and impurity C in the chromatogram obtained with reference solution (b); if necessary, adjust the concentration of acetonitrile in the mobile phase;

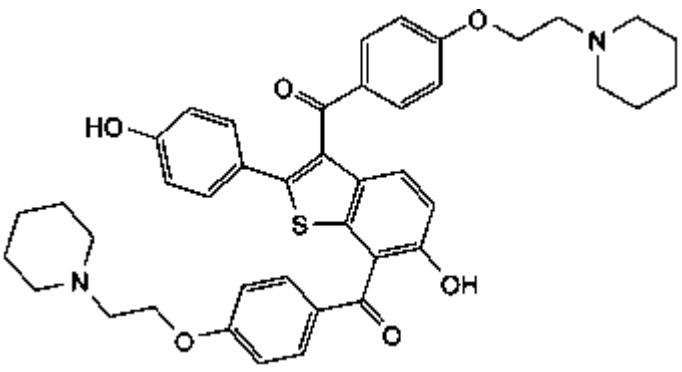
— *symmetry factor*: maximum 1.8 for the principal peak in the chromatogram obtained with reference solution (a).

Calculate the percentage content of $C_{28}H_{28}ClNO_4S$ from the declared content of *raloxifene hydrochloride CRS*.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C.*



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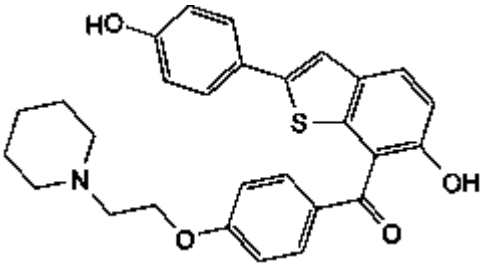
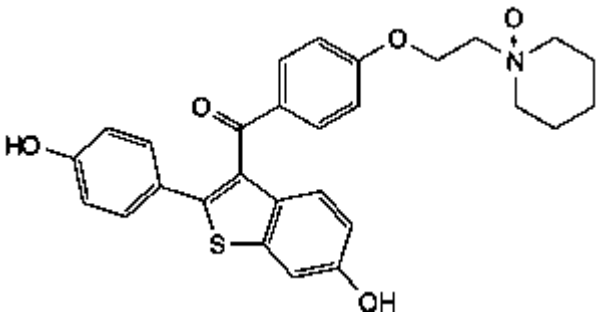
A. [6-hydroxy-2-(4-hydroxyphenyl)-7-[4-[2-(piperidin-1-yl)ethoxy]benzoyl]-1-benzothiophen-3-yl][4-[2-(piperidin-1-yl)ethoxy]phenyl]methanone,



B. [6-hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-7-yl][4-[2-(piperidin-1-yl)ethoxy]phenyl]methanone,



C. [6-hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl][4-[2-(piperidin-1-yl)ethoxy]phenyl]methanone *N*-oxide.

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Raltegravir Chewable Tablets

General Notices

(Ph. Eur. monograph 2939)

Action and use

Antiviral (HIV).

Ph Eur

DEFINITION

Chewable tablets containing *Raltegravir potassium (2887)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of raltegravir ($C_{20}H_{21}FN_6O_5$) stated on the label.

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay with a diode array detector in the range of 190-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Crush 1 tablet to a powder and homogenise.

Comparison *raltegravir potassium CRS*.

Results The spectrum obtained shows absorption maxima at about 1633 cm^{-1}, 1515 cm^{-1}, 1188 cm^{-1}, 810 cm^{-1} and 728 cm^{-1}, similar to the spectrum obtained with *raltegravir potassium CRS*.

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Other absorption maxima may be present in the spectra.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (30:70 *V/V*).

Test solution To 10 tablets, add a suitable volume of the solvent mixture to obtain a concentration of raltegravir of 1 mg/mL. Stir vigorously for 1 h. Centrifuge a portion of the solution and dilute 20.0 mL of the clear supernatant to 200.0 mL with the solvent mixture.

Reference solution (a) Dissolve 22.0 mg of raltegravir potassium CRS in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of raltegravir impurity E CRS in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 100 mL with the test solution.

Reference solution (d) In order to prepare impurities C and D *in situ*, dissolve 20 mg of raltegravir potassium R in a 40 g/L solution of sodium hydroxide R and dilute to 10 mL with the same solvent. Stir the solution for 2 h at room temperature. To 5 mL of the solution add 5 mL of a 103 g/L solution of hydrochloric acid R and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 20 volumes of acetonitrile for chromatography R and 80 volumes of a 1.36 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 3.0 with phosphoric acid R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 27	100 → 50	0 → 50

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 220 nm.

Injection 15 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities C and D; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E.

Relative retention With reference to raltegravir (retention time = about 22 min): impurity D = about 0.7; impurity C = about 0.8; impurity E = about 0.96.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity E and raltegravir.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.6; impurity D = 1.4;

— for each impurity, use the concentration of raltegravir in reference solution (b).

Limits:

— *impurity C*: maximum 0.3 per cent;

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.8 per cent;

— *reporting threshold*: 0.1 per cent.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium *water R*. Use 900 mL of the medium.

Rotation speed 50 r/min.

Time 15 min.

Analysis Liquid chromatography (*2.2.29*).

Test solutions Samples withdrawn from the dissolution vessel and filtered.

Reference solution Using sonication if necessary, dissolve a suitable quantity of *raltegravir potassium CRS* in a suitable quantity of a mixture of 30 volumes of *acetonitrile R* and 70 volumes of *water R* to obtain a concentration of raltegravir corresponding to the theoretical concentration of raltegravir in the test solution, based on the labelled content of the tablets.

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Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped monolithic octadecylsilyl silica gel for chromatography R*;

— *temperature*: 40 °C.

Mobile phase Mix 38 volumes of *acetonitrile R* and 62 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 5.0 mL/min.

Detection Spectrophotometer at 303 nm.

Injection 30 µL.

Run time 1 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the amount of dissolved raltegravir ($C_{20}H_{21}FN_6O_5$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *raltegravir potassium CRS* and applying a conversion factor of 0.9210.

Acceptance criterion:

— *Q* = 85 per cent after 15 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the percentage content of raltegravir ($C_{20}H_{21}FN_6O_5$) taking into account the assigned content of *raltegravir potassium CRS* and applying a conversion factor of 0.9210.

IMPURITIES

Specified impurities *C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, B, E.*

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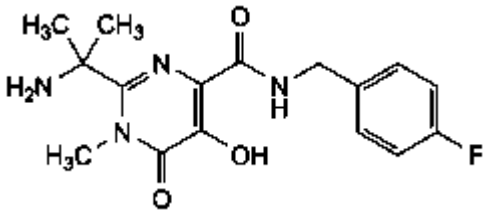
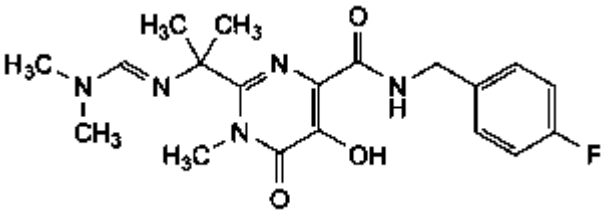
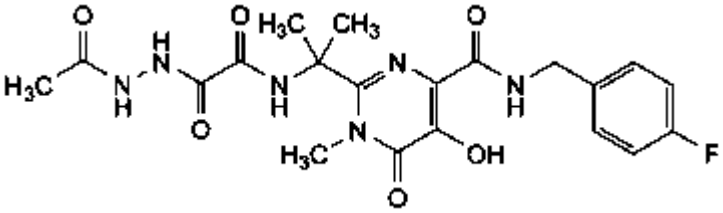


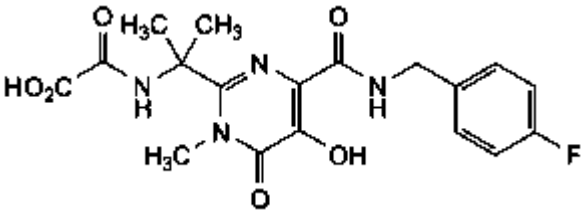
A. 2-(2-aminopropan-2-yl)-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



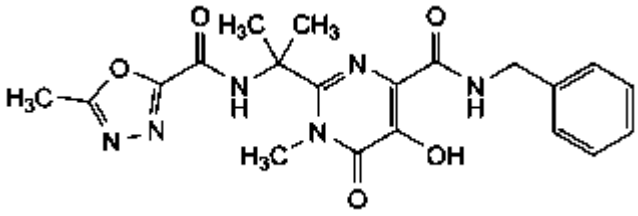
B. 2-[2-[(*E*)-[(dimethylamino)methylidene]amino]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



C. 2-[2-[2-(2-acetylhydrazin-1-yl)-2-oxoacetamido]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



D. [[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]amino]oxoacetic acid,



E. *N*-benzyl-5-hydroxy-1-methyl-2-[2-(5-methyl-1,3,4-oxadiazole-2-carboxamido)propan-2-yl]-6-oxo-1,6-dihydropyrimidine-4-carboxamide.

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[1] The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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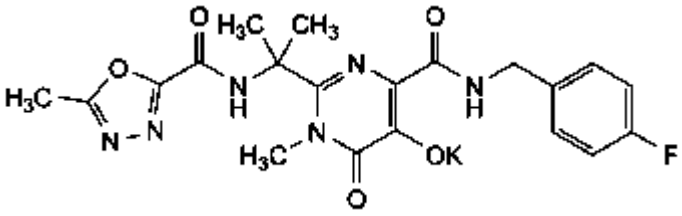
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Raltegravir Potassium

General Notices

(Ph. Eur. monograph 2887)



$C_{20}H_{20}FKN_6O_5$ 482.5 *871038-72-1*

Action and use

Antiviral (HIV).

Preparations

Raltegravir Chewable Tablets

Raltegravir Tablets

Ph Eur

DEFINITION

Potassium 4-[[(4-fluorophenyl)methyl]carbamoyl]-1-methyl-2-[2-(5-methyl-1,3,4-oxadiazole-2-carboxamido)propan-2-yl]-6-oxo-1,6-dihydropyrimidin-5-olate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *raltegravir potassium CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (b) of potassium (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (25:75 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in 100 mL of the solvent mixture using sonication for 5 min. Add about 140 mL of the solvent mixture then dilute to 250.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of *raltegravir potassium CRS* in 100 mL of the solvent mixture using sonication for 5 min. Add about 140 mL of the solvent mixture then dilute to 250.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *raltegravir impurity E CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with the test solution.

Reference solution (d) In order to prepare impurity C *in situ*, dissolve 20 mg of the substance to be examined in a 40 g/L solution of *sodium hydroxide R* and dilute to 10 mL with the same solvent. Stir the solution for 30 min. To 5 mL of the solution add 5 mL of a 103 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the solvent mixture.

Reference solution (e) Dissolve 5 mg of *raltegravir for peak identification CRS* (containing impurities F and G) in 20 mL of the solvent mixture using sonication for 5 min. Add about 25 mL of the solvent mixture then dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 15 °C.

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Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	75	25
2 - 5	75 → 60	25 → 40
5 - 10	60 → 55	40 → 45
10 - 19	55 → 10	45 → 90
19 - 22	10 → 5	90 → 95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (b), (c), (d) and (e).

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram supplied with *raltegravir for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities F and G.

Relative retention With reference to raltegravir (retention time = about 10 min): impurity C = about 0.7; impurity E = about 0.95; impurity G = about 1.1; impurity F = about 1.15.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity E and raltegravir.

Calculation of percentage contents:

— for each impurity, use the concentration of raltegravir potassium in reference solution (b).

Limits:

— *impurity C*: maximum 0.2 per cent;

— *impurities E, F, G*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

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— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.6 per cent, determined on 0.500 g. Use as the solvent a mixture of equal volumes of *methanol R* and *formamide R*.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

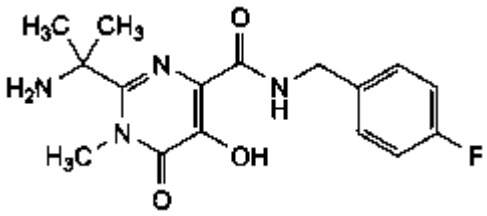
Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{20}H_{20}FKN_6O_5$ taking into account the assigned content of *raltegravir potassium CRS*.

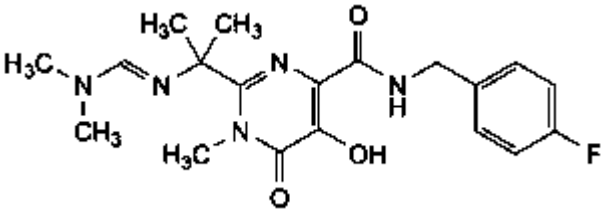
IMPURITIES

Specified impurities *C, E, F, G*.

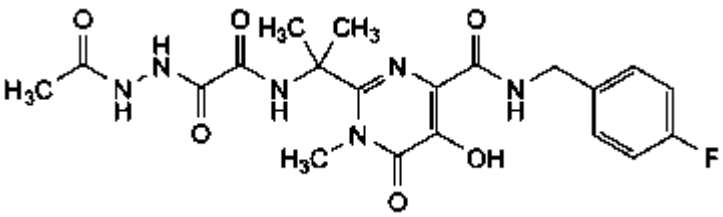
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D, H*.



A. 2-(2-aminopropan-2-yl)-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



B. 2-[2-[(*E*)-[(dimethylamino)methylidene]amino]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



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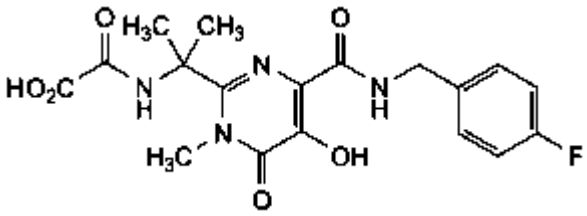
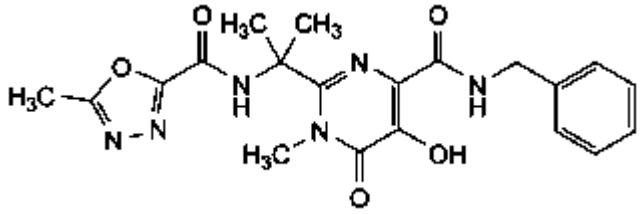
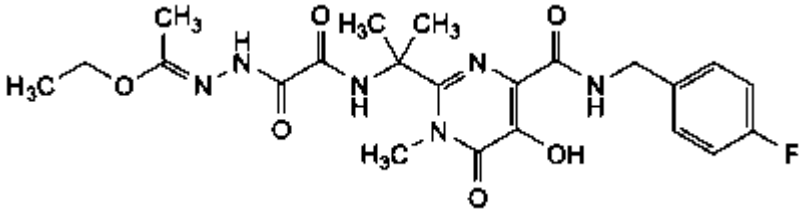
C. 2-[2-[2-(2-acetylhydrazin-1-yl)-2-oxoacetamido]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



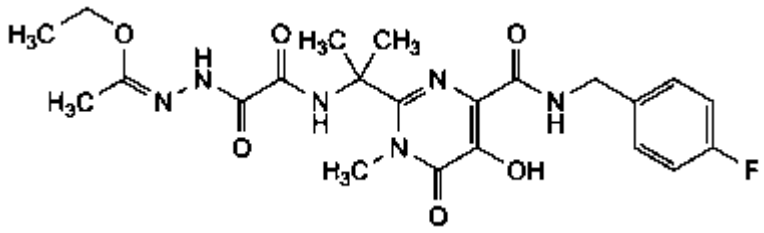
D. [[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]amino]oxoacetic acid,



E. *N*-benzyl-5-hydroxy-1-methyl-2-[2-(5-methyl-1,3,4-oxadiazole-2-carboxamido)propan-2-yl]-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



F. ethyl (1*E*)-*N*-[[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]oxamoyl]ethanehydrazonate,



G. ethyl (1*Z*)-*N*-[[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]oxamoyl]ethanehydrazonate,

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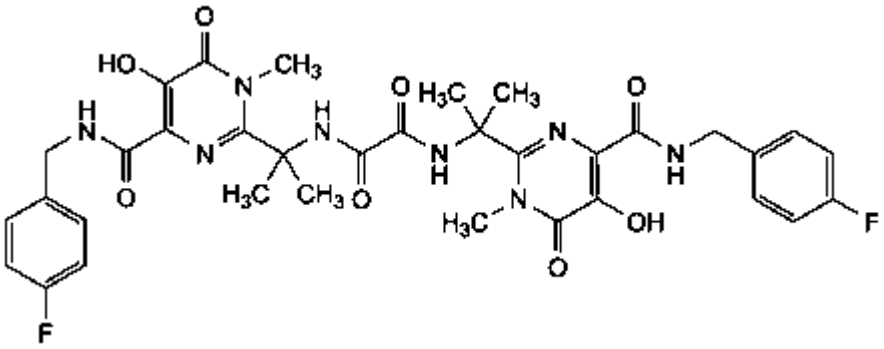

H. N^1,N^2-bis[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]oxamide.

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Raltegravir Tablets

General Notices

(Ph. Eur. monograph 2938)

Action and use

Antiviral (HIV).

Ph Eur

DEFINITION

Tablets containing *Raltegravir potassium (2887)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of raltegravir ($C_{20}H_{21}FN_6O_5$) stated on the label.

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay with a diode array detector in the range 190-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Crush 1 tablet to a powder and homogenise.

Comparison *raltegravir potassium CRS*.

Results The spectrum obtained shows absorption maxima at about 1633 cm^{-1}, 1515 cm^{-1}, 1188 cm^{-1}, 810 cm^{-1} and 728 cm^{-1}, similar to the spectrum obtained with *raltegravir potassium CRS*.

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Other absorption maxima may be present in the spectra.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (30:70 *V/V*).

Test solution To 10 tablets, add a suitable volume of the solvent mixture to obtain a concentration of raltegravir of 8 mg/mL. Stir vigorously for 1 h. Centrifuge a portion of the solution and dilute 5.0 mL of the clear supernatant to 100.0 mL with the solvent mixture. Dilute 50.0 mL of this solution to 200.0 mL with the solvent mixture.

Reference solution (a) Dissolve 22.0 mg of raltegravir potassium CRS in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of raltegravir impurity E CRS in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 100 mL with the test solution.

Reference solution (d) In order to prepare impurities C and D *in situ,* dissolve 20 mg of raltegravir potassium R in a 40 g/L solution of sodium hydroxide R and dilute to 10 mL with the same solvent. Stir the solution for 2 h at room temperature. To 5 mL of the solution add 5 mL of a 103 g/L solution of hydrochloric acid R and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 20 volumes of acetonitrile for chromatography R and 80 volumes of a 1.36 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 3.0 with phosphoric acid R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 27	100 → 50	0 → 50

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Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 15 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities C and D; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E.

Relative retention With reference to raltegravir (retention time = about 22 min): impurity D = about 0.7; impurity C = about 0.8; impurity E = about 0.96.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity E and raltegravir.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.6; impurity D = 1.4;

— for each impurity, use the concentration of raltegravir in reference solution (b).

Limits:

— *impurity C*: maximum 0.5 per cent;

— *impurity D*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.8 per cent;

— *reporting threshold*: 0.05 per cent.

Dissolution[1] (*2.9.3, Apparatus 2*). *Use sinker devices.*

Dissolution medium *water R*. Use 900 mL of the medium.

Rotation speed 100 r/min.

Time 15 min and 60 min.

Analysis Liquid chromatography (*2.2.29*).

Test solutions Samples withdrawn from the dissolution vessel.

Reference solution Using sonication, dissolve a suitable quantity of *raltegravir potassium CRS* in a suitable quantity of a mixture of 30 volumes of *acetonitrile R* and 70 volumes of *water R* to obtain a concentration of raltegravir corresponding to the theoretical

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concentration of raltegravir in the test solution, based on the labelled content of the tablets.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped monolithic octadecylsilyl silica gel for chromatography R*;

— *temperature*: 40 °C.

Mobile phase Mix 38 volumes of *acetonitrile R* and 62 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 5.0 mL/min.

Detection Spectrophotometer at 303 nm.

Injection 10 µL.

Run time 1 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the amount of dissolved raltegravir ($C_{20}H_{21}FN_6O_5$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *raltegravir potassium CRS* and applying a conversion factor of 0.9210.

Acceptance criteria:

— *level 1*: 15-45 per cent at 15 min; not less than 75 per cent at 60 min;

— *level 2*: the average value of the 12 tablets is within the range 15-45 per cent at 15 min and is not less than 75 per cent at 60 min; none of the units is outside of the range 5-55 per cent at 15 min and none of the values is less than 65 per cent of the labelled content at 60 min;

— *level 3*: the average value of the 24 tablets is within the range 15-45 per cent at 15 min and is not less than 75 per cent at 60 min; not more than 2 of the 24 units are outside of the range 5-55 per cent at 15 min and not more than 2 of the 24 units are less than 65 per cent of the labelled content at 60 min; none of the units is more than 65 per cent at 15 min and none is less than 55 per cent of the labelled content at 60 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

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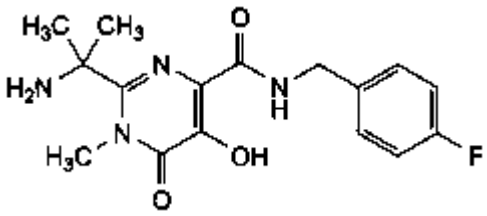
— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the percentage content of raltegravir ($C_{20}H_{21}FN_6O_5$) taking into account the assigned content of *raltegravir potassium CRS* and a conversion factor of 0.9210.

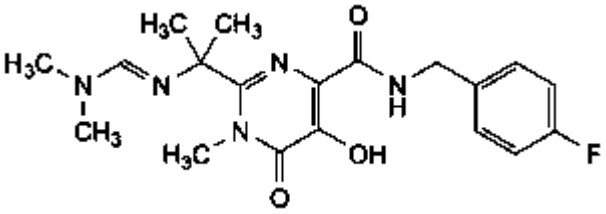
IMPURITIES

Specified impurities *C, D.*

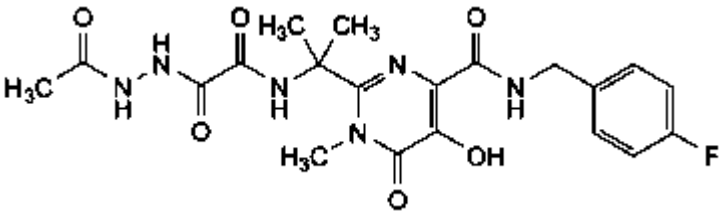
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, B, E.*



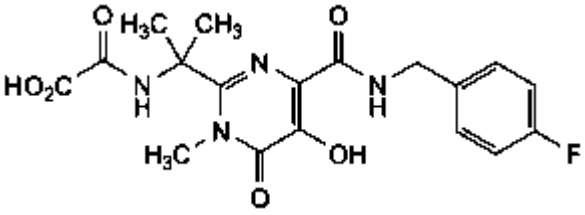
A. 2-(2-aminopropan-2-yl)-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



B. 2-[2-[(*E*)-[(dimethylamino)methylidene]amino]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



C. 2-[2-[2-(2-acetylhydrazin-1-yl)-2-oxoacetamido]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



D. [[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]amino]oxoacetic acid,

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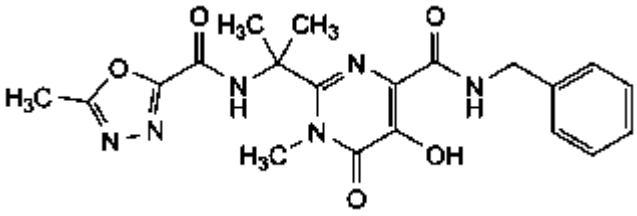

E. *N*-benzyl-5-hydroxy-1-methyl-2-[2-(5-methyl-1,3,4-oxadiazole-2-carboxamido)propan-2-yl]-6-oxo-1,6-dihydropyrimidine-4-carboxamide.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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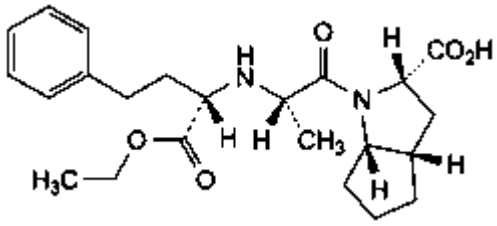
Ramipril

General Notices

(Ph. Eur. monograph 1368)



$C_{23}H_{32}N_2O_5$ 416.5 *87333-19-5*

Action and use

Angiotensin converting enzyme inhibitor.

Preparations

Ramipril Capsules

Ramipril Tablets

Ph Eur

DEFINITION

(2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in methanol.

IDENTIFICATION

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IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *ramipril CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.1 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 32.0 to + 38.0 (dried substance).

Dissolve 0.250 g in a mixture of 14 volumes of *hydrochloric acid R1* and 86 volumes of *methanol R* and dilute to 25.0 mL with the same mixture of solvents.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dissolve 2 mg of *ramipril impurity A CRS*, 2 mg of *ramipril impurity B CRS*, 2 mg of *ramipril impurity C CRS* and 2 mg of *ramipril impurity D CRS* in mobile phase A and dilute to 25 mL with mobile phase A. To 1 mL of this solution, add 5 mL of the test solution and dilute to 10 mL with mobile phase B.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with mobile phase B. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase B.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 65 °C.

Mobile phase:

— *mobile phase A*: dissolve 2.0 g of *sodium perchlorate R* in a mixture of 0.5 mL of *triethylamine R* and 800 mL of *water for chromatography R*; adjust to pH 3.6 with *phosphoric acid R* and add 200 mL of *acetonitrile R1*;

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— *mobile phase B*: dissolve 2.0 g of *sodium perchlorate R* in a mixture of 0.5 mL of *triethylamine R* and 300 mL of *water for chromatography R*; adjust to pH 2.6 with *phosphoric acid R* and add 700 mL of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	90	10
6 - 7	90 → 75	10 → 25
7 - 20	75 → 65	25 → 35
20 - 30	65 → 25	35 → 75
30 - 50	25	75

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Equilibration With the mobile phase at the initial composition for at least 35 min; if a suitable baseline cannot be obtained, use another grade of triethylamine.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to ramipril (retention time = about 18 min): impurity A = about 0.8; impurity B = about 1.3; impurity C = about 1.5; impurity D = about 1.7.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to impurity A and ramipril in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (c);

— *symmetry factor*: 0.8 to 2.0 for the peak due to ramipril in the chromatogram obtained with the test solution.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2.4;

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

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— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 25 mL of *methanol R* and add 25 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 41.65 mg of $C_{23}H_{32}N_2O_5$.

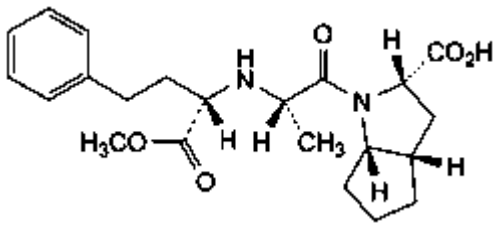
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B, C, D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E, F, G, H, I, J, K, L, M, N, O.



A. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-methoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril methyl ester),

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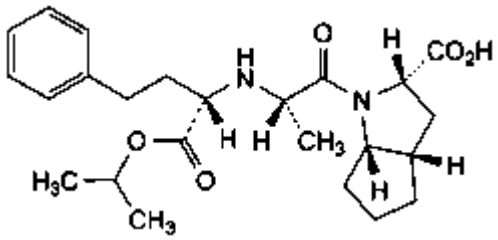
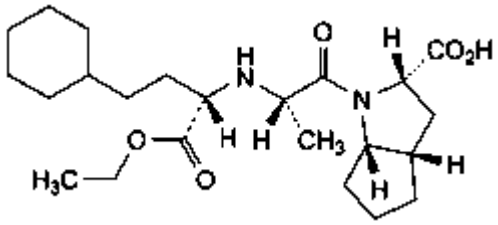
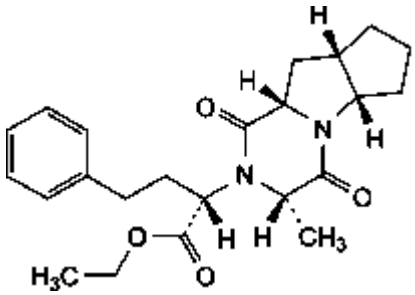


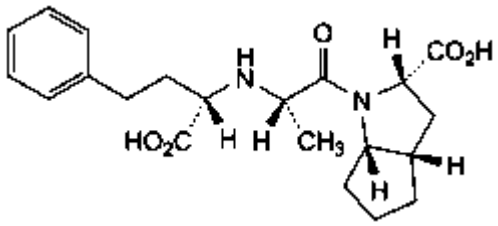
B. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-oxo-4-phenyl-1-[(propan2-yl)oxy]butan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril isopropyl ester),



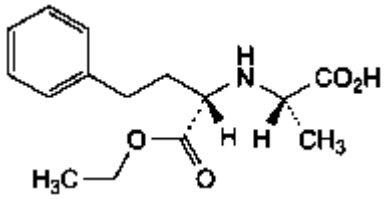
C. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-4-cyclohexyl-1-ethoxy-1oxobutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (hexahydroramipril),



D. ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril diketopiperazine),



E. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramiprilat),



F. (2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoic acid,

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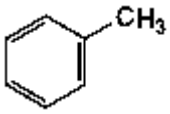
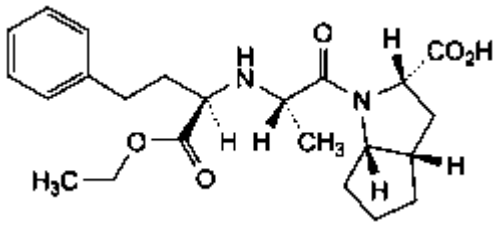
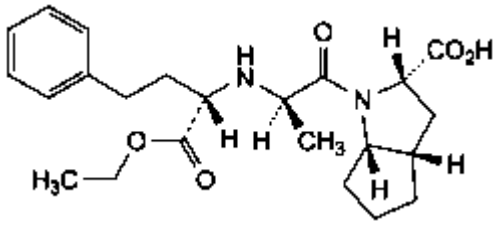


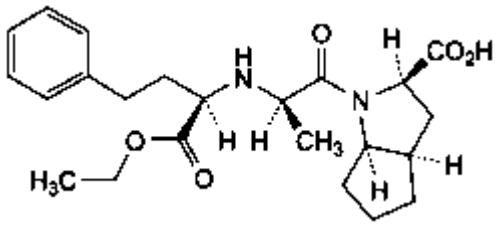
G. methylbenzene (toluene),



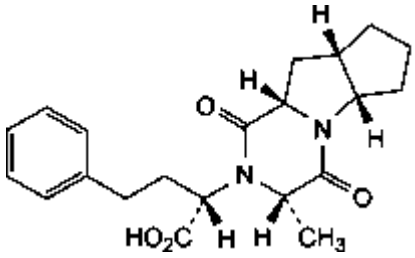
H. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*R*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*R*,*S*,*S*,*S*,*S*)-epimer of ramipril),



I. (2*S*,3a*S*,6a*S*)-1-[(2*R*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*R*,*S*,*S*,*S*)-epimer of ramipril),



J. (2*R*,3a*R*,6a*R*)-1-[(2*R*)-2-[[(2*R*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (enantiomer of ramipril),



K. (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoic acid (ramiprilate diketopiperazine),

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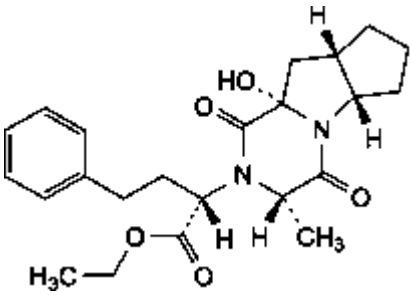
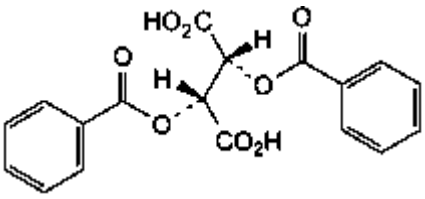
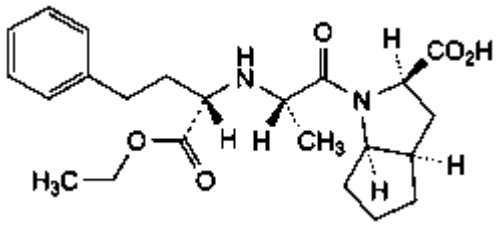


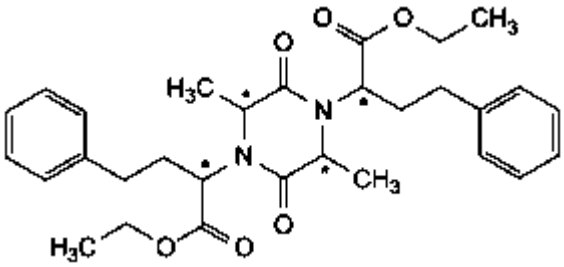
L. ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-9a-hydroxy-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril hydroxydiketopiperazine),



M. (2*R*,3*R*)-2,3-bis(benzoyloxy)butanedioic acid (dibenzoyl tartric acid),



N. (2*R*,3a*R*,6a*R*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*S*,*R*,*R*,*R*)-isomer of ramipril),



O. diethyl (2Ξ,2′Ξ)-2,2′-[(2Ξ,5Ξ)-2,5-dimethyl-3,6-dioxopiperazine-1,4-diyl]bis(4-phenylbutanoate).

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Ramipril Capsules

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Ramipril Capsules contain Ramipril.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of ramipril, $C_{23}H_{32}N_2O_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 12.5 mg of Ramipril with 50 mL of *acetone*, centrifuge for 10 minutes, filter the supernatant liquid through a 0.45-µm filter, evaporate the filtrate to dryness on a *water bath* and dry the residue for 3 hours at 60°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ramipril (*RS 417*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 500 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Withdraw a sample of the medium and filter immediately through a 0.45-µm glass-fibre filter (Whatman GD/X is suitable), discarding the first 5 mL of filtrate. Use the filtered medium, diluted with *0.1M hydrochloric acid* if necessary, expected to contain 0.00025% w/v of Ramipril.

(2) 0.00025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 28°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

420 volumes of *acetonitrile R1* and 580 volumes of a solution containing 1.4% w/v of *sodium perchlorate* and 0.58% w/v of *orthophosphoric acid* adjusted to pH 2.5 with *triethylamine*, and adjust the mixture to pH 2.1 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of ramipril, $C_{23}H_{32}N_2O_5$, in the medium using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound for 10 minutes and stirring, a quantity of the contents of the capsules containing 25 mg of Ramipril with 50 mL of the mobile phase and filter through a 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 20 volumes with the mobile phase.

(3) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(4) 0.05% w/v of *ramipril BPCRS* and 0.0005% w/v of each of *ramipril impurity A EPCRS*, *ramipril impurity D EPCRS* and *ramipril impurity K BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 15 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3 times the retention time of ramipril.

When the chromatograms are recorded under the prescribed conditions, the retention time of ramipril is about 10 minutes and retention times relative to ramipril are about 0.3 for ramipril impurity E (ramiprilat), about 0.5 for ramipril impurity K (diketopiperazine acid impurity), about 0.7 for ramipril impurity A (methyl ester impurity) and about 2.6 for ramipril impurity D (diketopiperazine impurity).

MOBILE PHASE

A mixture, adjusted to pH 2.6 with *orthophosphoric acid*, of 350 volumes of *acetonitrile R1* and 680 volumes of a solution adjusted to pH 3.9 with *triethylamine*, containing 1.4% w/v of *sodium perchlorate* and 0.58% w/v of *orthophosphoric acid*.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to ramipril impurity K and ramipril impurity A is at least 1.0.

LIMITS

For capsules containing more than 1.25 mg of Ramipril

In the chromatogram obtained with solution (1) the combined area of peaks corresponding to ramipril impurity D and ramipril impurity E is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%); the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%). The sum of the areas of all the *secondary peaks* is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%).

For capsules containing 1.25 mg or less of Ramipril

In the chromatogram obtained with solution (1) the combined area of peaks corresponding to ramipril impurity D and ramipril impurity E is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%); the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%). The sum of the areas of all the *secondary peaks* is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Ramipril comply with the requirements stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 80 mL of *0.1M hydrochloric acid* to the contents and shell of one capsule, mix with the aid of ultrasound for 10 minutes and immediately stir magnetically for 15 minutes. Add sufficient *0.1M hydrochloric acid* to produce 100 mL and filter through a 0.45-µm glass-fibre filter (Whatman GD/X is suitable). Dilute the resulting solution, if necessary, with sufficient *0.1M hydrochloric acid* to produce a solution containing 0.00025% w/v of Ramipril. Solution (2) contains 0.00025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

The chromatographic conditions described under Dissolution may be used.

Calculate the content of $C_{23}H_{32}N_2O_5$ in each capsule using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

ASSAY

For capsules containing less than 2 mg and/or less than 2% w/w of Ramipril

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing 2 mg or more and 2% w/w or more of Ramipril

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Add 150 mL of *0.1M hydrochloric acid* to a quantity of the mixed contents of 20 capsules containing 50 mg of Ramipril, mix with the aid of ultrasound for 10 minutes and immediately stir magnetically for 15 minutes. Add sufficient *0.1M hydrochloric acid* to produce 200 mL and filter through a 0.45-µm glass-fibre filter (Whatman GD/X is suitable). Dilute the resulting solution with sufficient *0.1M hydrochloric acid* to produce a solution containing 0.00025% w/v of Ramipril.

(2) 0.00025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{32}N_2O_5$ in the capsules using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Ramipril.

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Ramipril Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Ramipril Tablets contain Ramipril.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ramipril, $C_{23}H_{32}N_2O_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 25 mg of Ramipril with 50 mL of *acetone*, centrifuge for 10 minutes, filter the supernatant liquid through a 0.45-µm filter, evaporate the filtrate to dryness on a *water bath* and dry the residue for 3 hours at 60°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ramipril (*RS 417*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 500 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Withdraw a sample of the medium and filter immediately through a 0.45-µm glass-fibre filter (Whatman GD/X is suitable), discarding the first 5 mL of filtrate. Use the filtered medium, diluted with *0.1M hydrochloric acid* if necessary, expected to contain 0.00025% w/v of Ramipril.

(2) 0.00025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

420 volumes of *acetonitrile R1* and 580 volumes of a solution containing 1.4% w/v of *sodium perchlorate* and 0.58% w/v of *orthophosphoric acid* adjusted to pH 2.5 with *triethylamine*, and adjust the mixture to pH 2.1 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of ramipril, $C_{23}H_{32}N_2O_5$, in the medium using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound for 10 minutes, a quantity of the contents of the powdered tablets containing 25 mg of Ramipril with 50 mL of the mobile phase, centrifuge and use the clear supernatant liquid.

(2) Dilute 1 volume of solution (1) to 20 volumes with the mobile phase.

(3) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(4) 0.05% w/v of *ramipril BPCRS* and 0.0005% w/v of each of *ramipril impurity A EPCRS*, *ramipril impurity D EPCRS* and *ramipril impurity K BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 15 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3 times the retention time of ramipril.

When the chromatograms are recorded under the prescribed conditions, the retention time of ramipril is about 10 minutes and retention times relative to ramipril are about 0.3 for ramipril impurity E (ramiprilat), about 0.5 for ramipril impurity K (diketopiperazine acid impurity), about 0.7 for ramipril impurity A (methyl ester impurity) and about 2.6 for ramipril impurity D (diketopiperazine impurity).

MOBILE PHASE

A mixture, adjusted to pH 2.6 with *orthophosphoric acid*, of 350 volumes of *acetonitrile R1* and 680 volumes of a solution adjusted to pH 3.9 with *triethylamine*, containing 1.4% w/v of *sodium perchlorate* and 0.58% w/v of *orthophosphoric acid*.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to ramipril impurity K and ramipril impurity A is at least 1.0.

LIMITS

For tablets containing more than 1.25 mg of Ramipril

In the chromatogram obtained with solution (1) the combined area of peaks corresponding to ramipril impurity D and ramipril impurity E is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%); the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%). The sum of the areas of all the *secondary peaks* is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%).

For tablets containing 1.25 mg or less of Ramipril

In the chromatogram obtained with solution (1) the combined areas of peak corresponding to ramipril impurity D and ramipril impurity E is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%); the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%). The sum of the areas of all the *secondary peaks* is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Ramipril comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 5 mL of *0.1M hydrochloric acid* to one tablet, mix with the aid of ultrasound for 10 minutes, dilute, if necessary, with sufficient *0.1M hydrochloric acid* to produce a solution containing 0.025% w/v of Ramipril, centrifuge and use the supernatant liquid. Solution (2) contains 0.025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

The chromatographic conditions described under Dissolution may be used.

Calculate the content of $C_{23}H_{32}N_2O_5$ in each tablet using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Ramipril

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Ramipril

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 100 mL of *0.1M hydrochloric acid* to a quantity of powdered tablets containing 25 mg of Ramipril, mix with the aid of ultrasound for 10 minutes and centrifuge, use the supernatant liquid.

(2) 0.025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{32}N_2O_5$ in the tablets using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Ramipril.

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Ranitidine Effervescent Tablets

General Notices

Effervescent Ranitidine Tablets

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer disease.

DEFINITION

Ranitidine Effervescent Tablets contain Ranitidine Hydrochloride in a suitable effervescent basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ranitidine, $C_{13}H_{22}N_4O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 200 to 400 nm of the solution prepared by dissolving one tablet in 100 mL of *water* exhibits a maximum at 313 nm. Dilute the solution if necessary.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

C. Dissolves with vigorous effervescence on the addition of warm *water* to produce a clear solution.

TESTS

Disintegration

Comply with the requirement for Effervescent Tablets stated under Tablets.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.13 g of Ranitidine with 100 mL *methanol (10%)* and filter (Whatman No. 42. paper is suitable).

(2) Dilute 1 volume of solution (1) to 500 volumes with *methanol (10%)*.

(3) 0.0065% w/v of *ranitidine for impurity A identification EPCRS* in mobile phase A.

(4) Dissolve the contents of a vial of *ranitidine impurity J EPCRS* in 1 mL of solution (1).

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(5) Dilute 1 volume of solution (2) to 2 volumes with *methanol (10%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters Xterra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Buffer solution Adjust the pH of 950 mL of 0.05M *potassium dihydrogen orthophosphate* to 7.1 by adding *strong sodium hydroxide solution* and dilute to 1 litre.

Mobile phase A 2 volumes of *acetonitrile* and 98 volumes of the buffer solution.

Mobile phase B 22 volumes of *acetonitrile* and 78 volumes of the buffer solution.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100→0	0→100	linear gradient
10-15	0	100	isocratic
15-16	0→100	100→0	linear gradient
16-20	100	0	isocratic

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 1.5.

LIMITS

Identify any peak due to impurity A in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1):

the area of any *secondary peak* with a retention time relative to ranitidine of 0.66 is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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the area of any peak corresponding to impurity A is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the total area of any such peaks is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 tablets with 400 mL of *methanol (10%)* until the tablets have completely disintegrated, dilute to 500 mL with *methanol (10%)*, filter (Whatman GF/C paper is suitable) and dilute the filtrate with the mobile phase to produce a solution containing the equivalent of 0.01% w/v of ranitidine.

(2) 0.0112% w/v of *ranitidine hydrochloride BPCRS* in *methanol (10%)*.

(3) 0.0112% w/v of *ranitidine hydrochloride BPCRS* and 0.0002% w/v of *dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl]furfuryl}amine BPCRS* in *methanol (10%)*

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 322 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of 0.1M *ammonium acetate* and 85 volumes of *methanol*.

SYSTEM SUITABILITY

The assay is not valid unless the peak due to ranitidine in the chromatogram obtained with solution (3) shows baseline separation from the peak due to dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl]-furfuryl}amine.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{22}N_4O_3S$ in the tablets using the declared content of $C_{13}H_{22}N_4O_3S$ in *ranitidine hydrochloride BPCRS*.

STORAGE

Ranitidine Effervescent Tablets should be protected from light.

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LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ranitidine.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ranitidine Hydrochloride.

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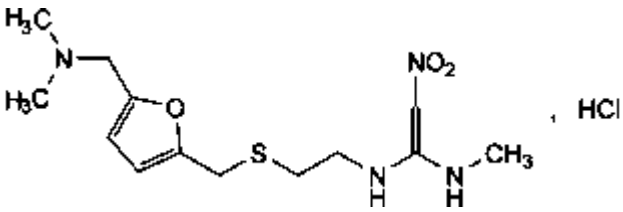
Ranitidine Hydrochloride

General Notices

(Ph. Eur. monograph 0946)



$C_{13}H_{23}ClN_4O_3S$ 350.9 *66357-59-3*

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer disease.

Preparations

Ranitidine Injection

Ranitidine Oral Solution

Ranitidine Tablets

Ranitidine Effervescent Tablets

Ph Eur

DEFINITION

N-[2-[[[5-[(Dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-*N*′-methyl-2-nitroeth-1-ene-1,1-diamine hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or pale yellow, crystalline powder, hygroscopic.

Solubility

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Freely soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, very slightly soluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ranitidine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve 10 mg of the substance to be examined and 10 mg of the reference substance separately in 0.5 mL of *methanol R* in an agate mortar. Evaporate to dryness under a stream of *nitrogen R*. Dry the residues under vacuum for 30 min. Add 3 drops of *liquid paraffin R* to the residues and triturate until the mull shows a milky appearance. Compress the mulls between 2 plates transparent to infrared radiation and record new spectra.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

pH (2.2.3)

4.5 to 6.0 for solution S.

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 6.8 g of *potassium dihydrogen phosphate R* in 950 mL of *water for chromatography R*. Adjust to pH 7.1 with *strong sodium hydroxide solution R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 13 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dissolve 6.5 mg of *ranitidine for impurity A identification CRS* in mobile phase A and dilute to 50 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of *ranitidine impurity J CRS* in 1 mL of the test solution.

Blank solution Mobile phase A.

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Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, buffer solution (2:98 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography R*, buffer solution (22:78 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100 → 0	0 → 100
10 - 15	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *ranitidine for impurity A identification CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity J.

Relative retention With reference to ranitidine (retention time = about 7 min): impurity J = about 0.9; impurity A = about 1.7.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity J and ranitidine in the chromatogram obtained with reference solution (c);

— the chromatogram obtained with the blank solution does not show any peak with the same relative retention as the peak due to impurity A in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity J by 2.0;

— for each impurity, use the concentration of ranitidine hydrochloride in reference solution (b).

Limits:

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— *impurity A*: maximum 0.3 per cent;

— *impurity J*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.75 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.280 g in 35 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.09 mg of $C_{13}H_{23}ClN_4O_3S$.

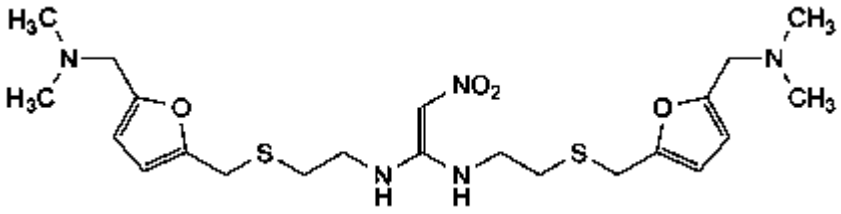
STORAGE

In airtight container, protected from light.

IMPURITIES

Specified impurities *A, J.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, G, H, I, K.*



A. *N*,*N*′-bis[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroeth-1-ene-1,1-diamine,

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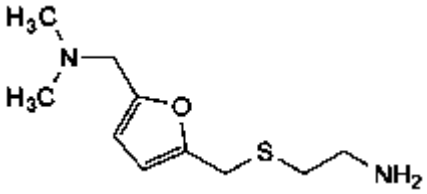
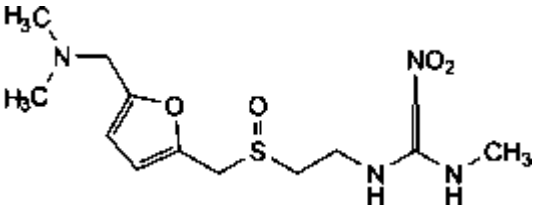
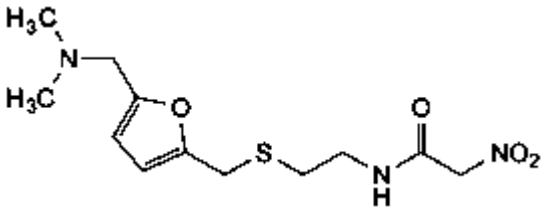


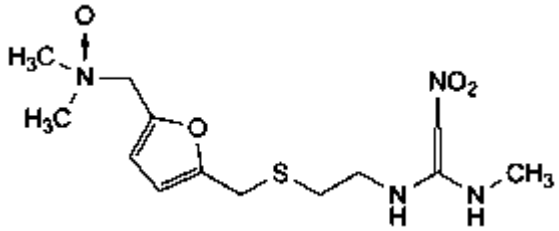
B. 2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethan-1-amine,



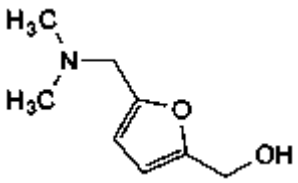
C. *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfinyl]ethyl]-*N*′-methyl-2-nitroeth-1-ene-1,1-diamine,



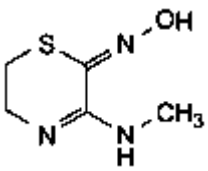
D. *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroacetamide,



E. [5-[[[2-[[1-(methylamino)-2-nitroeth-1-en-1-yl]amino]ethyl]sulfanyl]methyl]furan-2-yl]-*N*,*N*-dimethylmethanamine *N*-oxide,



F. [5-[(dimethylamino)methyl]furan-2-yl]methanol,



G. [3-(methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-ylidene]hydroxylamine,

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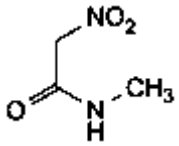
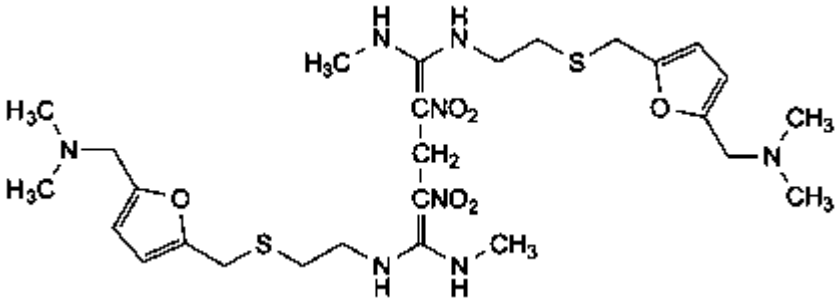
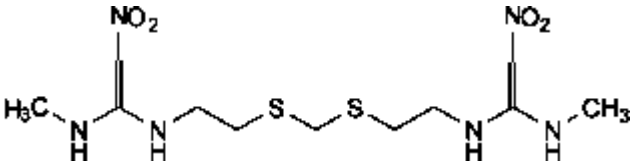


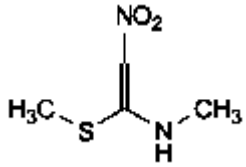
H. *N*-methyl-2-nitroacetamide,



I. 2,2′-methylenebis[*N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-*N*′-methyl-2-nitroeth-1-ene-1,1-diamine],



J. *N*,*N*″-[methylenebis(sulfanediylethan-2,1-diyl)]bis(*N*′-methyl-2-nitroeth-1-ene-1,1-diamine),



K. *N*-methyl-1-(methylsulfanyl)-2-nitroeth-1-en-1-amine.

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Ranitidine Injection

General Notices

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer disease.

DEFINITION

Ranitidine Injection is a sterile solution of Ranitidine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ranitidine, $C_{13}H_{22}N_4O_3S$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume of the injection containing the equivalent of 25 mg of ranitidine add 20 mL of *methanol*, mix and evaporate to dryness. Add 1 mL of *petroleum spirit* (*boiling range, 60° to 80°*) to the resulting residue, scratch the side of the vessel with a glass rod to induce crystallisation, evaporate to dryness and dry the residue at 60° for 10 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of ranitidine hydrochloride (*RS 311*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

Buffered formulations, pH 6.7 to 7.3; unbuffered formulations, pH 4.5 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, a volume of the injection with *water* to contain the equivalent of 0.1% w/v of ranitidine.

(2) Dilute 1 volume of solution (1) to 50 volumes with *water*.

(3) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(4) Dilute 1 volume of solution (1) to 200 volumes with *water*.

(5) Dilute 1 volume of solution (3) to 5 volumes with *water*.

(6) Dissolve the contents of a vial of *ranitidine impurity J EPCRS* in 1 mL of solution (1).

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CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters XTerra MS C18 is suitable).

(b) Gradient elution using the mobile phase described below.

(c) Flow rate of 1.5 mL per minute.

(d) Column temperature of 35°.

(e) Detection wavelength of 230 nm.

(f) Injection volume of 20 µL for each solution.

MOBILE PHASE

Buffer solution Adjust the pH of 950 mL of 0.05M potassium dihydrogen orthophosphate to 7.1 by adding strong sodium hydroxide solution and dilute to 1 litre.

Mobile phase A 2 volumes of *acetonitrile* and 98 volumes of buffer solution.

Mobile phase B 22 volumes of *acetonitrile* and 78 volumes of buffer solution.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100 → 0	0 → 100	linear gradient
10-15	0	100	isocratic
15-16	0 → 100	100 → 0	linear gradient
16-20	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the *resolution* between the two principal peaks is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of not more than one *secondary peak* is greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of not more than two other *secondary peaks* is greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%);

the area of not more than two further *secondary peaks* is greater than the principal peak in solution (5) (0.2%).

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection with sufficient of the mobile phase to contain the equivalent of 0.01% w/v of ranitidine.

(2) 0.0112% w/v of *ranitidine hydrochloride BPCRS* in mobile phase.

(3) 0.0112% w/v of *ranitidine hydrochloride BPCRS* and 0.0002% w/v of *dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl]furfuryl}amine BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS 1 is suitable).

(b) Isocratic elution using the mobile phase described below.

(c) Flow rate of 2 mL per minute.

(d) Ambient column temperature.

(e) Detection wavelength of 322 nm.

(f) Injection volume of 20 µL for each solution.

MOBILE PHASE

15 volumes of 0.1M *ammonium acetate* and 85 volumes of *methanol*.

SYSTEM SUITABILITY

The assay is not valid unless the peak due to ranitidine in the chromatogram obtained with solution (3) shows baseline separation from the peak due to dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl] furfuryl}amine.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{22}N_4O_3S$ in the injection using the declared content of $C_{13}H_{22}N_4O_3S$ in *ranitidine hydrochloride BPCRS*.

STORAGE

Ranitidine Injection should be protected from light.

LABELLING

The label states (1) the quantity of active ingredient in terms of the equivalent amount of ranitidine; (2) where appropriate, that the injection is buffered.

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Ranitidine Oral Solution

General Notices

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer disease.

DEFINITION

Ranitidine Oral Solution is a solution of Ranitidine Hydrochloride in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ranitidine, $C_{13}H_{22}N_4O_3S$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Prepare a solid phase extraction cartridge containing a C_{18} sorbent (Sep-Pak C_{18} cartridges are suitable) by passing 10 mL of *methanol* followed by 20 mL of 0.5M *ammonia* through the cartridge; attach the tip of a suitable syringe to the cartridge. Transfer a quantity of the oral solution containing the equivalent of 10 mg of ranitidine to the barrel of the syringe, add 2 mL of 0.5M *ammonia* to the syringe, insert the plunger and slowly force the mixture through the cartridge, discarding the eluant; repeat with two 4-mL quantities of 0.5M *ammonia* discarding the eluant. Pass two 5-mL quantities of a mixture of 25 volumes of 0.1M *hydrochloric acid* and 75 volumes of *methanol* through the cartridge and collect the eluant; add 40 mL of *absolute ethanol* to the collected eluant, evaporate the resulting solution to dryness at a temperature not exceeding 30° under reduced pressure and dissolve the residue in 1 mL of *methanol*.

(2) Prepare in the same manner as solution (1) using a solution containing 1.12% w/v of *ranitidine hydrochloride BPCRS* in *water* in place of the preparation being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and expose to iodine vapour in a closed chamber until the spots are visible.

MOBILE PHASE

4 volumes of *water*, 8 volumes of 18M *ammonia*, 30 volumes of *propan-2-ol* and 50 volumes of *ethyl acetate*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.7 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Prepare a solid phase extraction cartridge containing a C_{18} sorbent (Sep-Pak C_{18} cartridges are suitable) by passing 10 mL of *methanol* followed by 20 mL of 0.5M *ammonia* through the cartridge; attach the tip of a suitable syringe to the cartridge. Transfer a weighed quantity of the oral solution containing the equivalent of 15 mg of ranitidine to the barrel of the syringe, add 2 mL of 0.5M *ammonia* to the syringe, insert the plunger and slowly force the mixture through the cartridge, discarding the eluant; repeat with two 4 mL quantities of 0.5M *ammonia* discarding the eluant. Pass two 5-mL quantities of a mixture of 25 volumes of 0.1M *hydrochloric acid* and 75 volumes of *methanol* through the cartridge and collect the eluant; add 40 mL of *absolute ethanol* to the collected eluant, evaporate the resulting solution to dryness at a temperature not exceeding 30° under reduced pressure and dissolve the residue in 2 mL of *water*.

(2) Dilute 1 volume of solution (1) to 50 volumes with *water*.

(3) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(4) Dilute 1 volume of solution (1) to 200 volumes with *water*.

(5) Dilute 1 volume of solution (3) to 5 volumes with *water*.

(6) Dissolve the contents of a vial of *ranitidine impurity J EPCRS* in 1 mL of a solution containing 0.15% w/v of *ranitidine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (3.5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 230 nm.

(f) Use an injection volume of 20 µL for each solution.

MOBILE PHASE

Buffer solution Adjust the pH of 950 mL of 0.05M *potassium dihydrogen orthophosphate* to 7.1 by adding *strong sodium hydroxide solution* and dilute to 1 litre.

Mobile phase A 2 volumes of *acetonitrile* and 98 volumes of buffer solution.

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Mobile phase B 22 volumes of *acetonitrile* and 78 volumes of buffer solution.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100→0	0→100	linear gradient
10-15	0	100	isocratic
15-16	0→100	100→0	linear gradient
16-20	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the *resolution* between the two principal peaks is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of not more than one *secondary peak* is greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of not more than two other *secondary peaks* is greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%);

the area of not more than two further *secondary peaks* is greater than the principal peak in solution (5) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution containing the equivalent of 10 mg of ranitidine with sufficient of the mobile phase to produce 100 mL.

(2) 0.0112% w/v of *ranitidine hydrochloride BPCRS* in the mobile phase.

(3) 0.0112% w/v of *ranitidine hydrochloride BPCRS* and 0.0002% w/v of *dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl]furfuryl}amine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS 1 is suitable).

(b) Isocratic elution using the mobile phase described below.

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(c) Flow rate of 2 mL per minute.

(d) Ambient column temperature.

(e) Detection wavelength of 322 nm.

(f) Injection volume of 20 µL for each solution.

MOBILE PHASE

15 volumes of 0.1M *ammonium acetate* and 85 volumes of *methanol*.

SYSTEM SUITABILITY

The assay is not valid unless the peak due to ranitidine in the chromatogram obtained with solution (3) shows baseline separation from the peak due to dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl]furfuryl}amine.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{13}H_{22}N_4O_3S$, weight in volume, using the declared content of $C_{13}H_{22}N_4O_3S$ in *ranitidine hydrochloride BPCRS*.

STORAGE

Ranitidine Oral Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ranitidine.

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Ranitidine Tablets

General Notices

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer disease.

DEFINITION

Ranitidine Tablets contain Ranitidine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ranitidine, $C_{13}H_{22}N_4O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 25 mg of ranitidine with 5 mL of *methanol* for 5 minutes, filter and evaporate the filtrate to dryness. Add 1 mL of *petroleum spirit* (*boiling range, 60° to 80°*) to the residue, scratch the side of the vessel to induce crystallisation, evaporate to dryness and dry the residue at 60° for 10 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of ranitidine hydrochloride (*RS 311*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute the filtrate, if necessary, with dissolution medium to produce a solution containing the equivalent of 0.0083% w/v of ranitidine. Measure the *absorbance*, Appendix II B, at the maximum at 314 nm using *water* in the reference cell.

(2) 0.0093% w/v of *ranitidine hydrochloride BPCRS*. Measure the *absorbance*, Appendix II B, at the maximum at 314 nm using *water* in the reference cell.

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DETERMINATION OF CONTENT

Calculate the total content of $C_{13}H_{22}N_4O_3S$ in the medium from the absorbances obtained and using the declared content of $C_{13}H_{22}N_4O_3S$ in *ranitidine hydrochloride BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.13 g of ranitidine with 100 mL *water* and filter (Whatman No. 42. paper is suitable).

(2) Dilute 1 volume of solution (1) to 50 volumes with *water*. Dilute 1 volume to 10 volumes with *water*.

(3) 0.0065% w/v of *ranitidine for impurity A identification EPCRS* in mobile phase A.

(4) Dissolve the contents of a vial of *ranitidine impurity J EPCRS* in 1 mL of solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (3.5 µm) (Waters Xterra MS C18 is suitable).

(b) Use gradient elution using the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Buffer solution

Adjust the pH of 950 mL of 0.05M *potassium dihydrogen orthophosphate* to 7.1 by adding *strong sodium hydroxide solution* and dilute to 1 litre.

Mobile phase A

2 volumes of *acetonitrile* and 98 volumes of the buffer solution.

Mobile phase B

22 volumes of *acetonitrile* and 78 volumes of the buffer solution.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100 → 0	0 → 100	linear gradient
10-15	0	100	isocratic
15-16	0 → 100	100 → 0	linear gradient
16-20	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to ranitidine (retention time about 7 minutes) are; impurity H, about 0.1; impurity D, about 0.8; impurity J, about 0.9 and impurity A, about 1.7.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the impurity J and ranitidine is at least 1.5.

LIMITS

Identify any peak due to impurity A and impurity J in the chromatogram obtained with solution (1), using the chromatogram obtained with solutions (3) and (4) respectively. Multiply the area of the peak due to impurity J by a correction factor of 2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 tablets with 400 mL of the mobile phase until the tablets have completely disintegrated (about 15 minutes), dilute to 500 mL with the mobile phase, filter (Whatman GF/C paper is suitable) and dilute the filtrate with the mobile phase to produce a solution containing the equivalent of 0.01% w/v of ranitidine.

(2) 0.011% w/v of *ranitidine hydrochloride BPCRS* in the mobile phase.

(3) 0.011% w/v of *ranitidine hydrochloride BPCRS* and 0.0002% w/v of *dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl]furfuryl}amine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS 1 is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 322 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of 0.1M *ammonium acetate* and 85 volumes of *methanol*.

SYSTEM SUITABILITY

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The assay is not valid unless the peak due to ranitidine in the chromatogram obtained with solution (3) shows baseline separation from the peak due to dimethyl{5-[2-(1-methylamino-2-nitrovinylamino)ethylsulfinylmethyl] furfuryl}amine.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{22}N_4O_3S$ in the tablets using the declared content of $C_{13}H_{22}N_4O_3S$ in *ranitidine hydrochloride BPCRS*.

STORAGE

Ranitidine Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ranitidine.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ranitidine Hydrochloride.

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Refined Almond Oil

General Notices

(Ph. Eur. monograph 1064)

Ph Eur

DEFINITION

Fatty oil obtained from the ripe seeds of *Prunus dulcis* (Mill.) D.A. Webb var. *dulcis* or *Prunus dulcis* (Mill.) D.A. Webb var. *amara* (DC.) Buchheim or a mixture of both varieties by cold expression. It is then refined. A suitable antioxidant may be added.

CHARACTERS

Appearance

Pale yellow, clear liquid.

Solubility

Slightly soluble in ethanol (96 per cent), miscible with light petroleum.

Relative density

About 0.916.

It solidifies at about -18 °C.

IDENTIFICATION

A. Identification of fatty oils by thin-layer chromatography (*2.3.2*).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

TESTS

Specific absorbance (*2.2.25*)

0.2 to 6.0, determined at the absorption maximum at 270 nm.

To 0.100 g add *cyclohexane R* and dilute to 10.0 mL with the same solvent. Adapt the concentration of the solution so that the absorbance lies between 0.5 and 1.5, measured in a 1 cm cell.

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Acid value (2.5.1)

Maximum 0.5, determined on 5.0 g.

Peroxide value (2.5.5, Method A)

Maximum 5.0.

Unsaponifiable matter (2.5.7)

Maximum 0.9 per cent, determined on 5.0 g.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{16}: maximum 0.1 per cent;

— *palmitic acid*: 4.0 per cent to 9.0 per cent;

— *palmitoleic acid*: maximum 0.8 per cent;

— *margaric acid*: maximum 0.2 per cent;

— *stearic acid*: maximum 3.0 per cent;

— *oleic acid*: 62.0 per cent to 86.0 per cent;

— *linoleic acid*: 20.0 per cent to 30.0 per cent;

— *linolenic acid*: maximum 0.4 per cent;

— *arachidic acid*: maximum 0.2 per cent;

— *eicosenoic acid*: maximum 0.3 per cent;

— *behenic acid*: maximum 0.2 per cent;

— *erucic acid*: maximum 0.1 per cent.

Sterols (2.4.23)

Composition of the sterol fraction of the oil:

— *cholesterol*: maximum 0.7 per cent;

— *campesterol*: maximum 5.0 per cent;

— *stigmasterol*: maximum 4.0 per cent;

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— *β-sitosterol*: 73.0 per cent to 87.0 per cent;

— *Δ5-avenasterol*: minimum 5.0 per cent;

— *Δ7-stigmastenol*: maximum 3.0 per cent;

— *Δ7-avenasterol*: maximum 3.0 per cent;

— *brassicasterol*: maximum 0.3 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In a well-filled container, protected from light.

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Refined Borage Oil

General Notices

Refined Starflower Oil

(Refined Borage (Starflower) Oil, Ph. Eur. monograph 2105)

Ph Eur

DEFINITION

Fatty oil obtained from seeds of *Borago officinalis* L. by extraction and/or expression. It is then refined. A suitable antioxidant may be added.

PRODUCTION

The oil is prepared using materials and methods designed to ensure that the content of brassicasterol (*2.4.23*) in the sterol fraction of the oil is not greater than 0.3 per cent.

CHARACTERS

Appearance

Clear, light yellow or yellow liquid.

Solubility

Practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum.

Relative density

About 0.921.

Refractive index

About 1.476.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (*2.3.2*).

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Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

TESTS

Acid value (2.5.1)

Maximum 0.5, or maximum 0.3 if intended for use in the manufacture of parenteral preparations.

Peroxide value (2.5.5, Method A)

Maximum 10.0, or maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter (2.5.7)

Maximum 2.0 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{16}: maximum 0.3 per cent;

— *palmitic acid*: 9.0 per cent to 12.0 per cent;

— *palmitoleic acid*: maximum 0.6 per cent;

— *stearic acid*: 2.0 per cent to 6.0 per cent;

— *oleic acid*: 12.0 per cent to 22.0 per cent;

— *linoleic acid*: 30.0 per cent to 41.0 per cent;

— *gamma-linolenic acid*: 17.0 per cent to 27.0 per cent;

— *alpha-linolenic acid*: maximum 0.5 per cent;

— *arachidic acid*: maximum 0.5 per cent;

— *eicosenoic acid*: 2.8 per cent to 4.4 per cent;

— *erucic acid*: maximum 3.0 per cent;

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— *nervonic acid*: maximum 4.5 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

Under an inert gas, in a well-filled, airtight container, protected from light.

LABELLING

The label states:

— where applicable, that the oil is suitable for use in the manufacture of parenteral preparations;

— the name of the inert gas.

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Refined Castor Oil

General Notices

(Ph. Eur. monograph 2367)

Ph Eur

DEFINITION

Fatty oil obtained from the seeds of *Ricinus communis* L. by cold expression. It is then refined. A suitable antioxidant may be added.

PRODUCTION

During the expression step, the temperature of the oil must not exceed 50 °C.

CHARACTERS

Appearance

Clear, almost colourless or slightly yellow, viscous, hygroscopic liquid.

Solubility

Slightly soluble in light petroleum, miscible with ethanol (96 per cent) and with glacial acetic acid.

Relative density

About 0.958.

Refractive index

About 1.479.

Viscosity

About 1000 mPa·s.

IDENTIFICATION

First identification: B, C.

Second identification: A, B.

A. A mixture of 2 mL of the substance to be examined and 8 mL of *ethanol (96 per cent) R* is clear (2.2.1).

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B. Specific absorbance (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution BY_3 or Y_3 (*2.2.2, Method I*).

Optical rotation (*2.2.7*)

+ 3.5° to + 6.0°.

Specific absorbance (*2.2.25*)

0.7 to 1.5, determined at the absorption maximum at 270 nm.

To 1.00 g add *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent.

Acid value (*2.5.1*)

Maximum 0.8.

Dissolve 5.00 g in 25 mL of the prescribed mixture of solvents.

Hydroxyl value (*2.5.3, Method A*)

Minimum 160.

Peroxide value (*2.5.5, Method A*)

Maximum 5.0.

Unsaponifiable matter (*2.5.7*)

Maximum 0.8 per cent, determined on 5.0 g.

Oil obtained by extraction and adulteration

In a ground-glass-stoppered tube about 125 mm long and 18 mm in internal diameter, thoroughly mix 3 mL of the substance to be examined with 3 mL of *carbon disulfide R*. Shake for 3 min with 1 mL of *sulfuric acid R*. The mixture is less intensely coloured than a freshly prepared mixture of 3.2 mL of *ferric chloride solution R1*, 2.3 mL of *water R* and 0.5 mL of *dilute ammonia R1*.

Composition of fatty acids

Gas chromatography (*2.4.22*) with the following modifications.

Use the mixture of calibrating substances in Table 2.4.22.-3.

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Test solution Introduce 75 mg of the substance to be examined into a 10 mL centrifuge tube with a screw cap. Dissolve in 2 mL of *1,1-dimethylethyl methyl ether R1* with shaking and heat gently (50-60 °C). Add, while still warm, 1 mL of a 12 g/L solution of *sodium R* in *anhydrous methanol R*, prepared with the necessary precautions, and shake vigorously for at least 5 min. Add 5 mL of *distilled water R* and shake vigorously for about 30 s. Centrifuge for 15 min at 1500 *g*. Use the upper layer.

Reference solution Dissolve 50 mg of *methyl ricinoleate CRS* and 50 mg of *methyl stearate CRS* in 10.0 mL of *1,1-dimethylethyl methyl ether R1*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 0.9 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 55	215
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

System suitability:

— *symmetry factor*: 0.7 to 1.5 for the peak due to methyl stearate in the chromatogram obtained with the test solution.

Calculate the percentage content of each fatty acid by the normalisation procedure.

Correct the area of the peak due to methyl ricinoleate, by multiplying by a factor *R* calculated using the following expression:

$$\frac{m_1 \times A_2}{A_1 \times m_2}$$

m_1 = mass of methyl ricinoleate in the reference solution;

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m_2 = mass of methyl stearate in the reference solution;

A_1 = area of the peak due to methyl ricinoleate in the chromatogram obtained with the reference solution;

A_2 = area of the peak due to methyl stearate in the chromatogram obtained with the reference solution.

Composition of the fatty-acid fraction of the oil:

— *palmitic acid*: maximum 2.0 per cent;

— *stearic acid*: maximum 2.5 per cent;

— *oleic acid and isomer*: 2.5 per cent to 6.0 per cent;

— *linoleic acid*: 2.5 per cent to 7.0 per cent;

— *linolenic acid*: maximum 1.0 per cent;

— *eicosenoic acid*: maximum 1.0 per cent;

— *ricinoleic acid*: 85.0 per cent to 92.0 per cent;

— *any other fatty acid*: for each fatty acid, maximum 1.0 per cent.

Water (*2.5.32*)

Maximum 0.3 per cent, or maximum 0.2 per cent if intended for use in the manufacture of parenteral preparations, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light. If intended for use in the manufacture of parenteral preparations, store under an inert gas.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations and the name of the inert gas.

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Refined Evening Primrose Oil

General Notices

(Ph. Eur. monograph 2104)

Ph Eur

DEFINITION

Fatty oil obtained from seeds of *Oenothera biennis* L. or *Oenothera lamarckiana* L. by extraction and/or expression. It is then refined. A suitable antioxidant may be added.

PRODUCTION

The oil is prepared using materials and methods designed to ensure that the content of brassicasterol (*2.4.23*) in the sterol fraction of the oil is not greater than 0.3 per cent.

CHARACTERS

Appearance

Clear, light yellow or yellow liquid.

Solubility

Practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C).

Relative density

About 0.923.

Refractive index

About 1.478.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (*2.3.2*).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

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B. Composition of fatty acids (see Tests).

TESTS

Acid value (2.5.1)

Maximum 0.5, or maximum 0.3 if intended for use in the manufacture of parenteral preparations.

Peroxide value (2.5.5, Method A)

Maximum 10.0, or maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter (2.5.7)

Maximum 2.5 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{16}: maximum 0.3 per cent;

— *palmitic acid*: 4.0 per cent to 10.0 per cent;

— *stearic acid*: 1.0 per cent to 4.0 per cent;

— *oleic acid*: 5.0 per cent to 12.0 per cent;

— *linoleic acid*: 65.0 per cent to 85.0 per cent;

— *gamma-linolenic acid*: 7.0 per cent to 14.0 per cent;

— *alpha-linolenic acid*: maximum 0.5 per cent.

Water (2.5.32)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

Under an inert gas, in a well-filled, airtight container, protected from light.

LABELLING

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The label states:

— where applicable, that the oil is suitable for use in the manufacture of parenteral preparations;

— the name of the inert gas.

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Refined Maize Oil

General Notices

(Ph. Eur. monograph 1342)

Ph Eur

DEFINITION

Fatty oil obtained from the seeds of *Zea mays* L. by mechanical expression or by extraction. It is then refined.

PRODUCTION

The oil is prepared using materials and methods designed to ensure that the content of brassicasterol (2.4.23) in the sterol fraction of the oil is not greater than 0.3 per cent.

CHARACTERS

Appearance

Clear, light yellow or yellow oil.

Solubility

Practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C) and with methylene chloride.

Relative density

About 0.920.

Refractive index

About 1.474.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained with the test solution is similar to the chromatogram obtained with the reference solution.

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B. Composition of fatty acids (see Tests).

TESTS

Acid value (2.5.1)

Maximum 0.5, or maximum 0.3 if intended for use in the manufacture of parenteral preparations, determined on 10.0 g.

Peroxide value (2.5.5, Method A)

Maximum 10.0, or maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter (2.5.7)

Maximum 2.8 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *sum of fatty acids of chain length less than* C_{16}: maximum 0.6 per cent;

— *palmitic acid*: 8.6 per cent to 16.5 per cent;

— *stearic acid*: maximum 3.3 per cent;

— *oleic acid and isomer*: 20.0 per cent to 42.2 per cent;

— *linoleic acid*: 39.4 per cent to 65.6 per cent;

— *linolenic acid*: 0.5 per cent to 1.5 per cent;

— *arachidic acid*: maximum 0.8 per cent;

— *eicosenoic acid*: maximum 0.5 per cent;

— *behenic acid*: maximum 0.5 per cent;

— *any other fatty acid*: for each fatty acid, maximum 0.5 per cent.

Water (2.5.32)

Maximum 0.1 per cent, determined on 1.00 g.

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STORAGE

Protected from light, at a temperature not exceeding 25 °C.

LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

— whether the oil is obtained by mechanical expression or by extraction.

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Refined Olive Oil

General Notices

(Ph. Eur. monograph 1456)

Ph Eur

DEFINITION

Fatty oil obtained by refining of crude olive oil, obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea* L. A suitable antioxidant may be added.

CHARACTERS

Appearance

Clear, colourless or greenish-yellow transparent liquid.

Solubility

Practically insoluble in ethanol (96 per cent), miscible with light petroleum (bp: 50-70 °C).

When cooled, it begins to become cloudy at 10 °C and becomes a butter-like mass at about 0 °C.

Relative density

About 0.913.

IDENTIFICATION

First identification: A, C.

Second identification: A, B.

A. Acid value (see Tests).

B. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1. For certain types of olive oil, the difference in the size of spots E and F is less pronounced than in the corresponding chromatogram shown in Figure 2.3.2.-1.

C. Composition of fatty acids (see Tests).

TESTS

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Specific absorbance (*2.2.25*)

Maximum 1.20, determined at the absorption maximum at 270 nm.

To 1.00 g add *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Acid value (*2.5.1*)

Maximum 0.3, determined on 10.0 g.

Peroxide value (*2.5.5, Method A*)

Maximum 10.0, or maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter

Maximum 1.5 per cent.

Place 5.0 g (*m* g) in a 150 mL flask fitted with a reflux condenser. Add 50 mL of *2 M alcoholic potassium hydroxide R* and heat on a water-bath for 1 h, shaking frequently. Add 50 mL of *water R* through the top of the condenser, shake, allow to cool and transfer the contents of the flask to a separating funnel. Rinse the flask with several portions totalling 50 mL of *light petroleum R1* and add the rinsings to the separating funnel. Shake vigorously for 1 min. Allow to separate and transfer the aqueous layer to a 2nd separating funnel. If an emulsion forms, add small quantities of *ethanol (96 per cent) R* or a concentrated solution of *potassium hydroxide R*. Shake the aqueous layer with 2 quantities, each of 50 mL, of *light petroleum R1*. Combine the light petroleum layers in a 3rd separating funnel and wash with 3 quantities, each of 50 mL, of *ethanol (50 per cent V/V) R*. Transfer the light petroleum layer to a tared 250 mL flask. Rinse the separating funnel with small quantities of *light petroleum R1* and add to the flask. Evaporate the light petroleum on a water-bath and dry the residue at 100-105 °C for 15 min, keeping the flask horizontal. Allow to cool in a desiccator and weigh (*a* g). Repeat the drying for successive periods of 15 min until the loss of mass between 2 successive weighings does not exceed 0.1 per cent. Dissolve the residue in 20 mL of *ethanol (96 per cent) R*, previously neutralised to 0.1 mL of *bromophenol blue solution R*. If necessary, titrate with *0.1 M hydrochloric acid* (*b* mL).

Calculate the percentage content of unsaponifiable matter using the following expression:

$$\frac{100\,(a - 0.032b)}{m}$$

If 0.032*b* is greater than 5 per cent of *a*, the test is not valid and must be repeated.

Alkaline impurities (*2.4.19*)

It complies with the test.

Composition of fatty acids (*2.4.22, Method A*)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{16}: maximum 0.1 per cent;

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— *palmitic acid*: 7.5 per cent to 20.0 per cent;

— *palmitoleic acid*: maximum 3.5 per cent;

— *stearic acid*: 0.5 per cent to 5.0 per cent;

— *oleic acid and isomer*: 56.0 per cent to 85.0 per cent;

— *linoleic acid*: 3.5 per cent to 20.0 per cent;

— *linolenic acid*: maximum 1.2 per cent;

— *arachidic acid*: maximum 0.7 per cent;

— *eicosenoic acid*: maximum 0.4 per cent;

— *behenic acid*: maximum 0.2 per cent;

— *lignoceric acid*: maximum 0.2 per cent.

Sterols (*2.4.23, Method B*)

Composition of the sterol fraction of the oil:

— *cholesterol*: maximum 0.5 per cent;

— *campesterol*: maximum 4.0 per cent;

— *Δ7-stigmastenol*: maximum 0.5 per cent;

— *sum of contents of Δ5,23-stigmastadienol, clerosterol, β-sitosterol, sitostanol, Δ5-avenasterol and Δ5,24-stigmastadienol*: minimum 93.0 per cent.

The content of stigmasterol is not greater than that of campesterol.

Sesame oil

In a ground-glass-stoppered cylinder shake 10 mL for about 1 min with a mixture of 0.5 mL of a 0.35 per cent *V/V* solution of furfural R in *acetic anhydride R* and 4.5 mL of *acetic anhydride R*. Filter through a filter paper impregnated with *acetic anhydride R*. To the filtrate add 0.2 mL of *sulfuric acid R*. No bluish-green colour develops.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In a well-filled container, protected from light, at a temperature not exceeding 25 °C. If intended for use in the manufacture of parenteral preparations, store under an inert gas.

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LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations and the name of the inert gas.

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Refined Rapeseed Oil

General Notices

(Ph. Eur. monograph 1369)

Ph Eur

DEFINITION

Fatty oil obtained from the seeds of *Brassica napus* L. and *Brassica campestris* L. by mechanical expression or by extraction. It is then refined. A suitable antioxidant may be added.

CHARACTERS

Appearance

Clear, light yellow liquid.

Solubility

Practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C).

Relative density

About 0.917.

Refractive index

About 1.473.

IDENTIFICATION

Identification of fatty oils by thin-layer chromatography (*2.3.2*).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

TESTS

Acid value (*2.5.1*)

Maximum 0.5, determined on 10.0 g.

Peroxide value (*2.5.5, Method A*)

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Maximum 10.0.

Unsaponifiable matter (*2.5.7*)

Maximum 1.5 per cent, determined on 5.0 g.

Alkaline impurities (*2.4.19*)

It complies with the test.

Composition of fatty acids (*2.4.22, Method A*)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *palmitic acid*: 2.5 per cent to 6.0 per cent,

— *stearic acid*: maximum 3.0 per cent,

— *oleic acid*: 50.0 per cent to 67.0 per cent,

— *linoleic acid*: 16.0 per cent to 30.0 per cent,

— *linolenic acid*: 6.0 per cent to 14.0 per cent,

— *eicosenoic acid*: maximum 5.0 per cent,

— *erucic acid*: maximum 2.0 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light.

LABELLING

The label states whether the oil is obtained by mechanical expression or by extraction.

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Refined Safflower Oil

General Notices

(Ph. Eur. monograph 2088)

Ph Eur

DEFINITION

Fatty oil obtained from seeds of *Carthamus tinctorius* L. (type I) or from seeds of hybrids of *Carthamus tinctorius* L. (type II), by expression and/or extraction followed by refining. Type II refined safflower oil is rich in oleic ((9Z)-octadec-9-enoic) acid. A suitable antioxidant may be added.

PRODUCTION

The oil is prepared using materials and methods designed to ensure that the content of brassicasterol (*2.4.23*) in the sterol fraction of the oil is not greater than 0.3 per cent.

CHARACTERS

Appearance

Clear, viscous, yellow or pale yellow liquid.

Solubility

Practically insoluble in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C).

	Type I refined safflower oil	Type II refined safflower oil
Relative density	about 0.922	about 0.914
Refractive index	about 1.476	about 1.472

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (*2.3.2*).

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Results The chromatogram obtained is similar to the corresponding chromatogram for type I or type II shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 0.5.

Peroxide value (*2.5.5, Method A*)

Maximum 10.0, or maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter (*2.5.7*)

Maximum 1.5 per cent, determined on 5.0 g.

Alkaline impurities (*2.4.19*)

It complies with the test.

Composition of fatty acids (*2.4.22, Method A*)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of type I refined safflower oil:

— *saturated fatty acids of chain length less than C14*: maximum 0.2 per cent;

— *myristic acid*: maximum 0.2 per cent;

— *palmitic acid*: 4.0 per cent to 10.0 per cent;

— *stearic acid*: 1.0 per cent to 5.0 per cent;

— *oleic acid*: 8.0 per cent to 21.0 per cent;

— *linoleic acid*: 68.0 per cent to 83.0 per cent;

— *linolenic acid*: maximum 0.5 per cent;

— *arachidic acid*: maximum 0.5 per cent;

— *eicosenoic acid*: maximum 0.5 per cent;

— *behenic acid*: maximum 1.0 per cent.

Composition of the fatty-acid fraction of type II refined safflower oil:

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— *saturated fatty acids of chain length less than C14*: maximum 0.2 per cent;

— *myristic acid*: maximum 0.2 per cent;

— *palmitic acid*: 3.6 per cent to 6.0 per cent;

— *stearic acid*: 1.0 per cent to 5.0 per cent;

— *oleic acid*: 70.0 per cent to 84.0 per cent;

— *linoleic acid*: 7.0 per cent to 23.0 per cent;

— *linolenic acid*: maximum 0.5 per cent;

— *arachidic acid*: maximum 1.0 per cent;

— *eicosenoic acid*: maximum 1.0 per cent;

— *behenic acid*: maximum 1.2 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In a well-filled, airtight container, protected from light.

LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

— the type of oil (type I or type II).

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Refined Sesame Oil

General Notices

Sesame Oil

(Ph. Eur. monograph 0433)

Ph Eur

DEFINITION

Fatty oil obtained from the ripe seeds of *Sesamum indicum* L. by expression or extraction. It is then refined. Improved colour and odour may be obtained by further refining. It may contain a suitable antioxidant.

CHARACTERS

Appearance

Clear, light yellow liquid, almost colourless.

Solubility

Practically insoluble in ethanol (96 per cent), miscible with light petroleum.

Relative density

About 0.919.

Refractive index

About 1.473.

It solidifies to a butter-like mass at about -4 °C.

IDENTIFICATION

First identification: A.

Second identification: B.

A. Composition of triglycerides (see Tests).

B. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2-1.

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TESTS

Acid value (2.5.1)

Maximum 0.5, determined on 10.0 g; maximum 0.3 if intended for use in the manufacture of parenteral preparations.

Peroxide value (2.5.5)

Maximum 10.0; maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter (2.5.7)

Maximum 2.0 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test for alkaline impurities in fatty oils.

Cottonseed oil

Mix 5 mL in a test-tube with 5 mL of a mixture of equal volumes of pentanol R and a 10 g/L solution of *sulfur R* in *carbon disulfide R*. Warm the mixture carefully until the carbon disulfide is expelled, and immerse the tube to 1/3 of its depth in boiling *saturated sodium chloride solution R*. No reddish colour develops within 15 min.

Composition of triglycerides

Liquid chromatography (2.2.29).

Test solution Dilute 50.0 mg of the substance to be examined to 10.0 mL with a mixture of equal volumes of *acetone R* and *methylene chloride R*.

Reference solutions Dissolve 80.0 mg of *triolein R* in a mixture of equal volumes of *acetone R* and *methylene chloride R* and dilute to 50.0 mL with the same mixture of solvents. Prepare 5 reference solutions by dilution of this solution so as to cover concentrations ranging from the disregard limit (0.5 per cent) to the upper limit for OLL (30.0 per cent).

Plot the logarithm of the area of the peak due to triolein against the logarithm of the concentration of triolein in the reference solution.

Column 2 columns coupled in series:

— *size of each column*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase:

— *mobile phase A*: *acetone R*, *methylene chloride R*, *acetonitrile R* (5:15:80 *V/V/V*);

— *mobile phase B*: *acetone R*, *acetonitrile R*, *methylene chloride R* (20:20:60 *V/V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100 → 75	0 → 25
15 - 25	75	25
25 - 70	75 → 0	25 → 100
70 - 75	0 → 100	100 → 0
75 - 80	100	0

Flow rate 1.0 mL/min.

Detection Evaporative light-scattering detector; the following settings have been found to be suitable; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criterion:

— *carrier gas*: *nitrogen R*;

— *flow rate*: 0.7 L/min;

— *evaporator temperature*: 85 °C;

— *nebuliser temperature*: 45 °C.

Injection 20 µL.

Identification of peaks Use the chromatograms obtained with the reference solutions to identify the peak due to triolein; identify the other peaks using the chromatogram shown in Figure 0433.-1. The fatty acids are designated as linolenic (Ln), linoleic (L), oleic (O), palmitic (P) and stearic (S).

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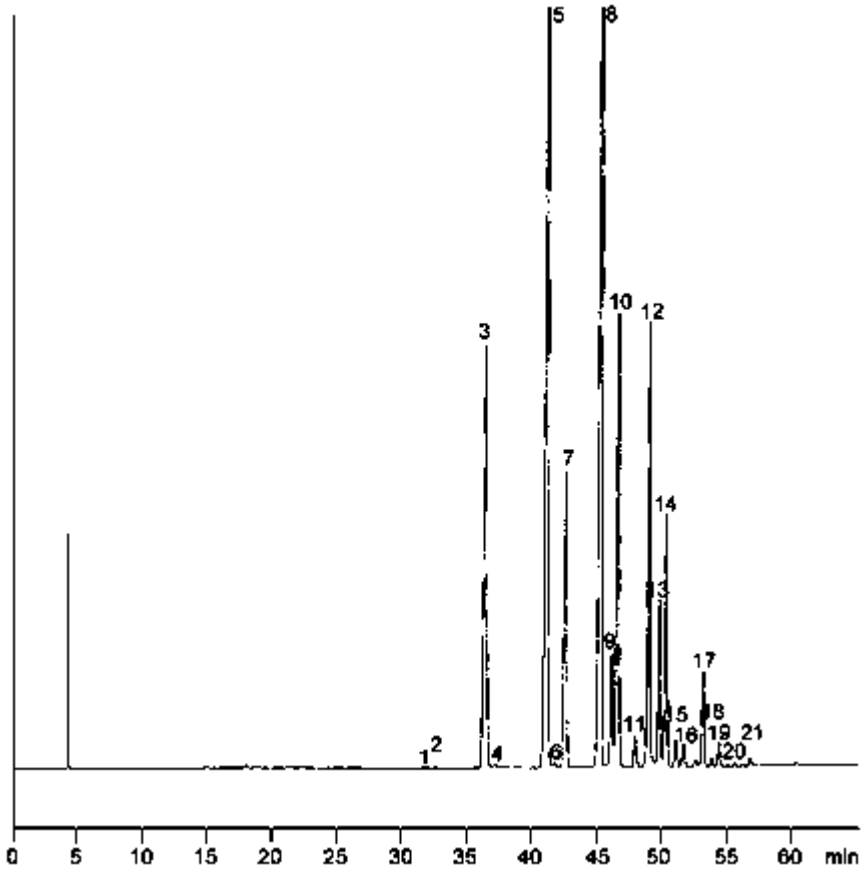

1. LLLn	4. OLLn	7. PLL	10. POL	13. SOL	16. PPO	19. SSL
2. OLnLn	5. OLL	8. OOL	11. PPL	14. POO	17. SOO	20. PPS
3. LLL	6. OOLn	9. SLL	12. OOO	15. PSL	18. PSO	21. SSO

Figure 0433.-1. – *Chromatogram for the composition of triglycerides in refined sesame oil*

System suitability Test solution:

— *resolution*: minimum 1.5 between the peaks due to OOO (triolein) and SOL.

Using the calibration curve obtained with the reference solutions, determine the percentage content of each peak with an area greater than that of the peak corresponding to the disregard limit (0.5 per cent). Assuming that the sum of these percentage contents is 100 per cent, normalise the percentage content of each of the 8 triglycerides specified below.

Composition of triglycerides:

— *LLL*: 7.0 per cent to 19.0 per cent;

— *OLL*: 13.0 per cent to 30.0 per cent;

— *PLL*: 5.0 per cent to 9.0 per cent;

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— *OOL*: 12.0 per cent to 23.0 per cent;

— *POL*: 6.0 per cent to 14.0 per cent;

— *OOO*: 5.0 per cent to 16.0 per cent;

— *SOL*: 2.0 per cent to 8.0 per cent;

— *POO*: 2.0 per cent to 10.0 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light; if intended for use in the manufacture of parenteral preparations store under an inert gas in an airtight container.

When the container has been opened, its contents are to be used as soon as possible. Any part of the contents not used at once is protected by an atmosphere of an inert gas.

LABELLING

The label states:

— whether the oil is obtained by expression or extraction;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

— where applicable, the name of the inert gas used.

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Refined Soya Oil

General Notices

Refined Soyabean Oil

(Refined Soya-bean Oil, Ph. Eur. monograph 1473)

Action and use

Excipient.

When Soya Oil, Soyabean Oil or Soya-bean Oil is demanded, Refined Soya Oil shall be supplied.

When intended for use in the manufacture of a parenteral dosage form, Refined Soya Oil complying with the requirement for Water below should be used.

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DEFINITION

Fatty oil obtained from seeds of *Glycine max* (L.) Merr. (*Glycine hispida* (Moench) Maxim.) by extraction and subsequent refining. It may contain a suitable antioxidant.

PRODUCTION

The oil is prepared using materials and methods designed to ensure that the content of brassicasterol (*2.4.23*) in the sterol fraction of the oil is not greater than 0.3 per cent.

CHARACTERS

Appearance

Clear, pale yellow liquid.

Solubility

Practically insoluble in ethanol (96 per cent), miscible with light petroleum (bp: 50-70 °C).

Relative density

About 0.922.

Refractive index

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About 1.475.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (*2.3.2*).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 0.5.

Peroxide value (*2.5.5, Method A*)

Maximum 10.0, or maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter (*2.5.7*)

Maximum 1.5 per cent, determined on 5.0 g.

Alkaline impurities (*2.4.19*)

It complies with the test.

Composition of fatty acids (*2.4.22, Method A*)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{14}: maximum 0.1 per cent;

— *myristic acid*: maximum 0.2 per cent;

— *palmitic acid*: 9.0 per cent to 13.0 per cent;

— *palmitoleic acid*: maximum 0.3 per cent;

— *stearic acid*: 2.5 per cent to 5.0 per cent;

— *oleic acid and isomer*: 17.0 per cent to 30.0 per cent;

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— *linoleic acid*: 48.0 per cent to 58.0 per cent;

— *linolenic acid*: 5.0 per cent to 11.0 per cent;

— *arachidic acid*: maximum 1.0 per cent;

— *eicosenoic acid*: maximum 1.0 per cent;

— *behenic acid*: maximum 1.0 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In a well-filled container, protected from light, at a temperature not exceeding 25 °C. If intended for use in the manufacture of parenteral preparations, store under an inert gas.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations and the name of the inert gas.

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Refined Sunflower Oil

General Notices

(Ph. Eur. monograph 1371)

Ph Eur

DEFINITION

Fatty oil obtained from the seeds of *Helianthus annuus* L. by mechanical expression or by extraction. It is then refined. A suitable antioxidant may be added.

CHARACTERS

Appearance

Clear, light yellow liquid.

Solubility

Practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C).

Relative density

About 0.921.

Refractive index

About 1.474.

IDENTIFICATION

Identification of fatty oils by thin-layer chromatography (*2.3.2*).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

TESTS

Acid value (*2.5.1*)

Maximum 0.5, determined on 10.0 g.

Peroxide value (*2.5.5, Method A*)

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Maximum 10.0.

Unsaponifiable matter (2.5.7)

Maximum 1.5 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *palmitic acid*: 4.0 per cent to 9.0 per cent,

— *stearic acid*: 1.0 per cent to 7.0 per cent,

— *oleic acid*: 14.0 per cent to 40.0 per cent,

— *linoleic acid*: 48.0 per cent to 74.0 per cent.

Water (2.5.32)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light.

LABELLING

The label states whether the oil is obtained by mechanical expression or by extraction.

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Refined Wheat-germ Oil

General Notices

(Ph. Eur. monograph 1379)

Ph Eur

DEFINITION

Fatty oil obtained from the germ of the grain of *Triticum aestivum* L. by cold expression or by other suitable mechanical means and/or by extraction. It is then refined. A suitable antioxidant may be added.

PRODUCTION

The oil is prepared using materials and methods designed to ensure that the content of brassicasterol (*2.4.23*) in the sterol fraction of the oil is not greater than 0.3 per cent.

CHARACTERS

Appearance

Clear, light yellow liquid.

Solubility

Practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C).

Relative density

About 0.925.

Refractive index

About 1.475.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (*2.3.2*).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

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TESTS

Acid value (2.5.1)

Maximum 0.9, or maximum 0.3 if intended for use in the manufacture of parenteral preparations.

Peroxide value (2.5.5, Method A)

Maximum 10.0, or maximum 5.0 if intended for use in the manufacture of parenteral preparations.

Unsaponifiable matter (2.5.7)

Maximum 5.0 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test.

Composition of fatty acids (2.4.22, Method C)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *palmitic acid*: 14.0 per cent to 19.0 per cent;

— *stearic acid*: maximum 2.0 per cent;

— *oleic acid*: 12.0 per cent to 23.0 per cent;

— *linoleic acid*: 52.0 per cent to 59.0 per cent;

— *linolenic acid*: 3.0 per cent to 10.0 per cent;

— *eicosenoic acid*: maximum 2.0 per cent.

Water (2.5.32)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light.

LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

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— whether the oil is obtained by mechanical means, by extraction or by a combination of the 2.

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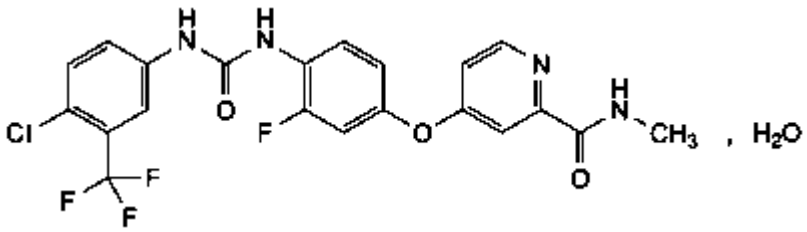
Regorafenib Monohydrate

General Notices

(Ph. Eur. monograph 3012)



$C_{21}H_{15}ClF_4N_4O_3,H_2O$ 500.8 *1019206-88-2*

Action and use

Tyrosine kinase inhibitor; treatment of metastatic colorectal cancer and unresectable or metastatic gastrointestinal stromal tumours.

Preparation

Regorafenib Tablets

Ph Eur

DEFINITION

4-[4-[[[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or pinkish or brownish powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent) and in methanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison regorafenib monohydrate CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

B. Water (see Tests).

TESTS

Impurity A

Liquid chromatography (2.2.29). *Carry out the test protected from light and store the solutions at 2-8 °C.*

Test solution Dissolve 0.250 g of the substance to be examined in tetrahydrofuran R and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 5.0 mg of regorafenib impurity A CRS in tetrahydrofuran R and dilute to 50.0 mL with the same solvent. Dilute 2.5 mL of the solution to 50.0 mL with tetrahydrofuran R.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped ethylene-bridged polar-embedded octadecylsilyl silica gel for chromatography (hybrid material) R (3.5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 8 volumes of acetonitrile for chromatography R and 92 volumes of a solution containing 0.5 g/L of dipotassium hydrogen phosphate R and 1.5 g/L of potassium dihydrogen phosphate R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 17	100 → 22	0 → 78

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 228 nm.

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Autosampler Set at 8 °C.

Injection 3.0 µL.

Relative retention With reference to regorafenib (retention time = about 14 min): impurity A = about 0.6.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 10.0 per cent determined on 6 injections.

Calculation of content:

— for impurity A, use the concentration of impurity A in the reference solution.

Limit:

— *impurity A*: maximum 100 ppm.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and store the solutions at 2-8 °C.*

Test solution (a) Dissolve 30.0 mg of the substance to be examined in *methanol R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dilute 15.0 mL of test solution (a) to 50.0 mL with *methanol R*.

Reference solution (a) Dissolve 30.0 mg of *regorafenib monohydrate CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 15.0 mL of the solution to 50.0 mL with *methanol R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 2 mg of *sorafenib CRS* in *methanol R* and dilute to 50 mL with the same solvent. Dilute 0.2 mL of the solution to 2 mL with test solution (a).

Reference solution (d) Dissolve 3 mg of *regorafenib impurity C CRS* in *methanol R* and dilute to 100 mL with the same solvent.

Reference solution (e) Dissolve 3 mg of *regorafenib impurity D CRS* in *dimethyl sulfoxide R* and dilute to 100 mL with the same solvent.

Reference solution (f) Mix 1 mL of reference solution (d) and 1 mL of reference solution (e) and dilute to 20 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 63 °C.

Mobile phase:

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— *mobile phase A*: *acetonitrile for chromatography R*, 0.1 per cent *V/V* solution of *trifluoroacetic acid R* (3:97 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 15	100 → 78	0 → 22
15 - 25	78 → 60	22 → 40
25 - 33	60 → 36	40 → 64
33 - 37	36	64

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 232 nm.

Autosampler Set at 8 °C.

Injection 5 µL of test solution (a) and reference solutions (b), (c) and (f).

Identification of peaks Use the chromatogram obtained with reference solution (f) to identify the peaks due to impurities C and D; use the chromatogram obtained with reference solution (c) to identify the peak due to sorafenib.

Relative retention With reference to regorafenib (retention time = about 25 min): impurity C = about 0.4; impurity D = about 0.8; sorafenib = about 0.95.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to sorafenib and regorafenib.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.5; impurity D = 0.6;

— for each impurity, use the concentration of regorafenib monohydrate in reference solution (b).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *impurity C*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

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— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

3.2 per cent to 4.0 per cent, determined on 50.0 mg using the evaporation technique at 150 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

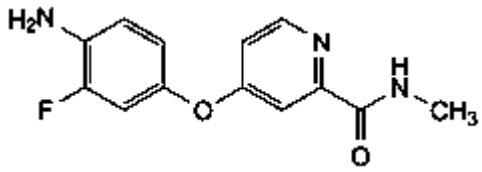
Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{21}H_{15}ClF_4N_4O_3$ taking into account the assigned content of *regorafenib monohydrate CRS*.

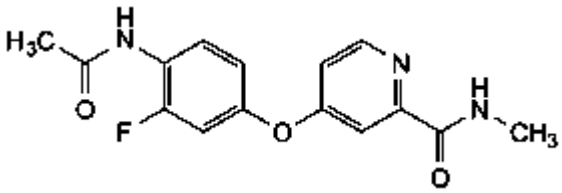
IMPURITIES

Specified impurities *A, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, E.*



A. 4-(4-amino-3-fluorophenoxy)-*N*-methylpyridine-2-carboxamide,



B. 4-(4-acetamido-3-fluorophenoxy)-*N*-methylpyridine-2-carboxamide,

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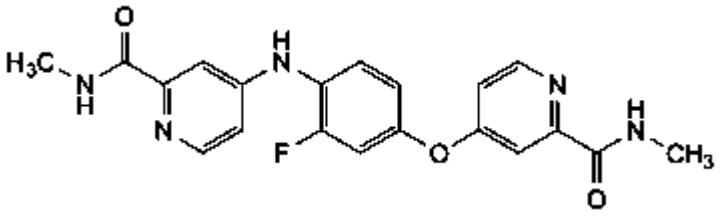
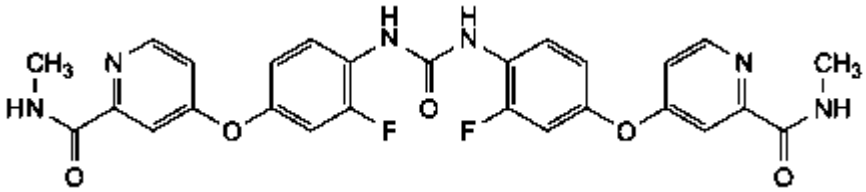
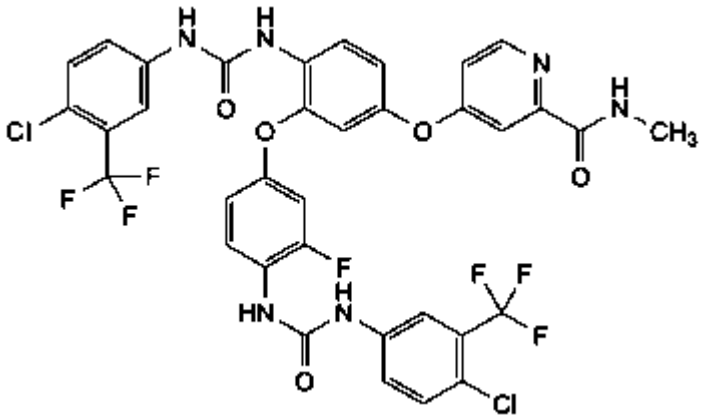


C. 4-[3-fluoro-4-[[2-(methylcarbamoyl)pyridin-4-yl]amino]phenoxy]-*N*-methylpyridine-2-carboxamide,



D. 3^3,7^2-difluoro-*N*,*N*′-dimethyl-5-oxo-2,8-dioxa-4,6-diaza-1(4),9(4)-dipyridina-3(1,4),7(1,4)-dibenzenanonaphane-1^2,9^2-dicarboxamide,



E. 9^4-chloro-3^4-[[[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]-5^3-fluoro-*N*-methyl-7-oxo-9^3-(trifluoromethyl)-2,4-dioxa-6,8-diaza-1(4)-pyridina-3(1,3),5(1,4),9(1)-tribenzenanonaphane-1^2-carboxamide.

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You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Regorafenib Tablets

General Notices

(Ph. Eur. monograph 3023)

Action and use

Tyrosine kinase inhibitor; treatment of metastatic colorectal cancer and unresectable or metastatic gastrointestinal stromal tumour.

Ph Eur

DEFINITION

Tablets containing *Regorafenib monohydrate (3012)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of regorafenib ($C_{21}H_{15}ClF_4N_4O_3$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (b).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Impurity A

Liquid chromatography (*2.2.29*). *Carry out the test protected from light and store the solutions at 2-8 °C*.

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Internal standard solution Dissolve 2.0 mg of *4-(4-aminophenoxy)-N-methylpicolinamide R* in *methanol R* and dilute to 200.0 mL with the same solvent.

Buffer solution To 0.4 mL of *concentrated ammonia R* add 0.7 mL of *acetic acid R* and dilute to 1000 mL with *water for chromatography R*; adjust to pH 4.6 with *acetic acid R* or *concentrated ammonia R*.

Test solution Cut 5 tablets into pieces and add about 60 mL of *methanol R* and 2.0 mL of the internal standard solution. Sonicate for at least 15 min then shake for about 30 min until the tablet cores are finely dispersed. Dilute with *methanol R* to obtain a concentration of regorafenib of 2 mg/mL and shake vigorously. Centrifuge about 10 mL of the solution at 3400 *g* for 10 min. Dilute 5.0 mL of the supernatant to 10.0 mL with a 10 per cent *V/V* solution of *tetrahydrofuran R* and sonicate for another 30 s. Keep the solution on ice for at least 30 min with intermittent shaking. Filter through a 0.45 µm filter, discarding the initial 2 mL. Transfer an aliquot of the filtrate into a vial and allow to cool in an autosampler maintained at 8 °C for at least 1 h prior to injecting.

Reference solution (a) Dissolve 3.0 mg of *regorafenib impurity A CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 10.0 mL of reference solution (a) to 20.0 mL with a 50 per cent *V/V* solution of *methanol R*. To 7.0 mL of this solution add 5.0 mL of *tetrahydrofuran R* and 1.0 mL of the internal standard solution then dilute to 100.0 mL with a 50 per cent *V/V* solution of *methanol R*.

Reference solution (c) Dilute 5 mL of reference solution (a) to 20 mL with a 50 per cent *V/V* solution of *methanol R*. To 7 mL of this solution add 5 mL of *tetrahydrofuran R* and 1 mL of the internal standard solution then dilute to 100 mL with a 50 per cent *V/V* solution of *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: *anhydrous ethanol R*, buffer solution (25:75 *V/V*);

— *mobile phase B*: *anhydrous ethanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 11	100	0
11 - 15	100 → 95	0 → 5
15 - 17	95	5
17 - 17.5	95 → 10	5 → 90
17.5 - 20	10	90

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Flow rate 0.4 mL/min.

Detection Spectrophotometer at 228 nm.

Autosampler Set at 8 °C.

Injection 40 µL of the test solution and reference solutions (b) and (c).

Relative retention With reference to the internal standard (retention time = about 7 min): impurity A = about 1.9.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to the internal standard and impurity A;

— *repeatability*: maximum relative standard deviation of 5.0 per cent for the ratio of the area of the peak due to impurity A to the area of the peak due to the internal standard, determined on 6 injections.

Calculation of percentage content:

— for impurity A, use the concentration of impurity A in reference solution (b).

Limit:

— *impurity A*: maximum 0.10 per cent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Solvent mixture *water R*, *acetonitrile R* (25:75 *V/V*).

Test solution Cut 5 tablets into pieces and add 60 mL of *methanol R*. Sonicate for at least 15 min then shake for about 30 min until the tablet cores are finely dispersed. Dilute with *methanol R* to obtain a concentration of regorafenib of 2 mg/mL and shake vigorously. Centrifuge about 10 mL of the solution at 3400 *g* for 5 min. Dilute 4.0 mL of the supernatant to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 16.0 mg of *regorafenib monohydrate CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *regorafenib impurity C CRS* and 2 mg of *regorafenib impurity D CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 4 mL of the solution to 10 mL with the solvent mixture. To 5 mg of *regorafenib for FP system suitability CRS* (containing impurity FP-A) add 1 mL of this solution and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 2.0 mg of *regorafenib impurity FP-B CRS* and 4.0 mg of *regorafenib impurity FP-C CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 2.0 mL of the solution to 100.0 mL with the solvent mixture.

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Reference solution (e) Dissolve 3.2 mg of *regorafenib impurity FP-C CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. To 3.2 mg of *regorafenib monohydrate CRS*, add 2 mL of this solution and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *acetonitrile R*, *water for chromatography R* (1.5:250:748.5 *V/V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 4.5	100 → 66.6	0 → 33.4
4.5 - 12.5	66.6 → 57.3	33.4 → 42.7
12.5 - 14	57.3 → 20	42.7 → 80
14 - 17	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 5 µL of the test solution and reference solutions (a), (c), (d) and (e).

Identification of impurities Use the chromatogram supplied with *regorafenib for FP system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A + C, D and FP-A; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities FP-B and FP-C.

Relative retention With reference to regorafenib (retention time = about 12 min): impurities A and C = about 0.17; impurity FP-A = about 0.49; impurity D = about 0.53; impurity FP-B = about 0.63; impurity FP-C = about 1.05.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurities FP-A and D in the chromatogram obtained with reference solution (c);

— *resolution*: minimum 2.5 between the peaks due to regorafenib and impurity FP-C in the chromatogram obtained with reference solution (e).

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Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity FP-A by 4.0;

— for impurity FP-A and unspecified impurities, use the concentration of regorafenib in reference solution (a);

— for impurities FP-B and FP-C, use the concentration of each substance in reference solution (d).

Limits:

— *impurities FP-A, FP-B and FP-C*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.1 per cent; disregard the peaks due to impurities A + C and D.

Dissolution[1] (2.9.3, Apparatus 2). *Carry out the test protected from light*.

Dissolution medium Dissolve 29.9 g of *sodium acetate R*, 16.6 mL of *glacial acetic acid R* and 10.0 g of *sodium dodecyl sulfate R* in *water R* and dilute to 10 L with the same solvent. Adjust to pH 4.5 with *glacial acetic acid R* or a 4 g/L solution of *sodium hydroxide R*. Use 900 mL of the medium.

Rotation speed 75 r/min.

Time 30 min.

Analysis Ultraviolet and visible absorption spectrophotometry (2.2.25), using a path length of 2 mm.

Test solutions Samples withdrawn from the dissolution vessel and filtered.

When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 5-fold dilution for 40 mg tablets).

Measure the absorbance of the solutions at 265 nm.

Calculate the amount of dissolved regorafenib ($C_{21}H_{15}ClF_4N_4O_3$), expressed as a percentage of the content stated on the label, taking the specific absorbance to be 988.

Acceptance criterion:

— *Q* = 80 per cent after 30 min.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (b).

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System suitability Reference solution (b):

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of regorafenib ($C_{21}H_{15}ClF_4N_4O_3$) taking into account the assigned content of *regorafenib monohydrate CRS*.

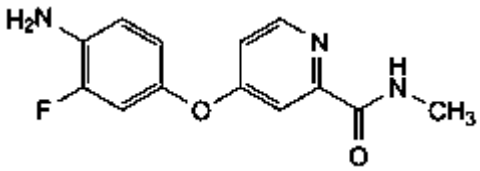
STORAGE

Protected from moisture.

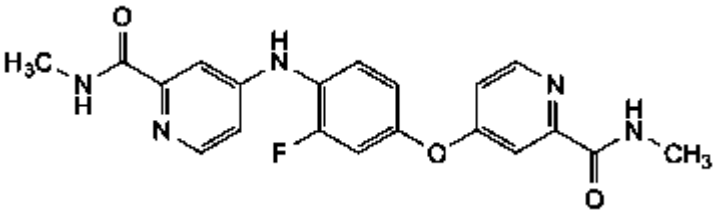
IMPURITIES

Specified impurities *A, FP-A, FP-B, FP-C*.

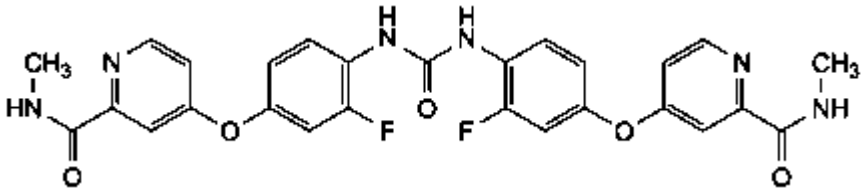
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: C, D, E*.



A. 4-(4-amino-3-fluorophenoxy)-*N*-methylpyridine-2-carboxamide,



C. 4-[3-fluoro-4-[[2-(methylcarbamoyl)pyridin-4-yl]amino]phenoxy]-*N*-methylpyridine-2-carboxamide,



D. $3^3,7^2$-difluoro-*N*,*N*′-dimethyl-5-oxo-2,8-dioxa-4,6-diaza-1(4),9(4)-dipyridina-3(1,4),7(1,4)-dibenzenanonaphane-$1^2,9^2$-dicarboxamide,

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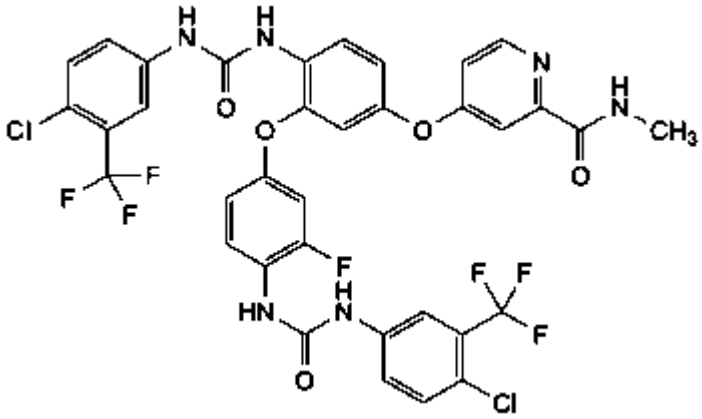
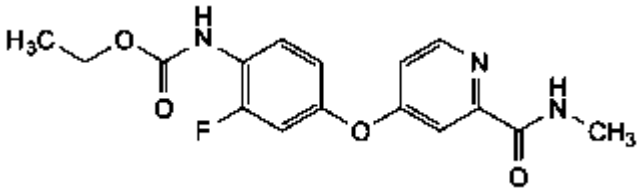
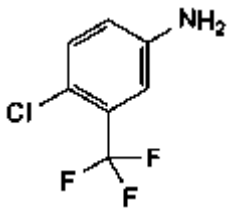


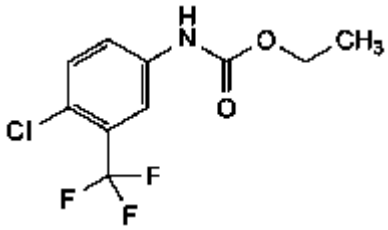
E. 9^4-chloro-3^4-[[[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]-5^3-fluoro-*N*-methyl-7-oxo-9^3-(trifluoromethyl)-2,4-dioxa-6,8-diaza-1(4)-pyridina-3(1,3),5(1,4),9(1)-tribenzenanonaphane-1^2-carboxamide,



FP-A. ethyl [2-fluoro-4-[[2-(methylcarbamoyl)pyridin-4-yl]oxy]phenyl]carbamate,



FP-B. 4-chloro-3-(trifluoromethyl)aniline,



FP-C. ethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate.

Ph Eur

[1] The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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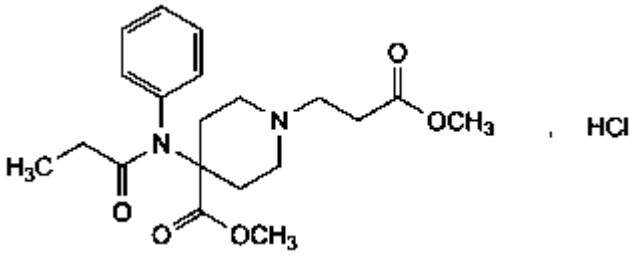
Remifentanil Hydrochloride

General Notices

(Ph. Eur. monograph 2644)



$C_{20}H_{29}ClN_2O_5$ 412.9 *132539-07-2*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

Methyl 1-(3-methoxy-3-oxopropyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate hydrochloride.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in acetonitrile and in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *remifentanil hydrochloride CRS*.

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B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.5 g in water R and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and keep them at not more than 5 °C.*

Buffer solution Dissolve 6.0 g of anhydrous sodium dihydrogen phosphate R in 950 mL of water for chromatography R, adjust to pH 3.0 with phosphoric acid R and dilute to 1000 mL with water for chromatography R.

Test solution (a) Dissolve 30.0 mg of the substance to be examined in mobile phase B and dilute to 20.0 mL with mobile phase B.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with mobile phase B.

Reference solution (a) Dissolve 3 mg of remifentanil impurity mixture CRS (containing impurities A, B, C, E, L, N and O) in mobile phase B and dilute to 2 mL with mobile phase B.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase B. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase B.

Reference solution (c) Dissolve 30.0 mg of remifentanil hydrochloride CRS in mobile phase B and dilute to 20.0 mL with mobile phase B. Dilute 1.0 mL of the solution to 20.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: end-capped octadecylphenylsilyl silica gel for chromatography R (2 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R1, methanol R2, buffer solution (1:9:90 *V/V/V*);

— *mobile phase B*: acetonitrile R1, buffer solution, methanol R2 (12:40:48 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	85	15

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
8 - 40	85 → 45	15 → 55

Flow rate 0.65 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 5.0 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *remifentanil impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, E, L, N and O.

Relative retention With reference to remifentanil (retention time = about 10 min): impurity L = about 0.2; impurity O = about 0.40; impurity B = about 0.44; impurity A = about 0.7; impurity C = about 0.80; impurity N = about 0.85; impurity E = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities O and B; minimum 2.0 between the peaks due to impurities C and N.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity L by 1.5;

— for each impurity, use the concentration of remifentanil hydrochloride in reference solution (b).

Limits:

— *impurity C*: maximum 0.5 per cent;

— *impurity A*: maximum 0.2 per cent;

— *impurities B, E, L*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Methyl acrylate

Head-space gas chromatography (*2.2.28*).

Internal standard solution Dilute 25.0 µL of *propanol R* to 100.0 mL with *water for chromatography R*. Dilute 50.0 mL of the solution to 1000.0 mL with *water for chromatography R*.

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Test solution Dissolve 0.100 g of the substance to be examined in the internal standard solution and dilute to 5.0 mL with the internal standard solution.

Reference solution Dilute 75.0 µL of *methyl acrylate R* to 100.0 mL with the internal standard solution. Dilute 10.0 mL of the solution to 100.0 mL with the internal standard solution. Dilute 7.0 mL of this solution to 100.0 mL with the internal standard solution.

Precolumn:

— *material*: deactivated fused silica;

— *size*: *l* = 5 m, Ø = 0.25 mm.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.53 mm;

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (film thickness 3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 8.3 mL/min.

Pressure 68.9 kPa.

Split ratio 1:10.

Static head-space conditions that may be used:

— *equilibration temperature*: 90 °C;

— *equilibration time*: 5 min;

— *transfer-line temperature*: 180 °C;

— *pressurisation time*: 2 min;

— *injection*: 6 s or 1 mL;

— *withdrawal time*: 12 s;

— *shaker*: on.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 35	35

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	Time (min)	Temperature (°C)
	35 - 40	35 → 210
	40 - 50	210
Injection port		180
Detector		250

Detection Flame ionisation.

Retention time Propanol = about 25 min; methyl acrylate = about 27 min.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to propanol and methyl acrylate.

Calculate the content of methyl acrylate, taking its relative density to be 0.955 at 20 °C.

Limit:

— *methyl acrylate*: maximum 250 ppm.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	85	15
8 - 12	85 → 83	15 → 17
12 - 15	83 → 15	17 → 85
15 - 25	15	85

Injection Test solution (b) and reference solution (c).

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Retention time Remifentanil = about 11 min.

System suitability Reference solution (c):

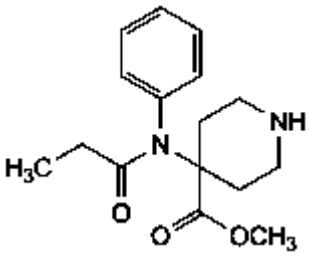
— *symmetry factor*: maximum 2.2 for the peak due to remifentanil.

Calculate the percentage content of $C_{20}H_{29}ClN_2O_5$ taking into account the assigned content of *remifentanil hydrochloride CRS*.

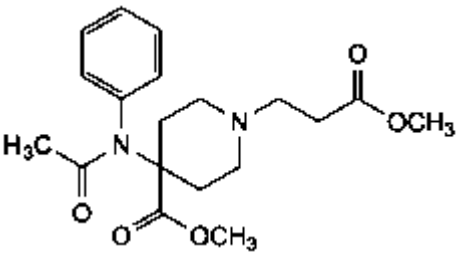
IMPURITIES

Specified impurities *A, B, C, E, L.*

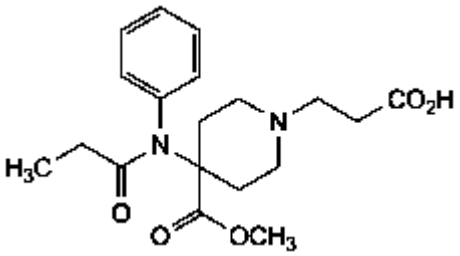
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, G, H, I, J, K, M, N, O.*



A. methyl 4-[phenyl(propanoyl)amino]piperidine-4-carboxylate,



B. methyl 4-[acetyl(phenyl)amino]-1-(3-methoxy-3-oxopropyl)piperidine-4-carboxylate,



C. 3-[4-(methoxycarbonyl)-4-[phenyl(propanoyl)amino]piperidin-1-yl]propanoic acid,

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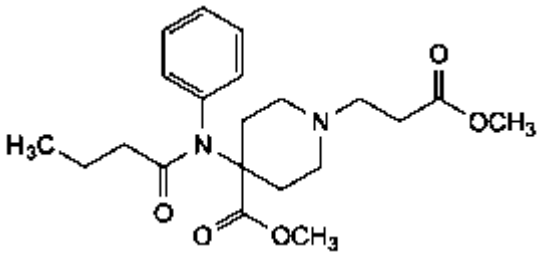
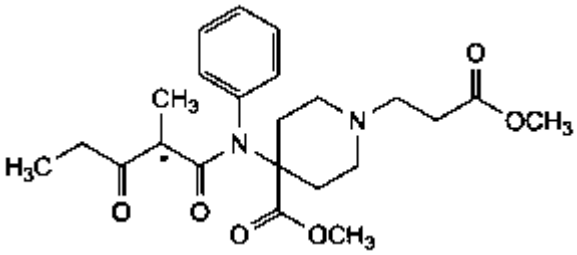
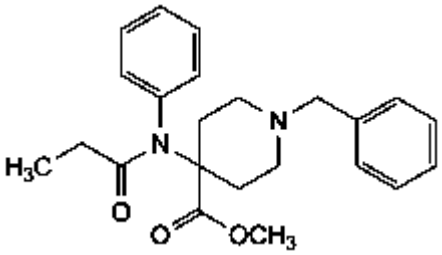


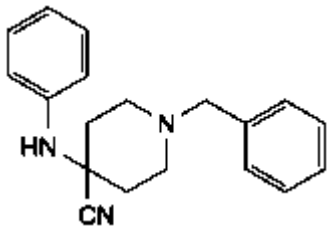
D. methyl 4-[butanoyl(phenyl)amino]-1-(3-methoxy-3-oxopropyl)piperidine-4-carboxylate,



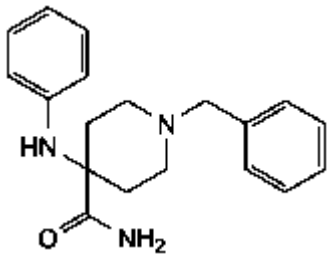
E. methyl 1-(3-methoxy-3-oxopropyl)-4-[(2-methyl-3-oxopentanoyl)(phenyl)amino]piperidine-4-carboxylate,



G. methyl 1-benzyl-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate,



H. 1-benzyl-4-(phenylamino)piperidine-4-carbonitrile,



I. 1-benzyl-4-(phenylamino)piperidine-4-carboxamide,

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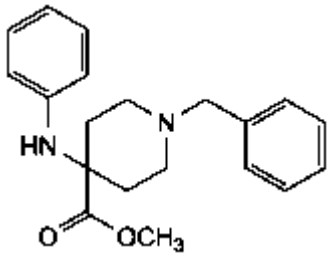
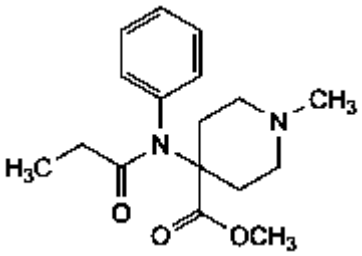
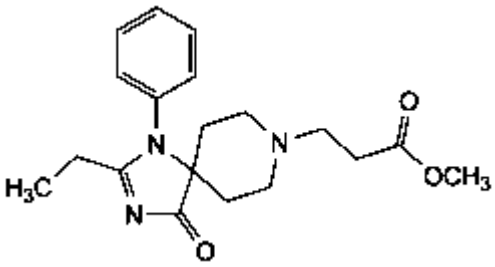


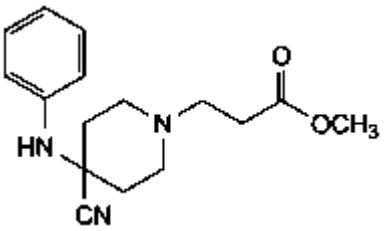
J. methyl 1-benzyl-4-(phenylamino)piperidine-4-carboxylate,



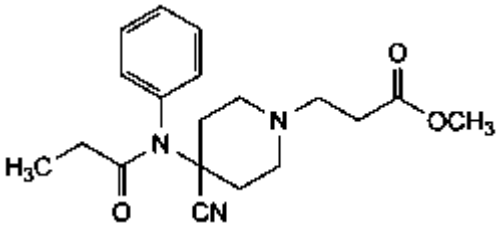
K. methyl 1-methyl-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate,



L. methyl 3-(2-ethyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)propanoate,



M. methyl 3-[4-cyano-4-(phenylamino)piperidin-1-yl]propanoate,



N. methyl 3-[4-cyano-4-[phenyl(propanoyl)amino]piperidin-1-yl]propanoate,

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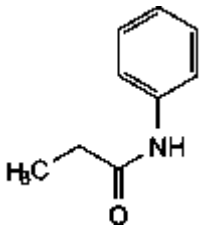

O. *N*-phenylpropanamide.

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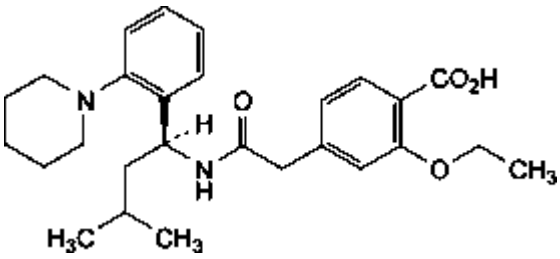
Repaglinide

General Notices

(Ph. Eur. monograph 2135)



$C_{27}H_{36}N_2O_4$ 452.6 *135062-02-1*

Action and use

Stimulates insulin release; treatment of diabetes mellitus.

Preparation

Repaglinide Tablets

Ph Eur

DEFINITION

2-Ethoxy-4-[2-[[(1*S*)-3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl]amino]-2-oxoethyl]benzoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol and in methylene chloride.

It shows polymorphism (*5.9*).

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IDENTIFICATION

A. Specific optical rotation (2.2.7): + 6.3 to + 7.7.

Dissolve 1.00 g in *methanol R* and dilute to 20.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *repaglinide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29). *Prepare the solutions in amber flasks and vials.*

Test solution Dissolve 10.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *repaglinide impurity E CRS* in *methanol R* and dilute to 50.0 mL with the same of solvent.

Reference solution (b) Dilute 2.0 mL of reference solution (a) to 100.0 mL with *methanol R*.

Reference solution (c) Mix 1.0 mL of the test solution and 10 mL of reference solution (a) and dilute to 50.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.0 mm,

— *stationary phase*: *silica gel AGP for chiral chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.0 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 4.7 with *dilute sodium hydroxide solution R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	80 → 60	20 → 40
4 - 6	60	40

Equilibration after installation of the column for use Using *water R*, slowly increase the flow rate from 0.2 mL/min to 0.5 mL/min. Maintain the flow rate at 0.5 mL/min for 5 min. The column must be washed for 1 h at a flow rate of 1 mL/min with *water R* and for 1 h with the mobile phase at the initial composition prior to the 1st analysis.

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 240 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Retention time Repaglinide = about 3.3 min; impurity E = about 5.0 min.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to repaglinide and impurity E.

Limit:

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 2.0 mL of this solution to 100.0 mL with *acetonitrile R*.

Reference solution (b) With the aid of an ultrasonic bath, dissolve the contents of 1 vial of *repaglinide for system suitability CRS* in 2.0 mL of *acetonitrile R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *silica gel for chromatography, alkyl-bonded for use with highly aqueous mobile phases R* (5 µm),

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: 4.0 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.2 with *dilute phosphoric acid R*;

— *mobile phase B*: mobile phase A, *acetonitrile R* (300:700 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	50 → 7	50 → 93
20 - 30	7	93

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 240 nm.

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Injection 10 µL.

Relative retention With reference to repaglinide (retention time = about 10 min): impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.4; impurity D = about 1.5.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity B and impurity C,

— the chromatogram obtained is similar to the chromatogram supplied with *repaglinide for system suitability CRS*.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity B = 0.7; impurity C = 3.1;

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.320 g in 10 mL *methanol R* and add 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 45.26 mg of $C_{27}H_{36}N_2O_4$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*

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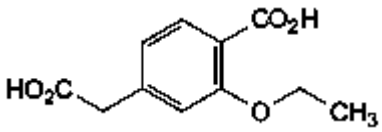
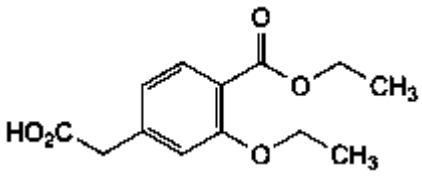
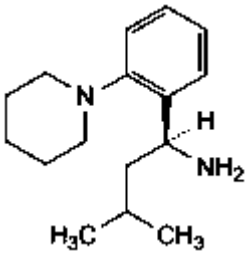


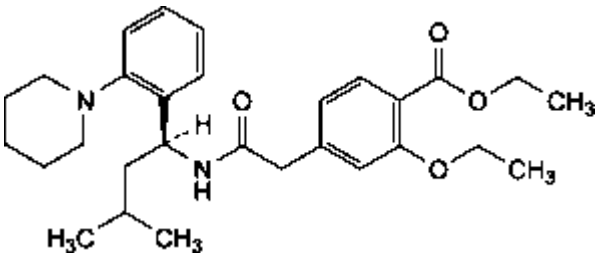
A. 4-(carboxymethyl)-2-ethoxybenzoic acid,



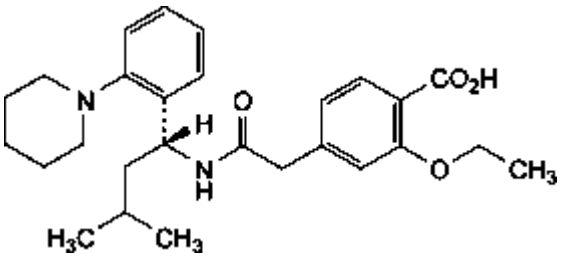
B. [3-ethoxy-4-(ethoxycarbonyl)phenyl]acetic acid,



C. (1*S*)-3-methyl-1-[2-(piperidin-1-yl)phenyl]butan-1-amine,



D. ethyl 2-ethoxy-4-[2-[[(1*S*)-3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl]amino]-2-oxoethyl]benzoate,



E. 2-ethoxy-4-[2-[[(1*R*)-3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl]amino]-2-oxoethyl]benzoic acid.

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Repaglinide Tablets

General Notices

Action and use

Stimulates insulin release; treatment of diabetes mellitus.

DEFINITION

Repaglinide Tablets contain Repaglinide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of repaglinide, $C_{27}H_{36}N_2O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared in *methanol*.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 5 mg of Repaglinide with 15 mL of *methanol*. Dilute to 50 mL, filter (a 0.45-µm nylon filter is suitable) and use the filtrate.

(2) 0.01% w/v of *repaglinide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 25 µL of each solution.

(d) Develop the plate to 5 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

25 volumes of *methanol*, 30 volumes of *toluene* and 45 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and filter (a 0.45-µm Millex LCR PTFE filter is suitable). Use the filtered medium, diluted with the dissolution medium if necessary to produce a solution expected to contain 0.00006% w/v of Repaglinide.

(2) 0.006% w/v of *repaglinide BPCRS* in *methanol*. Dilute 1 volume to 100 volumes with the medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use fluorimetric detection with an excitation wavelength of 244 nm and an emission wavelength of 348 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

11 volumes of *methanol*, 40 volumes of 0.01M *potassium dihydrogen orthophosphate* adjusted to pH 2.3 with *orthophosphoric acid* and 49 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to repaglinide is between 0.8 and 1.8.

DETERMINATION OF CONTENT

Calculate the total content of repaglinide, $C_{27}H_{36}N_2O_4$, in the medium from the chromatograms obtained and using the declared content of $C_{27}H_{36}N_2O_4$, in *repaglinide BPCRS*.

LIMITS

The amount of repaglinide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light and prepared in a mixture of equal volumes of *acetonitrile R1* and mobile phase A (solution A).

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(1) Shake a quantity of the powdered tablets containing 5 mg of Repaglinide in 2 mL of water. Add 10 mL of solution A, mix with the aid of ultrasound and dilute to 20 mL. Centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes. Further dilute 1 volume of this solution to 5 volumes.

(3) Dilute 1 volume of *repaglinide impurity standard solution BPCRS* to 10 volumes with solution A.

(4) 0.1% w/v of *repaglinide for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped extra-dense bonded octylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use detection wavelengths of 210 nm and 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.02M *potassium dihydrogen orthophosphate* adjusted to pH 2.9 with *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	75	25	isocratic
4-30	75→50	25→50	linear gradient
30-40	50	50	isocratic
40-41	50→75	50→25	linear gradient
41-50	75	25	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to repaglinide (retention time about 24 minutes) are: impurity A, about 0.1; impurity B, about 0.4; impurity C, about 0.6; impurity 1, about 1.05; and impurity D, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless:

At 210 nm

in the chromatogram obtained with solution (2), the *signal to noise ratio* of the peak due to repaglinide is at least 40;

At 240 nm

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to repaglinide and impurity 1 is at least 1.8.

LIMITS

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At 210 nm

Identify any peak corresponding to impurity C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 2.5 times the area of the peak in the chromatogram obtained with solution (2) (0.5%).

At 240 nm

Identify any peak corresponding to impurities A and B in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the areas of these peak by a correction factor of: 0.6 and 0.7 respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 2.5 times the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

The sum of all impurities, including impurity C, is not greater than 1.0%.

Uniformity of content

Repaglinide Tablets containing less than 2 mg and/or less than 2% w/w of Repaglinide comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To one tablet add 3 mL of the mobile phase, mix with the aid of ultrasound and shake for 15 minutes. Dilute to 5 mL with mobile phase and filter (a 0.45-µm Millex LCR PTFE filter is suitable). Dilute the filtrate, if necessary, with mobile phase to produce a solution containing the equivalent of 0.01% w/v of repaglinide.

(2) 0.1% w/v of *repaglinide BPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.

(3) Dilute 1 volume of *repaglinide impurity standard solution BPCRS* to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped extra-dense bonded octylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 242 nm.

(f) Inject 10 µL of each solution.

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MOBILE PHASE

25 volumes of 0.007M *potassium dihydrogen orthophosphate* adjusted to pH 2.5 with *orthophosphoric acid* and 75 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of repaglinide is about 6 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 1 and repaglinide is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of repaglinide, $C_{27}H_{36}N_2O_4$, in the tablets from the chromatograms obtained and using the declared content of $C_{27}H_{36}N_2O_4$ in *repaglinide BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of Repaglinide

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of Repaglinide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 75 mL of the mobile phase to 10 whole tablets, mix with the aid of ultrasound and shake for 15 minutes. Dilute to 100 mL with mobile phase and filter (a 0.45-µm Millex LCR PTFE filter is suitable). Further dilute this solution, if necessary, with the mobile phase to produce a solution containing 0.01% w/v of Repaglinide.

(2) 0.1% w/v of *repaglinide BPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.

(3) Dilute 1 volume of *repaglinide impurity standard solution BPCRS* to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 1 and repaglinide is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of repaglinide, $C_{27}H_{36}N_2O_4$, in the tablets from the chromatograms obtained and using the declared content of $C_{27}H_{36}N_2O_4$ in *repaglinide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Repaglinide and:

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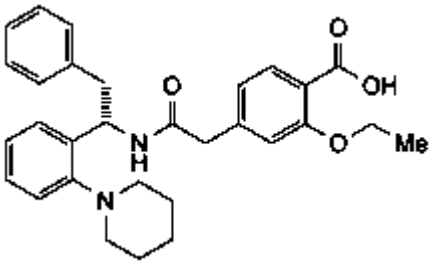

1. 2-ethoxy-4-(2-{(1*S*)-1-[2-(pyrolidin-1-yl)phenyl]-2-phenylethylamino}-2-oxoethyl)benzoic acid.

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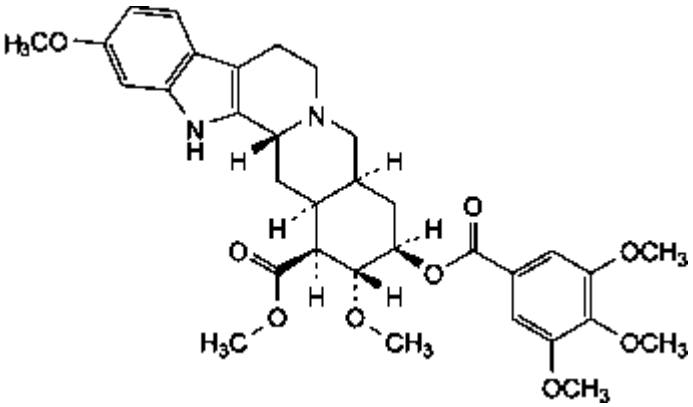
Reserpine

General Notices

(Ph. Eur. monograph 0528)



$C_{33}H_{40}N_2O_9$ 609 *50-55-5*

Action and use

Rauwolfia alkaloid; treatment of hypertension.

Ph Eur

DEFINITION

Methyl 11,17α-dimethoxy-18β-[(3,4,5-trimethoxybenzoyl)oxy]-3β,20α-yohimban-16β-carboxylate.

Content

— *reserpine*: 98.0 per cent to 102.0 per cent (dried substance),

— *total alkaloids*: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, small crystals or crystalline powder, darkening slowly on exposure to light.

Solubility

Practically insoluble in water, very slightly soluble in ethanol (96 per cent).

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IDENTIFICATION

First identification: B.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in *chloroform R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *ethanol (96 per cent) R*. Examine immediately.

Spectral range 230-350 nm.

Absorption maximum At 268 nm.

Specific absorbance at the absorption maximum 265 to 285.

Over the range 288-295 nm, the curve shows a slight absorption minimum followed by a shoulder or a slight absorption maximum; over this range, the specific absorbance is about 170.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *reserpine CRS*.

C. To about 1 mg add 0.1 mL of a 1 g/L solution of *sodium molybdate R* in *sulfuric acid R*. A yellow colour is produced which becomes blue within 2 min.

D. To about 1 mg add 0.2 mL of a freshly prepared 10 g/L solution of *vanillin R* in *hydrochloric acid R*. A pink colour develops within 2 min.

E. Mix about 0.5 mg with 5 mg of *dimethylaminobenzaldehyde R* and 0.2 mL of *glacial acetic acid R* and add 0.2 mL of *sulfuric acid R*. A green colour is produced. Add 1 mL of *glacial acetic acid R*. The colour becomes red.

TESTS

Specific optical rotation (2.2.7)

-116 to -128 (dried substance).

Dissolve 0.250 g in *chloroform R* and dilute to 25.0 mL with the same solvent. Examine immediately.

Oxidation products

Dissolve 20 mg in *glacial acetic acid R* and dilute to 100.0 mL with the same acid. The absorbance (2.2.25) measured immediately at the absorption maximum at 388 nm is not greater than 0.10.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 0.500 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.7 kPa for 3 h.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 0.5 g.

ASSAY

Total alkaloids

Dissolve 0.500 g in a mixture of 6 mL of *acetic anhydride R* and 40 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 60.9 mg of total alkaloids.

Reserpine

Protect the solutions from light Moisten 25.0 mg with 2 mL of *ethanol (96 per cent) R*, add 2 mL of *0.25 M sulfuric acid* and 10 mL of *ethanol (96 per cent) R*, and warm gently to dissolve. Cool and dilute to 100.0 mL with *ethanol (96 per cent) R*. Dilute 5.0 mL of this solution to 50.0 mL with *ethanol (96 per cent) R*. Prepare a reference solution in the same manner using 25.0 mg of *reserpine CRS*. Place 10.0 mL of each solution separately in 2 boiling-tubes, add 2.0 mL of *0.25 M sulfuric acid* and 2.0 mL of a freshly prepared 3 g/L solution of *sodium nitrite R*. Mix and heat in a water-bath at 55 °C for 35 min. Cool, add 1.0 mL of a freshly prepared 50 g/L solution of *sulfamic acid R* and dilute to 25.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) of each solution at the absorption maximum at 388 nm, using as the compensation liquid 10.0 mL of the same solution prepared at the same time in the same manner, but omitting the sodium nitrite.

Calculate the content of $C_{33}H_{40}N_2O_9$ from the absorbances measured and the concentrations of the solutions.

STORAGE

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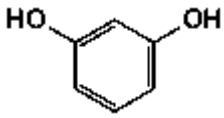
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Resorcinol

General Notices

(Ph. Eur. monograph 0290)



$C_6H_6O_2$ 110.1 *108-46-3*

Action and use

Keratolytic.

Ph Eur

DEFINITION

Resorcinol contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of benzene-1,3-diol, calculated with reference to the dried substance.

CHARACTERS

A colourless or slightly pinkish-grey, crystalline powder or crystals, turning red on exposure to light and air, very soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 109 °C to 112 °C.

B. Dissolve 0.1 g in 1 mL of *water R*, add 1 mL of *strong sodium hydroxide solution R* and 0.1 mL of *chloroform R*, heat and allow to cool. An intense, deep-red colour develops which becomes pale yellow on the addition of a slight excess of *hydrochloric acid R*.

C. Thoroughly mix about 10 mg with about 10 mg of *potassium hydrogen phthalate R*, both finely powdered. Heat over a naked flame until an orange-yellow colour is obtained. Cool and add 1 mL of *dilute sodium hydroxide solution R* and 10 mL of *water R* and shake to dissolve. The solution shows an intense green fluorescence.

TESTS

Solution S

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Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_5 or R_5 (*2.2.2, Method II*) and remains so when heated in a water-bath for 5 min.

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *bromophenol blue solution R2*. Not more than 0.05 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution Dissolve 0.5 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dilute 0.1 mL of the test solution to 20 mL with *methanol R*.

Apply separately to the plate 2 µL of each solution. Develop over a path of 15 cm using a mixture of 40 volumes of *ethyl acetate R* and 60 volumes of *hexane R*. Allow the plate to dry in air for 15 min and expose it to iodine vapour. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Pyrocatechol

To 2 mL of solution S add 1 mL of *ammonium molybdate solution R2* and mix. Any yellow colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 2 mL of a 0.1 g/L solution of *pyrocatechol R*.

Loss on drying (*2.2.32*)

Not more than 1.0 per cent, determined on 1.00 g of powdered substance by drying in a desiccator for 4 h.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in *water R* and dilute to 250.0 mL with the same solvent. To 25.0 mL of the solution in a ground-glass-stoppered flask add 1.0 g of *potassium bromide R*, 50.0 mL of *0.0167 M potassium bromate*, 15 mL of *chloroform R* and 15.0 mL of *hydrochloric acid R1*. Stopper the flask, shake and allow to stand in the dark for 15 min, shaking occasionally. Add 10 mL of a 100 g/L solution of *potassium iodide R*, shake thoroughly, allow to stand for 5 min and titrate with *0.1 M sodium thiosulfate*, using 1 mL of *starch solution R* as indicator.

1 mL of *0.0167 M potassium bromate* is equivalent to 1.835 mg of $C_6H_6O_2$.

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STORAGE

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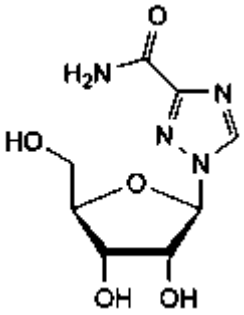
Ribavirin

General Notices

(Ph. Eur. monograph 2109)



$C_8H_{12}N_4O_5$ 244.2 *36791-04-5*

Action and use

Antiviral (hepatitis C, respiratory syncytial virus).

Preparation

Ribavirin Powder for Nebuliser Solution

Ph Eur

DEFINITION

1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), slightly soluble or very slightly soluble in methylene chloride.

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It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ribavirin CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

TESTS

pH (*2.2.3*)

4.0 to 6.5.

Dissolve 0.200 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-33 to -37 (dried substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent. Determine the specific optical rotation within 10 min of preparing the solution.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) In order to produce impurity A *in situ*, mix 5.0 mL of the test solution and 5.0 mL of a 42 g/L solution of *sodium hydroxide R* and allow to stand for 90 min. Neutralise with 5.0 mL of a 103 g/L solution of *hydrochloric acid R* and mix well.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water for chromatography R*. Dilute 1.0 mL of this solution to 10.0 mL with *water for chromatography R*.

Reference solution (c) Dissolve 50.0 mg of *ribavirin CRS* in *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (3 µm) suitable for use with highly aqueous mobile phases ;

— *temperature*: 25 °C.

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Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *anhydrous sodium sulfate R* in 950 mL of *water for chromatography R*, add 2.0 mL of a 5 per cent *V/V* solution of *phosphoric acid R*, adjust to pH 2.8 with a 5 per cent *V/V* solution of *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R1*, mobile phase A (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 25	100 → 0	0 → 100
25 - 35	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 5 µL of the test solution and reference solutions (a) and (b).

Relative retention With reference to ribavirin (retention time = about 6 min): impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity A and ribavirin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 2.3;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_8H_{12}N_4O_5$ from the declared content of *ribavirin CRS*.

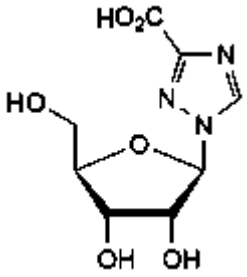
STORAGE

Protected from light.

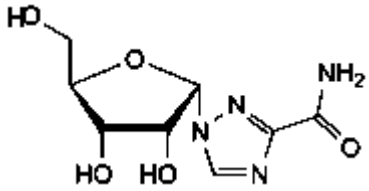
IMPURITIES

Specified impurities A.

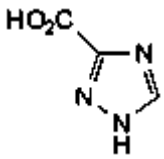
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, F, G.



A. 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylic acid,



B. 1-α-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide (anomer),



C. 1*H*-1,2,4-triazole-3-carboxylic acid,

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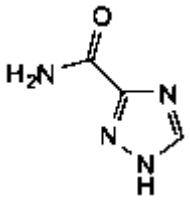
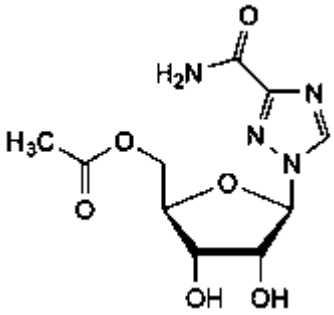
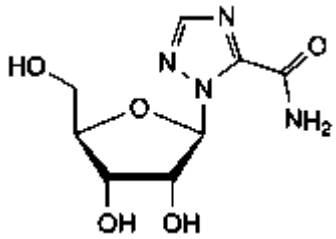


D. 1*H*-1,2,4-triazole-3-carboxamide,



F. 1-(5-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide (5′-*O*-acetylribavirin),



G. 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-5-carboxamide (*N*-isomer).

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Ribavirin Powder for Nebuliser Solution

General Notices

Ribavirin Nebuliser Solution

Action and use

Antiviral (Hepatitis C, respiratory syncytial virus).

DEFINITION

Ribavirin Powder for Nebuliser Solution consists of Ribavirin with or without excipients. It is supplied in a sealed container and it is reconstituted with an appropriate liquid in accordance with the manufacturer's instructions to obtain a nebuliser solution intended to be converted into aerosols by a nebuliser.

The contents of the sealed container comply with the requirements stated under Preparations for Inhalation and with the following requirements.

Content of ribavirin, $C_8H_{12}N_4O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* as the coating substance and a mixture of 20 volumes of 0.1M *ammonium chloride* and 90 volumes of *acetonitrile* as the mobile phase. Apply separately to the plate 10 µL of each of two solutions in *water* containing (1) 1% w/v Ribavirin and (2) 1% w/v of *ribavirin BPCRS*. After removal of the plate, allow the spots to dry in air for 15 minutes and spray the plate with mixture of 0.5 mL of *anisaldehyde*, 0.5 mL of *sulfuric acid*, 0.1 mL of *glacial acetic acid* and 9 mL of *ethanol* (*96%*). Heat the plate at 105° for 40 minutes. The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using two solutions of the contents of the container in the mobile phase containing (1) 0.050% w/v and (2) 0.000125% w/v of Ribavirin respectively. Solution (3) contains 0.050% w/v of *ribavirin impurity standard BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 7.8 mm) packed with a strong cation-exchange resin of sulfonated, cross-linked *styrene-divinylbenzene co-polymer* in the hydrogen form (7 to 11 µm) (Aminex HPAH is suitable) and maintained at 40°, (b) *water* adjusted to pH 2.5 with *sulfuric acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a

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detection wavelength of 207 nm. Inject separately 10 µL of each solution. For solution (1) allow the chromatography to proceed for ten times the retention time of the principal peak.

The test is not valid unless the *symmetry factor* for the principal peak in the chromatogram obtained with solution (1) is at least 0.7 and not more than 1.5 and unless the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *ribavirin impurity standard BPCRS*.

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than that of the principal peak in the chromatogram obtained with solution (2) (0.25%) and the sum of the areas of any such peaks is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. For solution (1) reconstitute the contents of one container as instructed on the label using an accurately measured volume of diluent, dilute a suitable volume of the solution to 200 volumes with the mobile phase to produce a solution containing 0.10% w/v of Ribavirin; mix and dilute 5 volumes of the resulting solution to 20 volumes with the mobile phase. Solution (2) contains 0.0025% w/v of *ribavirin BPCRS*.

The chromatographic procedure described under Related substances may be used.

Calculate the content of $C_8H_{12}N_4O_5$ in the container using the declared content of $C_8H_{12}N_4O_5$ in *ribavirin BPCRS*.

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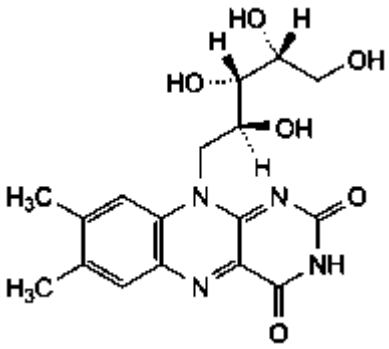
Riboflavin

General Notices

(Ph. Eur. monograph 0292)



$C_{17}H_{20}N_4O_6$ 376.4 *83-88-5*

Action and use

Vitamin B_2.

Ph Eur

DEFINITION

7,8-Dimethyl-10-[(2*S*,3*S*,4*R*)-2,3,4,5-tetrahydroxypentyl]benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione.

This monograph applies to riboflavin produced by fermentation.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow or orange-yellow, crystalline powder.

Solubility

Very slightly soluble in water, practically insoluble in ethanol (96 per cent).

Solutions deteriorate on exposure to light, especially in the presence of alkali.

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It shows polymorphism (5.9).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Thin-layer chromatography (2.2.27).

Test solution Suspend 25 mg of the substance to be examined in 10 mL of *water R*, shake for 5 min and filter the suspension to remove the undissolved material.

Reference solution Suspend 25 mg of *riboflavin CRS* in 10 mL of *water R*, shake for 5 min and filter the suspension to remove the undissolved material.

Plate *TLC silica gel plate R* (2-10 µm).

Mobile phase *water R*.

Application As follows, drying in a current of cold air after each individual application:

— *1st application*: 2 µL of *methylene chloride R* then 2 µL of the test solution;

— *2nd application*: 2 µL of *methylene chloride R* then 2 µL of the reference solution.

Development Over a path of 6 cm.

Drying In a current of cold air.

Detection Examine in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve about 1 mg in 100 mL of *water R*. The solution has, by transmitted light, a pale greenish-yellow colour, and, by reflected light, an intense yellowish-green fluorescence which disappears on the addition of mineral acids or alkalis.

TESTS

Specific optical rotation (2.2.7)

-115 to -135 (dried substance).

Dissolve 50.0 mg in *0.05 M sodium hydroxide* free from carbonate and dilute to 10.0 mL with the same alkaline solution. Measure the optical rotation within 30 min of dissolution.

Absorbance (2.2.25)

Test solution Dilute the final solution prepared for the assay with an equal volume of *water R*.

Absorption maxima At 223 nm, 267 nm, 373 nm and 444 nm.

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Absorbance ratios:

— A_{373}/A_{267} = 0.31 to 0.33;

— A_{444}/A_{267} = 0.36 to 0.39.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Solution A 13.6 g/L solution of *sodium acetate R*.

Test solution With the aid of ultrasound, dissolve 0.120 g of the substance to be examined in 10 mL of *0.1 M sodium hydroxide* and dilute to 100 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (b) With the aid of ultrasound, dissolve the contents of a vial of *riboflavin for peak identification CRS* (containing impurities C and D) in 1.0 mL of a mixture of 1 volume of mobile phase B and 9 volumes of mobile phase A.

Reference solution (c) In order to prepare *in situ* impurities A and B, dissolve 10 mg of the substance to be examined in 1 mL of *0.5 M sodium hydroxide*. Expose to daylight for 1.5 h. Add 0.5 mL of *acetic acid R* and dilute to 100 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *water R* (1:1000 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 20	90 → 80	10 → 20
20 - 25	80	20
25 - 35	80 → 50	20 → 50
35 - 45	50	50

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Flow rate 1.0 mL/min.

Detection Spectrophotometer at 267 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *riboflavin for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and D.

Relative retention With reference to riboflavin (retention time = about 16 min): impurity C = about 0.2; impurity D = about 0.5; impurity A = about 1.4; impurity B = about 1.9.

System suitability:

— *resolution*: minimum 5 between the peaks due to impurities A and B in the chromatogram obtained with reference solution (c);

— the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with *riboflavin for peak identification CRS*.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity B = 1.4; impurity C = 2.3; impurity D = 1.4;

— *impurity A*: not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.025 per cent);

— *impurities B, C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit for peaks other than those due to impurity A*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Carry out the assay protected from light.

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In a brown-glass 500 mL volumetric flask, suspend 65.0 mg in 5 mL of *water R* ensuring that it is completely wetted and dissolve in 5 mL of *dilute sodium hydroxide solution R*. As soon as dissolution is complete, add 100 mL of *water R* and 2.5 mL of *glacial acetic acid R* and dilute to 500.0 mL with *water R*. Place 20.0 mL of this solution in a 200 mL brown-glass volumetric flask, add 3.5 mL of a 14 g/L solution of *sodium acetate R* and dilute to 200.0 mL with *water R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 444 nm.

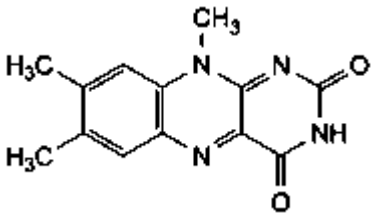
Calculate the content of $C_{17}H_{20}N_4O_6$ taking the specific absorbance to be 328.

STORAGE

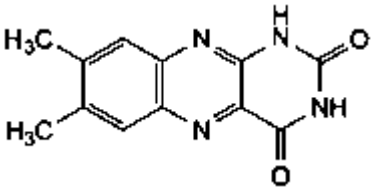
In an airtight container, protected from light.

IMPURITIES

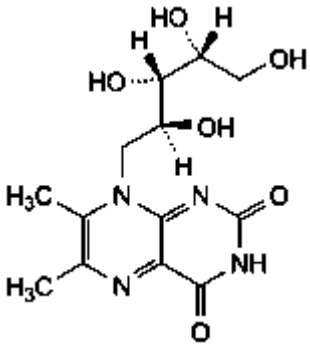
Specified impurities *A, B, C, D.*



A. 7,8,10-trimethylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (lumiflavine),



B. 7,8-dimethylbenzo[*g*]pteridine-2,4(1*H*,3*H*)-dione,



C. 6,7-dimethyl-8-[(2*S*,3*S*,4*R*)-2,3,4,5-tetrahydroxypentyl]pteridine-2,4(3*H*,8*H*)-dione,

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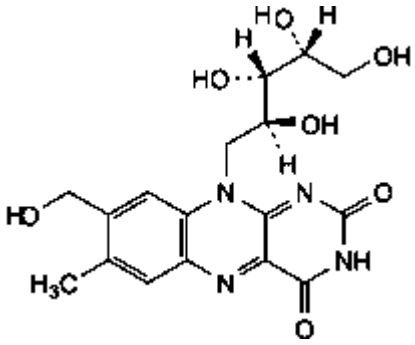

D. 8-(hydroxymethyl)-7-methyl-10-[(2*S*,3*S*,4*R*)-2,3,4,5-tetrahydroxypentyl]benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione.

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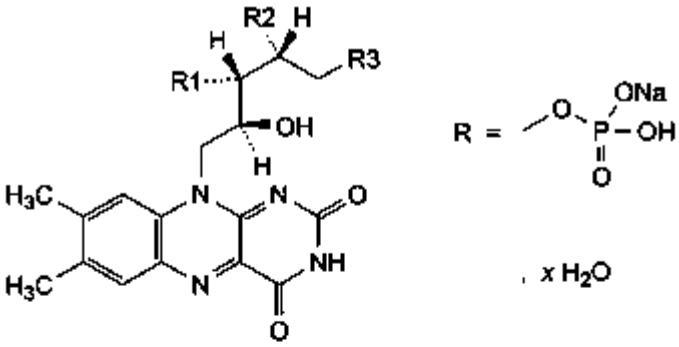
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Riboflavin Sodium Phosphate Hydrate

General Notices

Riboflavin Sodium Phosphate

(Ph. Eur. monograph 0786)



Anhydrous component	R1	R2	R3	Mol. formula	M_r
Riboflavin 3'-(sodium hydrogen phosphate)	R	OH	OH	$C_{17}H_{20}N_4NaO_9P$	478.3
Riboflavin 4'-(sodium hydrogen phosphate)	OH	R	OH	$C_{17}H_{20}N_4NaO_9P$	478.3
Riboflavin 5'-(sodium hydrogen phosphate)	OH	OH	R	$C_{17}H_{20}N_4NaO_9P$	478.3
Riboflavin 3',4'-bis(sodium hydrogen phosphate)	R	R	OH	$C_{17}H_{20}N_4Na_2O_{12}P_2$	580.3
Riboflavin 3',5'-bis(sodium hydrogen phosphate)	R	OH	R	$C_{17}H_{20}N_4Na_2O_{12}P_2$	580.3
Riboflavin 4',5'-bis(sodium hydrogen phosphate)	OH	R	R	$C_{17}H_{20}N_4Na_2O_{12}P_2$	580.3

Riboflavin 5′-(sodium hydrogen phosphate) *130-40-5*

Action and use

Vitamin B2.

Preparation

Vitamins B and C Injection

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DEFINITION

Semi-synthetic product derived from phosphorylation of *Riboflavin (0292)*.

Main component:

— riboflavin 5′-(sodium hydrogen phosphate): sodium (2*R*,3*S*,4*S*)-5-(7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[*g*]pteridin-10(2*H*)-yl)-2,3,4-trihydroxypentyl hydrogen phosphate.

Minor components:

— riboflavin 3′-(sodium hydrogen phosphate): sodium (2*S*,3*S*,4*R*)-1-(7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[*g*]pteridin-10(2*H*)-yl)-2,4,5-trihydroxypentan-3-yl hydrogen phosphate;

— riboflavin 4′-(sodium hydrogen phosphate): sodium (2*R*,3*S*,4*S*)-5-(7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[*g*]pteridin-10(2*H*)-yl)-1,3,4-trihydroxypentan-2-yl hydrogen phosphate;

— riboflavin 3′,4′-bis(sodium hydrogen phosphate): disodium (2*R*,3*S*,4*S*)-5-(7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[*g*]pteridin-10(2*H*)-yl)-1,4-dihydroxypentane-2,3-diyl bis(hydrogen phosphate);

— riboflavin 3′,5′-bis(sodium hydrogen phosphate): disodium (2*R*,3*S*,4*S*)-5-(7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[*g*]pteridin-10(2*H*)-yl)-2,4-dihydroxypentane-1,3-diyl bis(hydrogen phosphate);

— riboflavin 4′,5′-bis(sodium hydrogen phosphate): disodium (2*R*,3*S*,4*S*)-5-(7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[*g*]pteridin-10(2*H*)-yl)-3,4-dihydroxypentane-1,2-diyl bis(hydrogen phosphate).

It contains a variable quantity of water.

Content

73.0 per cent to 79.0 per cent of riboflavin ($C_{17}H_{20}N_4O_6$; M_r 376.4) (dried substance).

CHARACTERS

Appearance

Yellow or orange-yellow, crystalline, hygroscopic powder.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *riboflavin sodium phosphate CRS*.

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B. To 0.5 g add 10 mL of *nitric acid R* and evaporate the mixture to dryness. Ignite the residue until it becomes white, dissolve the residue in 5 mL of *water R* and filter. The filtrate gives reaction (a) of sodium (*2.3.1*).

C. The filtrate obtained in identification test B gives reaction (b) of phosphates (*2.3.1*).

TESTS

pH (*2.2.3*)

5.0 to 6.5.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 38.0 to + 43.0 (dried substance).

Dissolve 0.300 g in 18.2 mL of *hydrochloric acid R1* and dilute to 25.0 mL with *water R*.

Impurity E

To about 35 mg add 10 mL of *methylene chloride R*, shake for 5 min and filter. The filtrate is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Carry out the test protected from light.*

Test solution Dissolve 0.100 g of the substance to be examined in 50 mL of *water R* and dilute to 100.0 mL with the mobile phase. Dilute 8.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 60 mg of *riboflavin CRS* (impurity D) in 1 mL of *hydrochloric acid R* and dilute to 250 mL with *water R*. Dilute 4 mL of this solution to 100 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *riboflavin sodium phosphate CRS* in 5 mL of *water R* and dilute to 10 mL with the mobile phase. Dilute 8 mL of this solution to 50 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (d) Dissolve 5 mg of *riboflavin sodium phosphate for peak identification CRS* (containing impurities F, G and H) in 2.5 mL of *water R* and dilute to 5 mL with the mobile phase. Dilute 4 mL of the solution to 25 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

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Mobile phase *methanol R*, 7.35 g/L solution of *potassium dihydrogen phosphate R* (15:85 *V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 266 nm.

Injection 100 µL.

Run time 2.5 times the retention time of riboflavin 5′-monophosphate.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D; use the chromatogram supplied with *riboflavin sodium phosphate for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities F, G and H.

Relative retention With reference to riboflavin 5′-monophosphate (retention time = about 17 min): riboflavin 3′, 4′-diphosphate = about 0.2; riboflavin 3′, 5′-diphosphate = about 0.3; riboflavin 4′, 5′-diphosphate = about 0.5; impurity F = about 0.6; riboflavin 3′-monophosphate = about 0.7; impurity G = about 0.8; riboflavin 4′-monophosphate = about 0.9; impurity H = about 1.3; impurity D = about 2.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to riboflavin 4′-monophosphate and riboflavin 5′-monophosphate.

Limits:

— *impurity D*: maximum 6.0 per cent;

— *impurity F*: maximum 0.7 per cent;

— *impurity G*: maximum 0.6 per cent;

— *impurity H*: maximum 0.4 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 8.0 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (c)).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Composition

Liquid chromatography (*2.2.29*) as described in the test for related substances.

Identification of peaks Use the chromatogram supplied with *riboflavin sodium phosphate CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to the major and minor components listed under Definition.

Limits:

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— riboflavin 5′-(sodium hydrogen phosphate) hydrate: minimum 65.0 per cent;

— riboflavin 4′-(sodium hydrogen phosphate) hydrate: maximum 12.0 per cent;

— riboflavin 3′-(sodium hydrogen phosphate) hydrate: maximum 7.0 per cent;

— riboflavin 3′,5′-bis(sodium hydrogen phosphate) hydrate: maximum 3.5 per cent;

— riboflavin 4′,5′-bis(sodium hydrogen phosphate) hydrate: maximum 3.5 per cent;

— riboflavin 3′,4′-bis(sodium hydrogen phosphate) hydrate: maximum 1.0 per cent.

Inorganic phosphate

Maximum 1.0 per cent.

Acid molybdate solution Dilute 25 mL of a 70 g/L solution of *ammonium molybdate R* to 200 mL with *water R*. To this solution slowly add 25 mL of a 210 mL/L solution of *sulfuric acid R*.

Ferrous sulfate solution A 100 g/L solution of *ferrous sulfate R* in a 4.2 mL/L solution of *sulfuric acid R*.

Test solution Dissolve 0.150 g in *water R* and dilute to 50 mL with the same solvent. To 10.0 mL of the solution add 10.0 mL of acid molybdate solution and 5.0 mL of ferrous sulfate solution and mix.

Reference solution Immediately before use, dilute with *water R* to 10 times its volume a solution containing *potassium dihydrogen phosphate R* equivalent to 0.440 g of KH_2PO_4 in 1000.0 mL. To 10.0 mL of this solution add 10.0 mL of acid molybdate solution and 5.0 mL of ferrous sulfate solution and mix.

Measure the absorbance (*2.2.25*) of the test solution and the reference solution at 700 nm using *water R* as compensation liquid.

Results The absorbance of the test solution is not greater than that of the reference solution.

Loss on drying (*2.2.32*)

Maximum 8.0 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C for 5 h.

ASSAY

Carry out the assay protected from light.

Dissolve 0.100 g in 150 mL of *water R*, add 2 mL of *glacial acetic acid R* and dilute to 1000.0 mL with *water R*. To 10.0 mL of this solution add 3.5 mL of a 14 g/L solution of *sodium acetate R* and dilute to 50.0 mL with *water R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 444 nm.

Calculate the content of $C_{17}H_{20}N_4O_6$ taking the specific absorbance to be 328.

STORAGE

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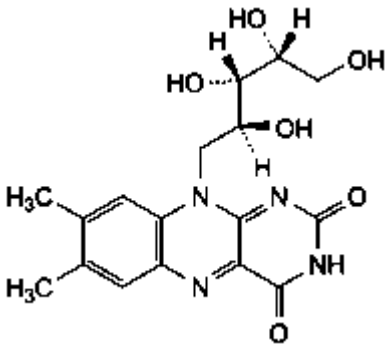
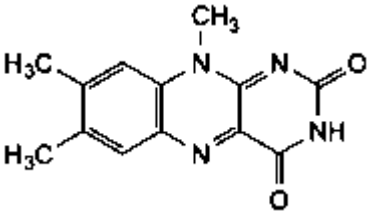
In an airtight container, protected from light.

IMPURITIES

Specified impurities *D, E, F, G, H.*



D. 7,8-dimethyl-10-[(2*S*,3*S*,4*R*)-2,3,4,5-tetrahydroxypentyl]benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (riboflavin),



E. 7,8,10-trimethylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (lumiflavin),

F. unknown structure,

G. unknown structure,

H. unknown structure.

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Rice Starch[1]

General Notices

(Ph. Eur. monograph 0349)

Action and use

Excipient.

When Starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch or, in tropical countries where these are not available, Tapioca Starch may be supplied or used.

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DEFINITION

Rice starch is obtained from the caryopsis of *Oryza sativa* L.

♦ CHARACTERS

Appearance

Very fine, white or almost white powder, which creaks when pressed between the fingers.

Solubility

Practically insoluble in cold water and in ethanol (96 per cent).

Rice starch does not contain starch granules of any other origin. It may contain traces of, if any, fragments of the endosperm tissue of the fruit.♦

IDENTIFICATION

A. Microscopic examination (*2.8.23*) using a 50 per cent *V/V* solution of *glycerol R*. It presents polyhedral, simple grains 1-10 µm (mostly 4-6 µm) in size (Figure 0349.-1). These simple grains often gather in ellipsoidal, compound grains 50-100 µm in diameter. The grains have a poorly visible central hilum and there are no concentric striations. Between orthogonally orientated polarising plates or prisms, the starch granules show a distinct black cross intersecting at the hilum.

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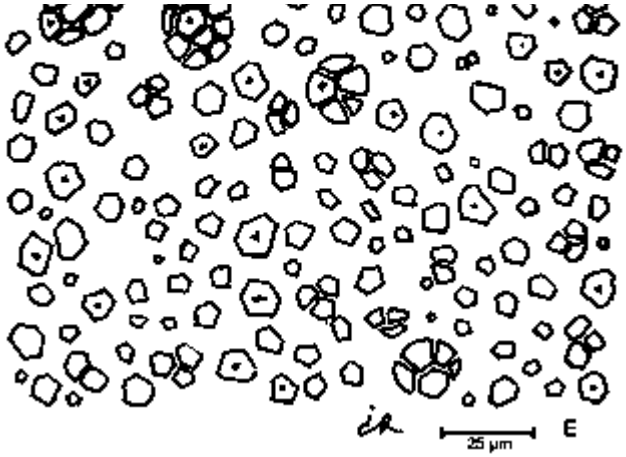

Figure 0349.-1. – *Illustration for identification test A of rice starch*

B. Suspend 1 g in 50 mL of *water R*, boil for 1 min and cool. A thin, cloudy mucilage is formed.

C. To 1 mL of the mucilage obtained in identification test B add 0.05 mL of *iodine solution R1*. An orange-red to dark blue colour is produced, which disappears on heating.

TESTS

pH (*2.2.3*)

5.0 to 8.0.

Shake 5.0 g with 25.0 mL of *carbon dioxide-free water R* for 60 s. Allow to stand for 15 min.

♦ Foreign matter

Examined under a microscope using a 50 per cent *V/V* solution of *glycerol R*, not more than traces of matter other than starch granules are present. No starch granules of any other origin are present.♦

Oxidising substances (*2.5.30*)

Maximum 20 ppm, calculated as H_2O_2.

Sulfur dioxide (*2.5.29*)

Maximum 50 ppm.

Iron (*2.4.9*)

Maximum 10 ppm.

Shake 1.5 g with 15 mL of *dilute hydrochloric acid R*. Filter. The filtrate complies with the test.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 1.00 g by drying in an oven at 130 °C for 90 min.

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Sulfated ash (*2.4.14*)

Maximum 0.6 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

◊ Absence of *Salmonella* (*2.6.13*).◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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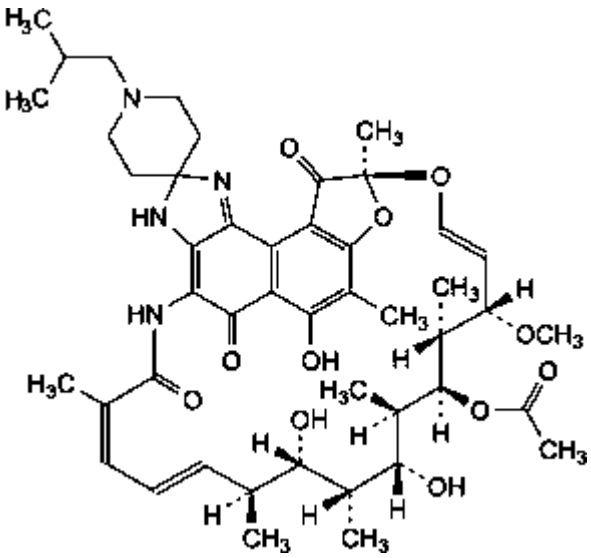
Rifabutin

General Notices

(Ph. Eur. monograph 1657)



$C_{46}H_{62}N_4O_{11}$ 847 *72559-06-9*

Action and use

Rifamycin antimycobacterial drug.

Ph Eur

DEFINITION

(9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,18,20-Trihydroxy-14-methoxy-7,9,15,17,19,21,25-heptamethyl-1′-(2-methylpropyl)-5,10,26-trioxo-3,5,9,10-tetrahydrospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2′,3′:7,8]naphtho[1,2-*d*]imidazole-2,4′-piperidine]-16-yl acetate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

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Appearance

Reddish-violet amorphous powder.

Solubility

Slightly soluble in water, soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison *rifabutin CRS*.

B. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Impurity A

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.100 g of the substance to be examined in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 10 mg of *rifabutin impurity A CRS* in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10 mL with the same mixture of solvents. Dilute 3 mL of the solution to 100 mL with a mixture of equal volumes of *methanol R* and *methylene chloride R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetone R*, *light petroleum R* (23:77 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose the plate to iodine vapour for about 5 min, then spray with *potassium iodide and starch solution R* and allow to stand for 5 min.

Limit:

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— *impurity A*: any spot corresponding to impurity A is not more intense than the spot in the chromatogram obtained with the reference solution (0.3 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *rifabutin CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve about 10 mg of *rifabutin CRS* in 2 mL of *methanol R*, add 1 mL of *dilute sodium hydroxide solution R* and allow to stand for about 4 min. Add 1 mL of *dilute hydrochloric acid R* and dilute to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.110 m, Ø = 4.6 mm,

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix equal volumes of *acetonitrile R* and a 13.6 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 6.5 with *dilute sodium hydroxide solution R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 2.5 times the retention time of rifabutin.

Relative retention With reference to rifabutin (retention time = about 9 min): impurity E = about 0.5; impurity B = about 0.6; impurity D = about 0.9; impurity C = about 1.3.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the second peak of the 3 peaks due to degradation products and the peak due to rifabutin.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent); not more than 1 such peak has an area greater than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

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Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.3 per cent, determined on 1.0 g.

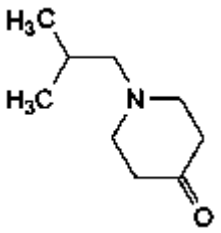
ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

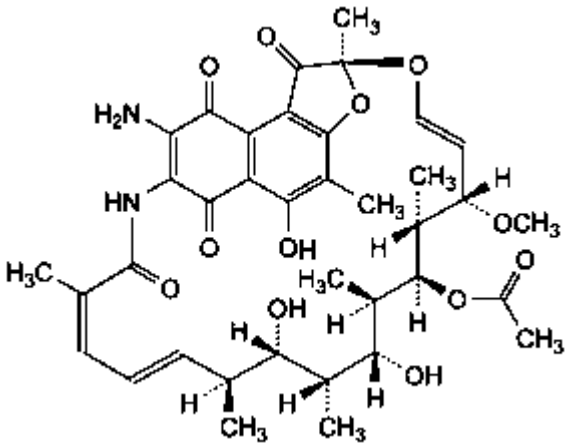
Injection Test solution and reference solution (a).

Calculate the percentage content of ribabutin.

IMPURITIES



A. 1-(2-methylpropyl)piperidin-4-one,



B. 3-aminorifamycin S,

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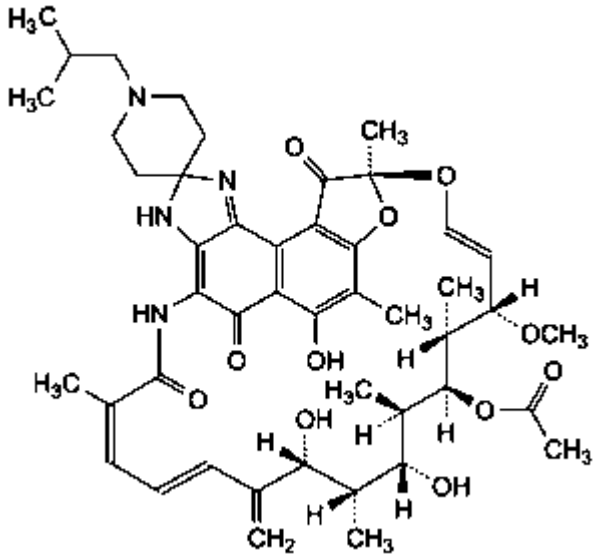
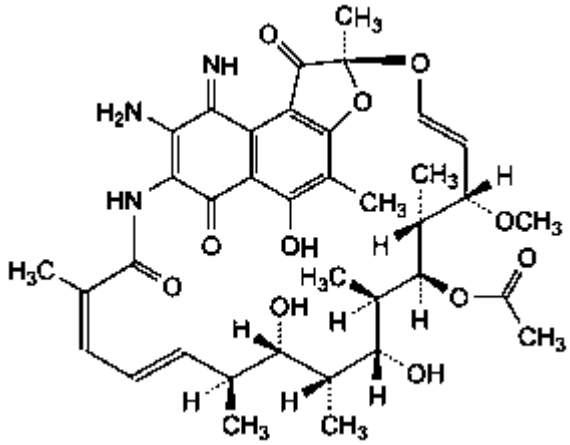
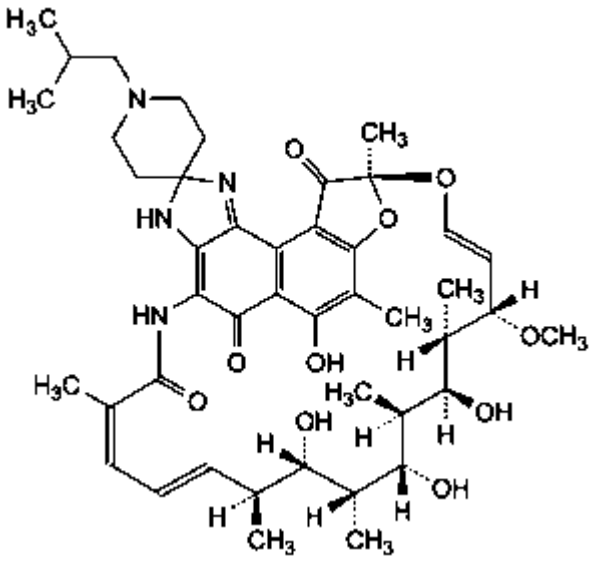


C. 21,31-didehydrorifabutin,



D. 3-amino-4-imidorifamycin S,



E. 16-deacetylrifabutin.

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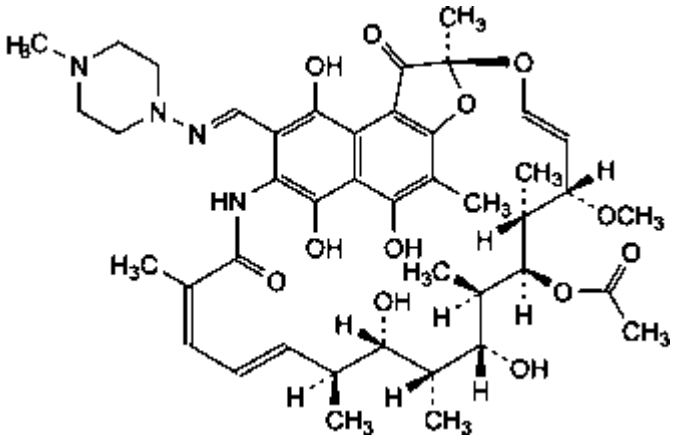
Rifampicin

General Notices

(Ph. Eur. monograph 0052)



$C_{43}H_{58}N_4O_{12}$ 823 *13292-46-1*

Action and use

Rifamycin antituberculosis drug.

Preparations

Rifampicin Capsules

Rifampicin Oral Suspension

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DEFINITION

(2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*,24*E*)-5,6,9,17,19-Pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[[(4-methylpiperazin-1-yl)imino]methyl]-1,11-dioxo-1,2-dihydro-2,7-(epoxypentadeca[1,11,13]trienimino)naphto[2,1-*b*]furan-21-yl acetate.

Semi-synthetic antibiotic obtained from rifamycin SV.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

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Appearance

Reddish-brown or brownish-red, crystalline powder.

Solubility

Slightly soluble in water, soluble in methanol, slightly soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in 50 mL of *methanol R*. Dilute 1 mL of this solution to 50 mL with *phosphate buffer solution pH 7.4 R*.

Spectral range 220-500 nm.

Absorption maxima At 237 nm, 254 nm, 334 nm and 475 nm.

Absorbance ratio A_{334}/A_{475} = about 1.75.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Mulls in *liquid paraffin R*.

Comparison *rifampicin CRS*.

C. Suspend about 25 mg in 25 mL of *water R*, shake for 5 min and filter. To 5 mL of the filtrate add 1 mL of a 100 g/L solution of *ammonium persulfate R* in *phosphate buffer solution pH 7.4 R* and shake for a few minutes. The colour changes from orange-yellow to violet-red and no precipitate is formed.

TESTS

pH (2.2.3)

4.5 to 6.5 for a 10 g/L suspension in *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the test solution and the reference solution immediately before use.*

Solvent mixture To 10 volumes of a 210.1 g/L solution of *citric acid monohydrate R* add 23 volumes of a 136.1 g/L solution of *potassium dihydrogen phosphate R*, 77 volumes of a 174.2 g/L solution of *dipotassium hydrogen phosphate R*, 250 volumes of *acetonitrile R* and 640 volumes of *water R*.

Test solution Dissolve 20.0 mg of the substance to be examined in *acetonitrile R* and dilute to 10.0 mL with the same solvent. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixure.

Reference solution Dissolve 20.0 mg of *rifampicin quinone CRS* (impurity A) in *acetonitrile R* and dilute to 100.0 mL with the same solvent. To 1.0 mL of this solution add 1.0 mL of the test solution and dilute to 100.0 mL with the solvent mixture.

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Column:

— *size*: *l* = 0.12 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 35 volumes of acetonitrile R and 65 volumes of a solution containing 0.1 per cent *V/V* of phosphoric acid R, 1.9 g/L of sodium perchlorate R, 5.9 g/L of citric acid monohydrate R and 20.9 g/L of potassium dihydrogen phosphate R.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time Twice the retention time of rifampicin.

System suitability Reference solution:

— resolution: minimum 4.0 between the peaks due to rifampicin and impurity A; if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (1.5 per cent);

— *any other impurity*: for each impurity, not more than the area of the peak due to rifampicin in the chromatogram obtained with the reference solution (1.0 per cent);

— *sum of impurities other than A*: not more than 3.5 times the area of the peak due to rifampicin in the chromatogram obtained with the reference solution (3.5 per cent);

— *disregard limit*: 0.05 times the area of the peak due to rifampicin in the chromatogram obtained with the reference solution (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying at 80 °C at a pressure not exceeding 0.67 kPa for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Dissolve 0.100 g in methanol R and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with phosphate buffer solution pH 7.4 R. Measure the absorbance (2.2.25) at the absorption maximum at 475 nm, using phosphate buffer solution pH 7.4 R as the compensation liquid.

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Calculate the content of $C_{43}H_{58}N_4O_{12}$, taking the specific absorbance to be 187.

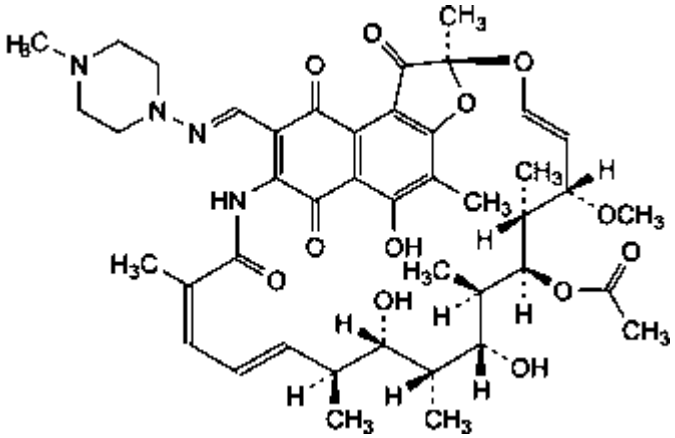
STORAGE

Under nitrogen in an airtight container, protected from light, at a temperature not exceeding 25 °C.

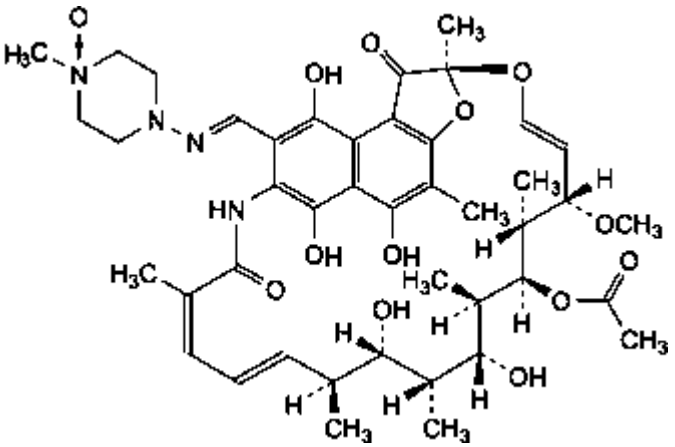
IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*



A. rifampicin quinone,



B. rifampicin *N*-oxide.

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Rifampicin Capsules

General Notices

Action and use

Rifamycin antituberculosis drug.

DEFINITION

Rifampicin Capsules contain Rifampicin.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of rifampicin, $C_{43}H_{58}N_4O_{12}$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing 0.15 g of Rifampicin with 5 mL of *chloroform*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of rifampicin (*RS 312*).

B. The *light absorption*, Appendix II B, in the range 220 to 500 nm of the final solution obtained in the Assay exhibits four maxima, at 237, 254, 334 and 475 nm.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 10 mL sample of the medium and filter. Measure the *absorbance* of the filtered sample, diluted if necessary with 0.1M *hydrochloric acid*, at the maximum at 336 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of rifampicin, $C_{43}H_{58}N_4O_{12}$, in the medium taking 263 as the value of A(1%, 1 cm) at the maximum at 336 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the solvent mixture described below. To 10 volumes of a 21.01% w/v solution of *citric acid* add 23 volumes of a 13.61% w/v solution of *potassium dihydrogen orthophosphate*, 77 volumes of a 17.42% w/v solution of *dipotassium hydrogen orthophosphate*, 250 volumes of *acetonitrile* and 640 volumes of *water* and mix. Prepare the solutions immediately before use.

(1) Shake a quantity of the contents of the capsules containing 20 mg of Rifampicin with 10 mL of *acetonitrile*, centrifuge and dilute 5 mL of the clear supernatant liquid to 50 mL with the solvent mixture.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.00080% w/v of *rifampicin quinone EPCRS*.
(4) 0.00030% w/v of *rifampicin* N-*oxide BPCRS*.
(5) 0.00010% w/v of *3-formylrifamycin SV BPCRS*.
(6) Dilute 1 volume of solution (3) to 4 volumes and mix 1 volume of the resulting solution with 1 volume of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Partisil C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for at least 3 times the retention time of the peak due to rifampicin.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of a solution containing 0.1% v/v of *orthophosphoric acid*, 0.19% w/v of *sodium perchlorate*, 0.59% w/v of *citric acid* and 2.09% w/v of *potassium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the *resolution factor* between the two principal peaks is at least 4.0. If necessary, adjust the concentration of *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to rifampicin quinone is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (4%);

the area of any peak corresponding to rifampicin *N*-oxide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1.5%);

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the area of any peak corresponding to 3-formylrifamycin SV is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Shake a quantity of the mixed contents of 20 capsules containing 0.1 g of Rifampicin with 80 mL of *methanol*, add sufficient *methanol* to produce 100 mL and filter. Dilute 2 mL of the filtrate to 100 mL with *phosphate buffer pH 7.4* and measure the *absorbance* of the resulting solution at the maximum at 475 nm, Appendix II B. Calculate the content of $C_{43}H_{58}N_4O_{12}$ taking 187 as the value of A(1%, 1 cm) at 475 nm.

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Rifampicin Oral Suspension

General Notices

Action and use

Rifamycin antituberculosis drug.

DEFINITION

Rifampicin Oral Suspension is a suspension of Rifampicin in powder of suitable fineness in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of rifampicin, $C_{43}H_{58}N_4O_{12}$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

To a quantity containing 0.1 g of Rifampicin add 30 mL of *water* and shake with two 50 mL quantities of *chloroform*. Dry the combined extracts with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness at a temperature not exceeding 70°. The residue, after washing with 1 mL of *ether* and drying at 70°, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of rifampicin (*RS 312*).

B. Dissolve 10 mg of the residue in 10 mL of *methanol* and dilute 2 mL to 100 mL with *phosphate buffer pH 7.4*. The *light absorption* of the resulting solution, Appendix II B, in the range 240 to 500 nm exhibits three maxima, at 254, 334 and 475 nm.

TESTS

Acidity

pH, 4.2 to 4.8, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the solvent mixture described below. To 10 volumes of a 21.01% w/v solution of *citric acid* add 23 volumes of a 13.61% w/v solution of *potassium dihydrogen orthophosphate*, 77 volumes of a 17.42% w/v solution of *dipotassium hydrogen orthophosphate*, 250 volumes of *acetonitrile* and 640 volumes of *water* and mix. Prepare the solutions immediately before use.

(1) Add 5 mL of *water* to a quantity of the oral suspension containing 20 mg of Rifampicin and extract with four 10-mL quantities of *dichloromethane*, filter the combined extracts and evaporate to dryness at a temperature not exceeding 40°. Dissolve the residue in 10 mL

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of *acetonitrile* and dilute 5 mL of the solution to 50 mL with the solvent mixture.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.00030% w/v of *rifampicin quinone EPCRS*.

(4) 0.00020% w/v of *rifampicin* N-*oxide BPCRS*.

(5) 0.0010% w/v of *3-formylrifamycin SV BPCRS*.

(6) Dilute 1 volume of solution (3) to 1.5 volumes and mix 1 volume of the resulting solution with 1 volume of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Partisil C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for at least 3 times the retention time of the peak due to rifampicin.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of a solution containing 0.1% v/v of *orthophosphoric acid*, 0.19% w/v of *sodium perchlorate*, 0.59% w/v of *citric acid* and 2.09% w/v of *potassium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the *resolution factor* between the two principal peaks is at least 4.0. If necessary, adjust the concentration of *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to rifampicin quinone is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1.5%);

the area of any peak corresponding to rifampicin *N*-oxide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1%);

the area of any peak corresponding to 3-formylrifamycin SV is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peaks eluting before the peak due to rifampicin quinone.

ASSAY

Dilute a weighed quantity containing 0.4 g of Rifampicin to 500 mL with *methanol*, mix thoroughly, dilute 2 mL to 100 mL with *phosphate buffer pH 7.4* and measure the *absorbance* of the resulting solution at the maximum at 475 nm, Appendix II B. Calculate the content of

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$C_{43}H_{58}N_4O_{12}$ taking 187 as the value of A(1%, 1 cm) at 475 nm. Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{43}H_{58}N_4O_{12}$, weight in volume.

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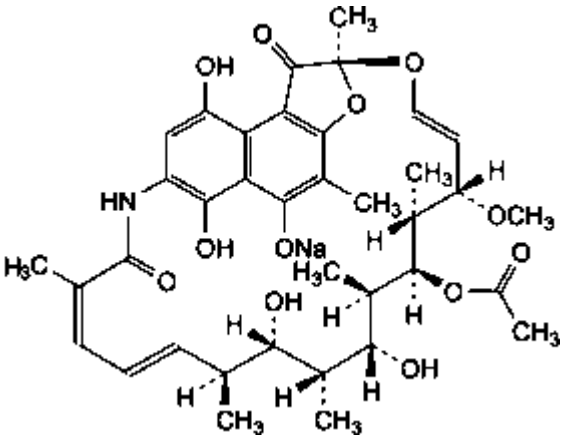
Rifamycin Sodium

General Notices

(Ph. Eur. monograph 0432)



$C_{37}H_{46}NNaO_{12}$ 720 *14897-39-3*

Action and use

Rifamycin antituberculosis drug.

Ph Eur

DEFINITION

Sodium (2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*,24*E*)-21-(acetyloxy)-6,9,17,19-tetrahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,11-dioxo-1,2-dihydro-2,7-(epoxypentadeca[1,11,13]trienazano)naphtho[2,1-*b*]furan-5-olate.

Monosodium salt of rifamycin SV, obtained by chemical transformation of rifamycin B, which is produced during the growth of certain strains of *Amycolatopsis mediterranei*. Rifamycin SV may also be obtained directly from certain *A. mediterranei* mutants.

Potency

Minimum 900 IU/mg (anhydrous substance).

PRODUCTION

It is produced by methods of manufacture designed to minimise or eliminate substances lowering blood pressure.

CHARACTERS

Appearance

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Fine or slightly granular, red powder.

Solubility

Soluble in water, freely soluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs of *potassium bromide R*.

Comparison *rifamycin sodium CRS*.

B. Suspend 70 mg of the substance to be examined in 0.5 mL of *water R*. Add 1.5 mL of *methoxyphenylacetic reagent R* to obtain a clear red solution. Cool in ice-water for 30 min. A precipitate is formed. Place in water at 20 °C and stir for 5 min. The precipitate does not disappear. Add 1 mL of *dilute ammonia R1*. The precipitate dissolves completely. Add 1 mL of *ammonium carbonate solution R*. No precipitate is formed.

TESTS

pH (*2.2.3*)

6.5 to 8.0.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Absorbance (*2.2.25*)

Dissolve 20.0 mg in 5 mL of *methanol R* and dilute to 100.0 mL with freshly prepared *phosphate buffer solution pH 7.0 R1* to which 1 g/L of *ascorbic acid R* has been added immediately before use. Dilute 5.0 mL of this solution to 50.0 mL with the same phosphate buffer solution containing ascorbic acid. Allow to stand for 30 min. The solution shows an absorption maximum at 445 nm. The specific absorbance at this absorption maximum is 190 to 210 (anhydrous substance).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture Mix 50 volumes of *acetonitrile R* and 50 volumes of a 3.9 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 10.0 mg of *rifamycin B CRS* (impurity A) and 40.0 mg of *rifamycin S CRS* (impurity B) in the solvent mixture and dilute to 200.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dissolve 25 mg of the substance to be examined and 8 mg of *rifamycin S CRS* in the solvent mixture and dilute to 250.0 mL with the solvent mixture.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 10 volumes of *acetonitrile R* and 90 volumes of a 3.9 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 7.5 with *dilute sodium hydroxide solution R*;

— *mobile phase B*: mix 30 volumes of a 3.9 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 7.5 with *dilute sodium hydroxide solution R* and 70 volumes of *acetonitrile R*;

— *temperature*: minimum 20 °C;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	80 → 20	20 → 80
40 - 45	20	80
45 - 47	20 → 80	80 → 20

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Elution order Impurity A, rifamycin SV, impurity B.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to rifamycin SV and impurity B.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (2 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *sum of impurities other than A and B*: not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (2 per cent);

— *disregard limit*: 0.05 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (0.1 per cent).

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Water (*2.5.12*)

12.0 per cent to 17.0 per cent, determined on 0.200 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.50 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *rifamycin sodium CRS* as the chemical reference substance.

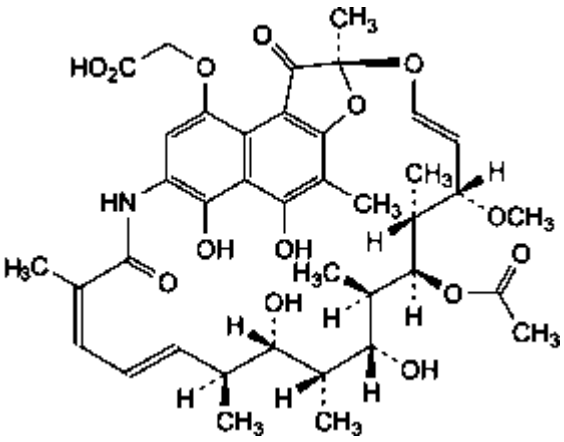
STORAGE

In an airtight container, protected from light at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



A. [(2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*,24*E*)-21-(acetyloxy)-5,6,17,19-tetrahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,11-dioxo-1,2-dihydro-2,7-(epoxypentadeca[1,11,13]trienazano)naphtho[2,1-*b*]furan-9-yl]acetic acid (rifamycin B),

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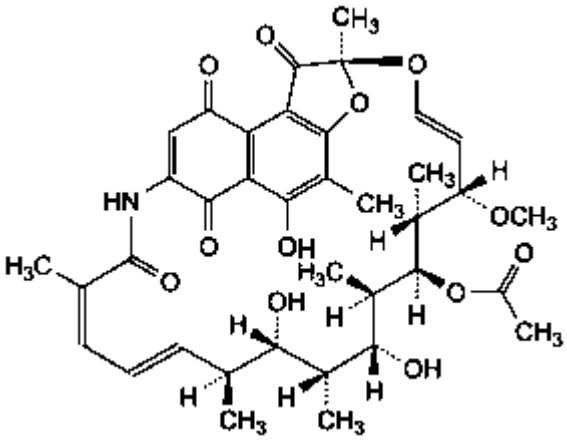
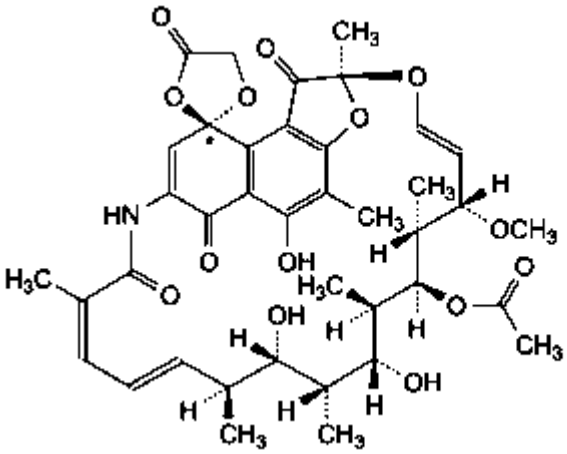


B. [(2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*,24*E*)-5,17,19-trihydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,6,9,11-tetraoxo-1,2-dihydro-2,7-(epoxypentadeca[1,11,13]trienazano)naphtho[2,1-*b*]furan-21-yl acetate (rifamycin S),



and epimer at C*

C. [(2*RS*,2′*S*,12′*Z*,14′*E*,16′*S*,17′*S*,18′*R*,19′*R*,20′*R*,21′*S*,22′*R*,23′*S*,24′*E*)-5′,17′,19′-trihydroxy-23′-methoxy-2′,4′,12′,16′,18′,20′,22′-heptamethyl-1′,4,6′,11′-tetraoxo-1′,2′-dihydrospiro[1,3-dioxolane-2,9′(6′*H*)-[2,7](epoxypentadeca[1,11,13]trienazano)naphtho[2,1-*b*]furan]-21′-yl acetate (rifamycin O).

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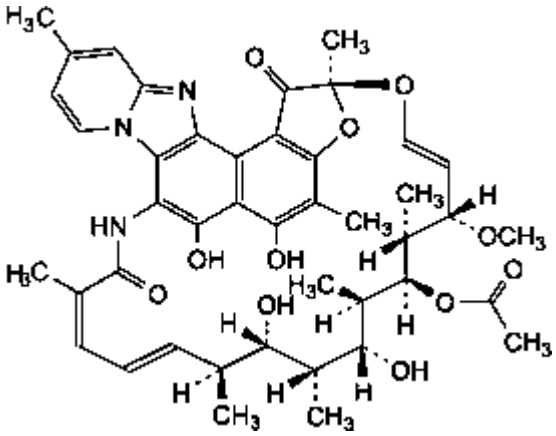
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Rifaximin

General Notices

(Ph. Eur. monograph 2362)



$C_{43}H_{51}N_3O_{11}$ 786 *80621-81-4*

Action and use

Antibacterial; treatment of infective diarrhoea.

Preparation

Rifaximin Tablets

Ph Eur

DEFINITION

(2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*R*,27*S*,28*E*)5,6,21,23-Tetrahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-1,15-dioxo-1,2-dihydro-2,7-(epoxypentadeca[1,11,13]trienoimino)[1]benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazol-25-yl acetate.

Semi-synthetic product derived from a fermentation product.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

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Appearance

Red-orange, hygroscopic, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone and in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *rifaximin CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (40:60 *V/V*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in 8 mL of *acetonitrile R* and dilute to 20 mL with *water R*.

Test solution (b) Dissolve 40.0 mg of the substance to be examined in 40.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 50.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *rifaximin for system suitability CRS* (containing impurity H) in 1.6 mL of *acetonitrile R* and dilute to 4.0 mL with *water R*.

Reference solution (c) Dissolve 40.0 mg of *rifaximin CRS* in 40.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

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Mobile phase Mix 37 volumes of a 3.16 g/L solution of *ammonium formate R* adjusted to pH 7.2 with *dilute ammonia R1* and 63 volumes of a mixture of equal volumes of *acetonitrile R* and *methanol R*.

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 3 times the retention time of rifaximin.

Relative retention With reference to rifaximin (retention time = about 12 min): impurities D and H = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities D + H and rifaximin.

Limits:

— *sum of impurities D and H*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 4.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{43}H_{51}N_3O_{11}$ using the chromatogram obtained with reference solution (c) and the declared content of *rifaximin CRS*.

STORAGE

In an airtight container, protected from light.

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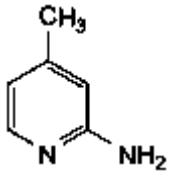
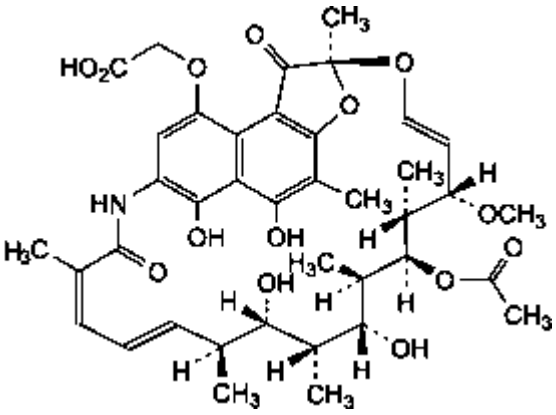
IMPURITIES

Specified impurities D, H.

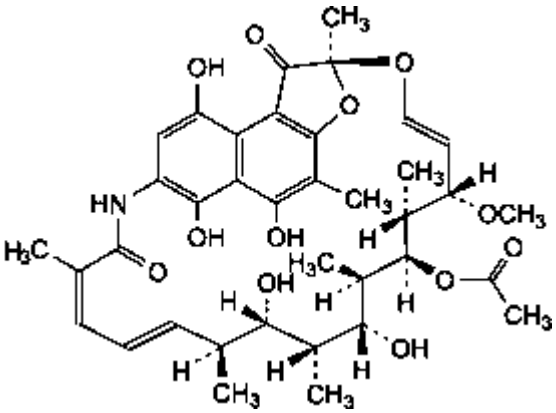
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, E, F, G.



A. 4-methylpyridin-2-amine,



B. rifamycin B,



C. rifamycin SV,

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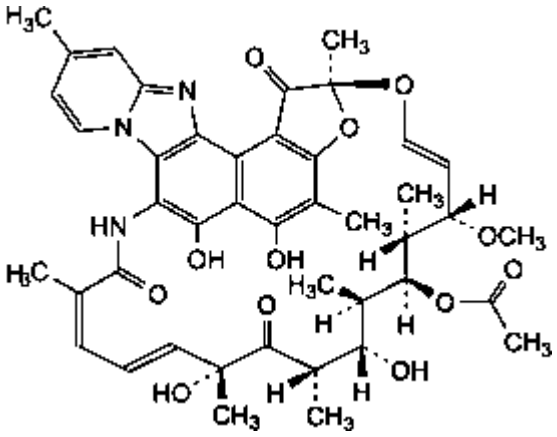
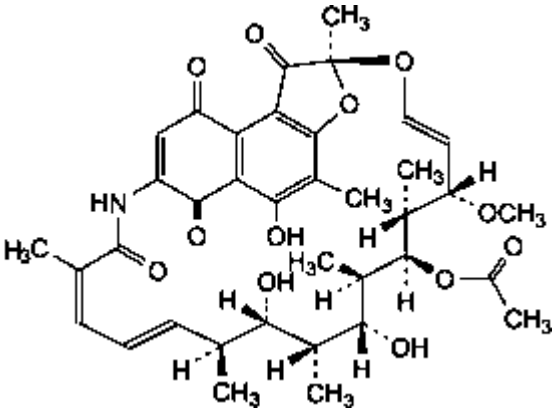
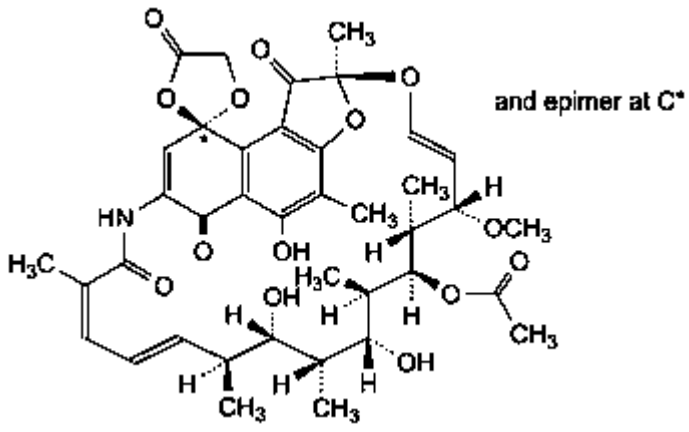


D. rifaximin Y,



E. rifamycin S,



F. rifamycin O,

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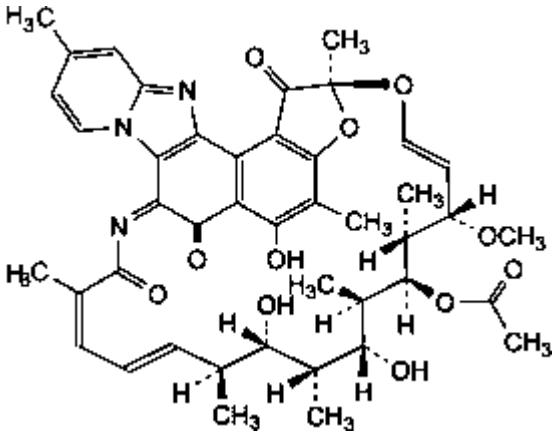
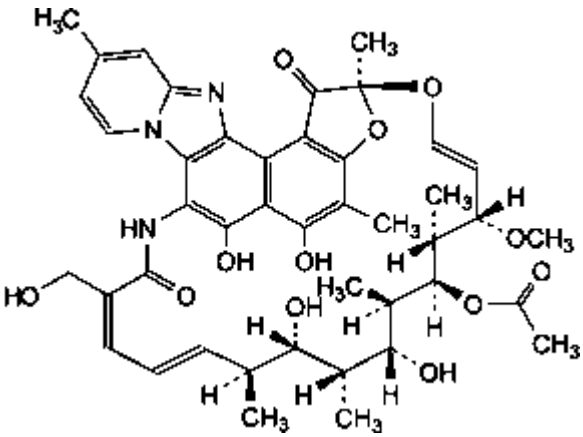


G. (2*S*,7*Z*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*R*,27*S*,28*E*)-5,21,23-trihydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-1,6,15-trioxo-1,2,6,7-tetrahydro-2,7-(epoxypentadeca[1,11,13]trienonitrilo)[1]benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazol-25-yl acetate (6-*O*,14-didehydrorifaximin),



H. (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*R*,27*S*,28*E*)-5,6,21,23-tetrahydroxy-16-(hydroxymethyl)-27-methoxy-2,4,11,20,22,24,26-heptamethyl-1,15-dioxo-1,2-dihydro2,7-(epoxypentadeca[1,11,13]trienoimino)[1]benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazol-25-yl acetate (16-desmethyl-16-(hydroxymethyl)rifaximin).

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Rifaximin Tablets

General Notices

Action and use

Antibacterial; treatment of infective diarrhoea.

DEFINITION

Rifaximin Tablets contain Rifaximin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of rifaximin, $C_{43}H_{51}N_3O_{11}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm:

the UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A Dissolve 13.6 g of *sodium acetate* in 800 mL *water*, add 6 mL of *glacial acetic acid* and dilute to 1000 mL using *water*. Add 2 g of *sodium lauryl sulfate* and mix.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of solution A, at a temperature of 37°, as the medium.

PROCEDURE

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(1) After 60 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.02% w/v of Rifaximin, at the maximum at 290 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.02% w/v solution of *rifaximin EPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of rifaximin, $C_{43}H_{51}N_3O_{11}$, in the medium from the absorbances obtained and using the declared content of $C_{43}H_{51}N_3O_{11}$ in *rifaximin EPCRS*.

LIMITS

The amount of rifaximin released is not less than 70% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Disperse a quantity of the powdered tablets containing 0.25 g of Rifaximin with the mobile phase. Dilute to 50 mL and filter through a 0.45-µm filter (Whatman GF-C filter is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.125% w/v of *rifaximin for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Alltima C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of rifaximin.

MOBILE PHASE

37 volumes of a 0.316% w/v solution of *ammonium formate*, adjusted to pH 7.2 using *dilute ammonia R1* and 63 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to rifaximin (retention time about 12 minutes) are: impurities D and H , about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to impurities D and H and the peak due to rifaximin is at least 3.0.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurities D and H is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Water

The tablets contain not more than 8.0% w/w of *water*, Appendix IX C, Method I. Use 0.1 g.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a portion of the powdered tablets containing 0.5 g of Rifaximin with mobile phase and dilute to 100 mL. Filter, and dilute the filtrate to produce a solution containing 0.004% w/v of Rifaximin.
(2) 0.004% w/v of *rifaximin EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under the Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{43}H_{51}N_3O_{11}$, in the tablets from the chromatograms obtained and using the declared content of $C_{43}H_{51}N_3O_{11}$ in *rifaximin EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Rifaximin.

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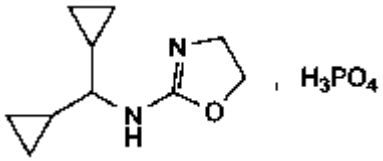
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Rilmenidine Dihydrogen Phosphate

General Notices

(Ph. Eur. monograph 2020)



$C_{10}H_{19}N_2O_5P$ 278.2 *85409-38-7*

Action and use

Antihypertensive.

Ph Eur

DEFINITION

N-(Dicyclopropylmethyl)-4,5-dihydro-oxazol-2-amine dihydrogen phosphate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of rilmenidine dihydrogen phosphate*.

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B. Dissolve 10 mg in *water R* and dilute to 1 mL with the same solvent. The solution gives reaction (b) of phosphates (*2.3.1*).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 60.0 mg of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R* and dilute 10.0 mL of this solution to 50.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 20.0 mL with *water R*.

Reference solution (c) Dissolve 15.0 mg of *rilmenidine for system suitability CRS* in *water R* and dilute to 5.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 3 mm,

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 25 per cent,

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 3 g of *sodium heptanesulfonate R* in *water R* and dilute to 860 mL with the same solvent; add 130 mL of *methanol R2*, 10 mL of *tetrahydrofuran for chromatography R* and 1.0 mL of *phosphoric acid R*,

— *mobile phase B*: dissolve 3 g of *sodium heptanesulfonate R* in *water R* and dilute to 600 mL with the same solvent; add 350 mL of *acetonitrile for chromatography R*, 50 mL of *tetrahydrofuran for chromatography R* and 1.0 mL of *phosphoric acid R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	100 → 0	0 → 100
14 - 15	0 → 100	100 → 0
15 - 30	100	0

Flow rate 1 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL.

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Relative retention With reference to rilmenidine (retention time = about 13 min): impurity A = about 0.6; impurity B = about 0.9; impurity C = about 1.4.

With these conditions the inflexion of the baseline, corresponding to the beginning of the gradient, appears on the recorder after a minimum time *t* of 5 min. If this is not the case (*t* < 5 min) modify the chromatographic sequence by adding an isocratic elution with 100 per cent of mobile phase A for a time corresponding to (5-*t*) min before the linear gradient.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rilmenidine.

Limits:

— *any impurity*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 50 °C for 2 h.

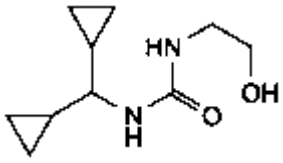
ASSAY

Dissolve 0.200 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 27.82 mg of $C_{10}H_{19}N_2O_5P$.

IMPURITIES

Specified impurities *A, B, C.*



A. 1-(dicyclopropylmethyl)-3-(2-hydroxyethyl)urea,

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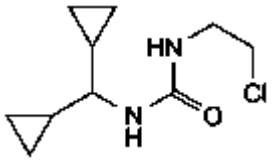
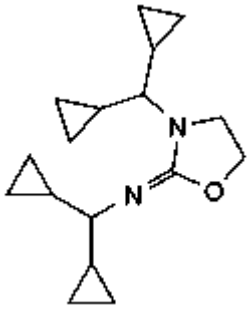


B. 1-(2-chloroethyl)-3-(dicyclopropylmethyl)urea,



C. *N*,3-bis(dicyclopropylmethyl)oxazolidin-2-imine.

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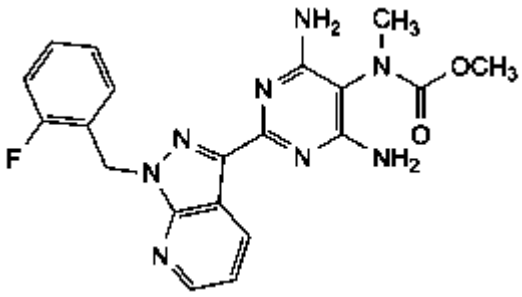
Riociguat

General Notices

(Ph. Eur. monograph 3078)



$C_{20}H_{19}FN_8O_2$ 422.4 *625115-55-1*

Action and use

Guanylate cyclase stimulator; treatment of pulmonary hypertension.

Preparation

Riociguat Tablets

Ph Eur

DEFINITION

Methyl [4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl](methyl)carbamate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish powder.

Solubility

Practically insoluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *riociguat CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Protect the solutions from light throughout the tests.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase A, *acetonitrile R* (20:80 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture using sonication and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 4 mg of *riociguat for system suitability CRS* (containing impurities B and C) in the solvent mixture using sonication and dilute to 10 mL with the solvent mixture.

Reference solution (c) Dissolve 20.0 mg of *riociguat CRS* in the solvent mixture using sonication and dilute to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *perchloric acid R*, *water for chromatography R* (0.4:100 *V/V*);

— *mobile phase B*: *acetonitrile R1*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	75	25
2 - 27	75 → 65	25 → 35
27 - 42	65 → 32	35 → 68
42 - 43	32 → 10	68 → 90
43 - 52	10	90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 15 °C.

Injection 5 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *riociguat for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to riociguat (retention time = about 22 min): impurity B = about 0.97; impurity C = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity B and riociguat.

Calculation of percentage contents:

— for each impurity, use the concentration of riociguat in reference solution (a).

Limits:

— *impurity C*: maximum 0.20 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity E

Head-space gas chromatography (*2.2.28*).

Test solution Dissolve 50 mg of the substance to be examined in 1.0 mL of *dimethyl sulfoxide R* in a head-space vial.

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Reference solution Dilute 50 µL of *benzene R* (impurity E) to 10.0 mL with *dimethyl sulfoxide R*. Dilute 11.5 µL of the solution to 10.0 mL with *dimethyl sulfoxide R*. Transfer 20 µL of this solution into a head-space vial and add 1.0 mL of *dimethyl sulfoxide R*.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 3.3 mL/min.

Split ratio 1:20.

Static head-space conditions that may be used:

— *equilibration temperature*: 100 °C;

— *equilibration time*: 30 min;

— *transfer-line temperature*: 120 °C;

— *pressurisation time*: 30 s;

— *injection volume*: 1.0 mL;

— *injection time*: 1 min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	40 → 60
	10 - 15	60
	15 - 18.2	60 → 140
	18.2 - 35	140
Injection port		120
Detector		250

Detection Flame ionisation.

Identification of impurities Use the chromatogram obtained with the reference solution to identify the peak due to impurity E.

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Retention time Impurity E = about 7.1 min.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 15 for the peak due to impurity E.

Limit:

— *impurity E*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (2 ppm).

Water (2.5.32)

Maximum 0.2 per cent, determined on 0.250 g using the evaporation technique at 150 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

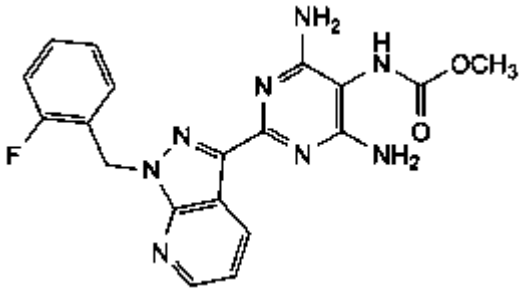
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{20}H_{19}FN_8O_2$ taking into account the assigned content of *riociguat CRS*.

IMPURITIES

Specified impurities *C, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D.*



A. methyl [4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl]carbamate,

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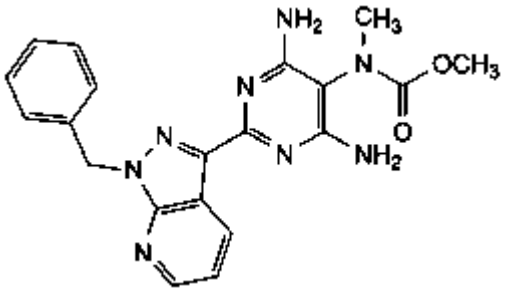
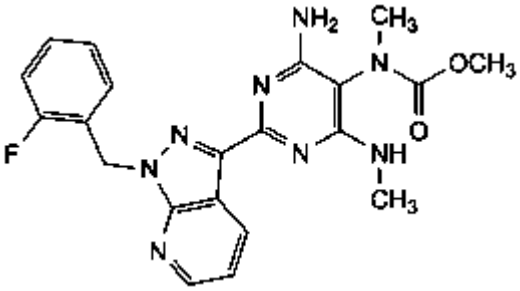
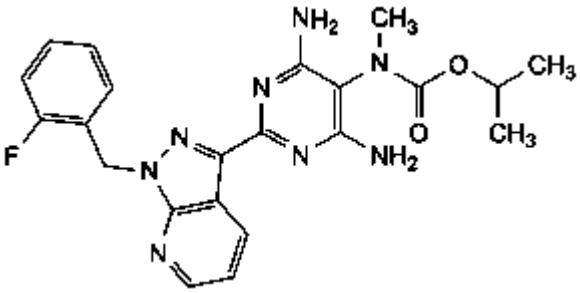


B. methyl [4,6-diamino-2-(1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)pyrimidin-5-yl](methyl)carbamate,



C. methyl [4-amino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-(methylamino)pyrimidin-5-yl](methyl)carbamate,



D. propan-2-yl [4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl](methyl)carbamate,

E. benzene.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Riociguat Tablets

General Notices

(Ph. Eur. monograph 3079)

Action and use

Guanylate cyclase stimulator; treatment of pulmonary hypertension.

Ph Eur

DEFINITION

Tablets containing *Riociguat (3078)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of riociguat ($C_{20}H_{19}FN_8O_2$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Protect the solutions from light throughout the tests.

Related substances

Liquid chromatography (*2.2.29*).

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Solution A Mix about 5.5 mL of *phosphoric acid R* and 1000 mL of *water for chromatography R* and adjust to pH 1.6 with *phosphoric acid R*.

Solvent mixture *acetonitrile R*, solution A (20:80 *V/V*).

Test solution To an appropriate number of tablets (at least 5) add a volume of the solvent mixture equivalent to about 2/3 of the final volume. Shake for at least 15 min or sonicate for at least 30 min, until the tablets have disintegrated completely. Dilute with the solvent mixture to obtain a concentration of riociguat of 0.10 mg/mL, shake, centrifuge and use the clear supernatant.

Reference solution (a) Dissolve 5.0 mg of *riociguat CRS* in the solvent mixture using sonication and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *riociguat for FP system suitability CRS* (containing impurities A and C) in the solvent mixture using sonication and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R1*, solution A (23:77 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Run time 4 times the retention time of riociguat.

Identification of impurities Use the chromatogram supplied with *riociguat for FP system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and C.

Relative retention With reference to riociguat (retention time = about 3 min): impurity A = about 0.7; impurity C = about 2.4.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity A and riociguat.

Calculation of percentage contents:

— for each impurity, use the concentration of riociguat in reference solution (b).

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Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.1 per cent; disregard the peak due to impurity C.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium Dissolve 4.75 g of *citric acid monohydrate R* and 27.47 g of *disodium hydrogen phosphate dihydrate R* in *water R*, add 1 L of a 10 g/L solution of *sodium laurilsulfate R* and dilute to 10 L with *water R*; adjust to pH 6.8 with a solution of *sodium hydroxide R* or *phosphoric acid R*. Use 900 mL of the medium.

Rotation speed 75 r/min.

Time 30 min.

Analysis Liquid chromatography (*2.2.29*).

Test solutions The samples withdrawn from the dissolution vessel and filtered.

Reference solution Dissolve 55.6 mg of *riociguat CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *methanol R*. Dilute a suitable volume of this solution with the dissolution medium to obtain a concentration of riociguat corresponding to the theoretical concentration of riociguat in the test solution, based on the labelled content of the tablets.

Column:

— *size*: *l* = 0.06 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 45 volumes of *acetonitrile R* and 55 volumes of a 1.54 g/L solution of *ammonium acetate R* previously adjusted to pH 4.0 with *glacial acetic acid R*.

Flow rate 2.3 mL/min.

Detection Spectrophotometer at 326 nm.

Injection 100 µL.

Run time Twice the retention time of riociguat.

Retention time Riociguat = about 1 min.

System suitability Reference solution:

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— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the amount of dissolved riociguat ($C_{20}H_{19}FN_8O_2$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *riociguat CRS*.

Acceptance criterion:

— *Q* = 80 per cent after 30 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

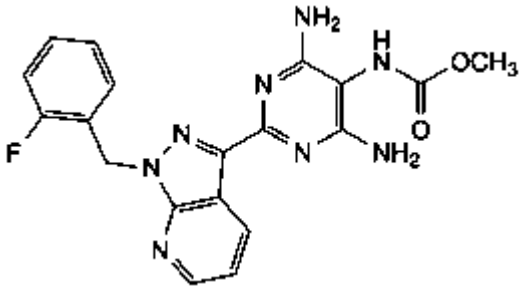
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

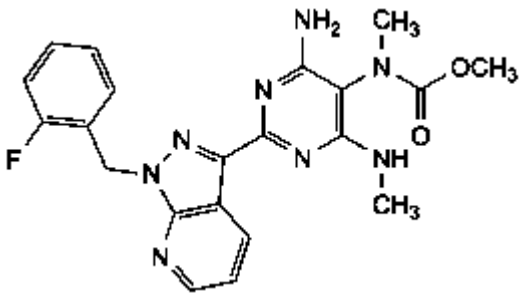
Calculate the percentage content of riociguat ($C_{20}H_{19}FN_8O_2$) taking into account the assigned content of *riociguat CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, C, D*.



A. methyl [4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl]carbamate,



C. methyl [4-amino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-(methylamino)pyrimidin-5-yl](methyl)carbamate,

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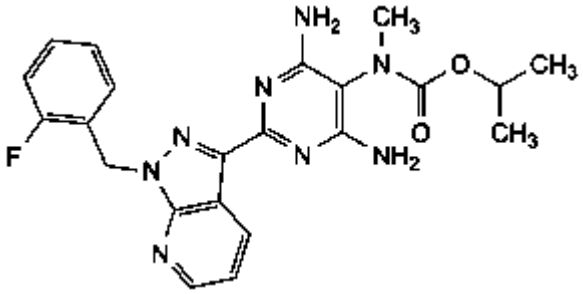

D. propan-2-yl [4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl](methyl)carbamate.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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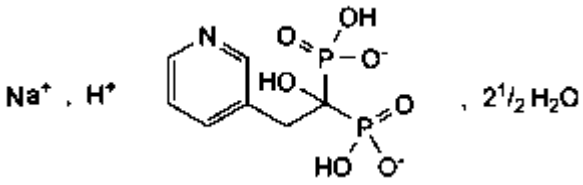
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Risedronate Sodium 2.5-Hydrate

General Notices

(Ph. Eur. monograph 2572)



$C_7H_{10}NNaO_7P_2,2½H_2O$ 350.1 *329003-65-8*

Action and use

Bisphosphonate; treatment of osteoporosis, Paget's disease.

Preparation

Risedronate Sodium Tablets

Ph Eur

DEFINITION

Monosodium trihydrogen [1-hydroxy-2-(pyridin-3-yl)ethane-1,1-diyl]bis(phosphonate) hemipentahydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in methanol. It dissolves in dilute solutions of alkali hydroxides and mineral acids.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *risedronate sodium 2.5-hydrate CRS*.

B. It gives reaction (a) of sodium (2.3.1). Dissolution of the substance to be examined is achieved after the addition of the 150 g/L solution of *potassium carbonate R*.

C. Water (see Tests).

TESTS

pH (2.2.3)

4.0 to 5.0.

Dissolve 0.10 g in *carbon dioxide-free water R* with the aid of an ultrasonic bath and dilute to 10 mL with the same solvent.

Related substances

A. Liquid chromatography (2.2.29).

Buffer solution Dissolve 0.410 g of *sodium edetate R*, 1.7 g of *dipotassium hydrogen phosphate R* and 1.7 g of *tetrabutylammonium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 7.5 with *1 M sodium hydroxide* and dilute to 1000 mL with *water for chromatography R*.

Solution A Dissolve 0.1 g of *sodium chloride R* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase by gentle swirling and heating for 5-10 min and dilute to 20.0 mL with the mobile phase.

Reference solution (a) To 2 mL of the test solution add 5 mg of *risedronate impurity E CRS* and dilute to 50 mL with the mobile phase. Dilute 1 mL of this solution to 10 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, buffer solution (10:90 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 263 nm.

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Injection 20 µL.

Run time Twice the retention time of risedronate.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention With reference to risedronate (retention time = about 17 min): impurity E = about 0.95.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity E and risedronate.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to solution A.

B. Liquid chromatography (2.2.29) as described in test A for related substances, with the following modifications.

Reference solution (a) Dissolve 5 mg of the substance to be examined in 50 mL of the mobile phase by gentle swirling and heating for 5-10 min, using an ultrasonic bath if necessary.

Reference solution (b) Dissolve the contents of a vial of *risedronate impurity A CRS* in 1 mL of reference solution (a), using an ultrasonic bath if necessary.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Mobile phase *acetonitrile R*, buffer solution (25:75 *V/V*).

Injection 10 µL of solution A, the test solution and reference solutions (b) and (c).

Run time 8 times the retention time of risedronate.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to risedronate (retention time = about 4 min): impurity A = about 2.2.

System suitability Reference solution (b):

— *resolution*: minimum 10.0 between the peaks due to risedronate and impurity A.

Limits:

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— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard any peak due to solution A and any peak eluting before the peak due to risedronate.

Water (*2.5.12*)

11.9 per cent to 13.9 per cent, determined on 0.100 g.

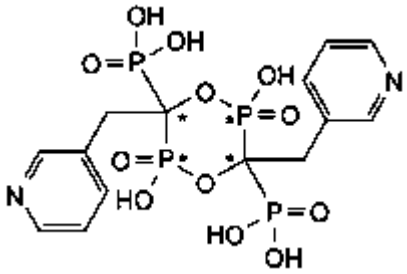
ASSAY

Dissolve 0.125 g in 50 mL of *carbon dioxide-free water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

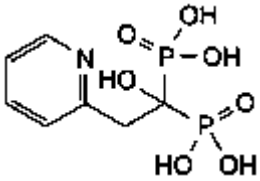
1 mL of *0.1 M sodium hydroxide* is equivalent to 15.26 mg of $C_7H_{10}NNaO_7P_2$.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E.*



A. [(2Ξ,3Ξ,5Ξ,6Ξ)-2,5-dihydroxy-2,5-dioxo-3,6-bis[(pyridin-3-yl)methyl]-1,4,2λ^5,5λ^5-dioxadiphosphinane-3,6-diyl]bis(phosphonic acid),



B. [1-hydroxy-2-(pyridin-2-yl)ethane-1,1-diyl]bis(phosphonic acid),

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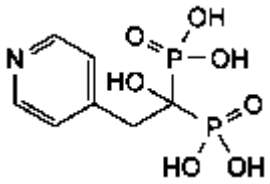
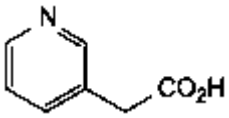
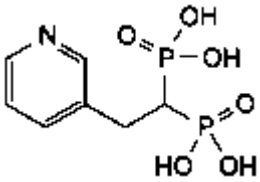


C. [1-hydroxy-2-(pyridin-4-yl)ethane-1,1-diyl]bis(phosphonic acid),



D. (pyridin-3-yl)acetic acid,



E. [2-(pyridin-3-yl)ethane-1,1-diyl]bis(phosphonic acid).

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Risedronate Sodium Tablets

General Notices

Action and use

Bisphosphonate; treatment of osteoporosis, Paget's disease.

DEFINITION

Risedronate Sodium Tablets contain Risedronate Sodium 2.5-Hydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous risedronate sodium, $C_7H_{10}NNaO_7P_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 25 mg of anhydrous risedronate sodium with 10 mL of *water* and filter (a 0.45-µm nylon filter is suitable). Mix the filtrate with 10 mL of 0.2M *copper(II) chloride* and allow to stand for 10 minutes. Add 2 mL of *ethanol* to this solution, mix and allow to stand for 1 hour (a precipitate is produced). Filter the suspension through a Whatman No. 1 filter and wash the precipitate with 10 mL of *ethanol*, discarding the washings and allow the residue to dry in air. The infrared absorption spectrum of the dried residue, Appendix II A, is concordant with the reference spectrum of anhydrous risedronate sodium *(RS 498)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, to produce a solution containing 0.001% w/v of anhydrous risedronate sodium.

(2) 0.0012% w/v of *risedronate sodium 2.5-hydrate BPCRS* in *water*.

(3) 0.00075% w/v of *risedronate impurity E EPCRS* and 0.005% w/v of *risedronate sodium 2.5-hydrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *anion exchange resin* (10 µm) (Dionex Ionpac AS7 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.18% w/v solution of *disodium edetate* adjusted to pH 9.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to risedronate and impurity E is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of anhydrous risedronate sodium, $C_7H_{10}NNaO_7P_2$, in the medium from the chromatograms obtained and using the declared content of $C_7H_{10}NNaO_7P_2$, in *risedronate sodium 2.5-hydrate BPCRS*.

LIMITS

The amount of anhydrous risedronate sodium released is not less than 75% (Q) of the stated amount.

Related substances

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare and store all solutions in plastic containers.*

Solution A Dissolve 0.410 g of *sodium edetate*, 1.7 g of *dipotassium hydrogen phosphate* and 1.7 g of *tetrabutylammonium dihydrogen phosphate* in 900 mL of *water*. Adjust to pH 7.5 with 1M *sodium hydroxide*, and dilute to 1000 mL with *water*.

(1) To a quantity of the powdered tablets containing 25 mg of anhydrous risedronate sodium, add 10 mL of the mobile phase and swirl for 10 minutes in a water-bath at 30° and filter (a nylon 0.45-µm filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

(3) 0.001% w/v solution of *risedronate impurity E EPCRS* and 0.00115% w/v of *risedronate sodium 2.5-hydrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Luna C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 263 nm.

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(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the run time of risedronate.

MOBILE PHASE

10 volumes of *acetonitrile* and 90 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to risedronate (retention time of about 16 minutes) of impurity E is about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity E and risedronate is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare and store all solutions in plastic containers.*

Solution A Dissolve 0.41 g of *sodium edetate*, 1.7 g of *dipotassium hydrogen phosphate* and 1.7 g of *tetrabutylammonium dihydrogen phosphate* in 900 mL of *water*. Adjust to pH 7.5 with 1M *sodium hydroxide*, and dilute to 1000 mL with *water*.

(1) To a quantity of the powdered tablets containing 25 mg of anhydrous risedronate sodium, add 10 mL of the mobile phase and swirl for 5 to 10 minutes in a water-bath at 30° and filter (a nylon 0.45-µm filter is suitable).

(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

(3) 0.000115% w/v of *risedronate sodium 2.5-hydrate BPCRS* and 0.00075% w/v of *risedronate impurity A EPCRS* in the mobile phase.

(4) Dissolve 0.1 g of *sodium chloride* in the mobile phase and dilute to 10 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Luna C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

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(g) Allow the chromatography to proceed for 8 times the retention time of risedronate.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to risedronate (retention time of about 4 minutes) of impurity A is about 2.2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 0.5 times the area of the peak due to risedronate in the chromatogram obtained with solution (3) (0.15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

Disregard any peak eluting before the peak due to risedronate, any peak corresponding to the peak obtained with solution (4) and any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound 10 whole tablets with 150 mL of the mobile phase and dilute to 250 mL with the mobile phase. Filter (a nylon 0.45-µm filter is suitable) and dilute a volume of the filtrate, if necessary, with sufficient mobile phase to produce a solution containing 0.016% w/v solution of anhydrous risedronate sodium.

(2) 0.018% w/v of *risedronate sodium 2.5-hydrate BPCRS* in the mobile phase.

(3) 0.00075% w/v of *risedronate impurity E EPCRS* and 0.005% w/v of *risedronate sodium 2.5-hydrate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to risedronate and impurity E is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_{10}NNaO_7P_2$, in the tablets using the declared content of $C_7H_{10}NNaO_7P_2$, in *risedronate sodium 2.5-hydrate BPCRS*.

LABELLING

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The quantity of active ingredient is stated in terms of the equivalent amount of *risedronic acid*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Risedronate Sodium 2.5-Hydrate.

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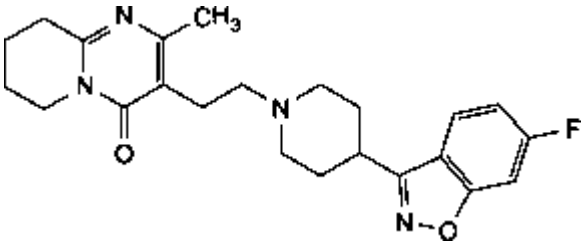
Risperidone

General Notices

(Ph. Eur. monograph 1559)



$C_{23}H_{27}FN_4O_2$ 410.5 *106266-06-2*

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

Preparations

Risperidone Oral Solution

Risperidone Tablets

Risperidone Dispersible Tablets

Ph Eur

DEFINITION

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent). It dissolves in dilute acid solutions.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison risperidone CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.1 g in a 7.5 g/L solution of tartaric acid R and dilute to 100 mL with the same acid solution.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in methanol R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of risperidone for system suitability CRS (containing impurities A, B, C, D and E) in 1.0 mL of methanol R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with methanol R. Dilute 5.0 mL of this solution to 25.0 mL with methanol R.

Reference solution (c) Dissolve the contents of a vial of risperidone impurity K CRS in 1.0 mL of methanol R.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase:

— *mobile phase A*: 5 g/L solution of ammonium acetate R;

— *mobile phase B*: methanol R;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	70	30
2 - 17	70 → 30	30 → 70
17 - 22	30	70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *risperidone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity K.

Relative retention With reference to risperidone (retention time = about 12 min): impurity A = about 0.7; impurity B = about 0.75; impurity C = about 0.8; impurity K = about 0.9; impurity D = about 0.94; impurity E = about 1.1.

System suitability Reference solution (a):

— the chromatogram obtained is similar to the chromatogram supplied with *risperidone for system suitability CRS*;

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to risperidone.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity K*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.160 g in 70 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R* and titrate with *0.1 M perchloric acid*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 20.53 mg of $C_{23}H_{27}FN_4O_2$.

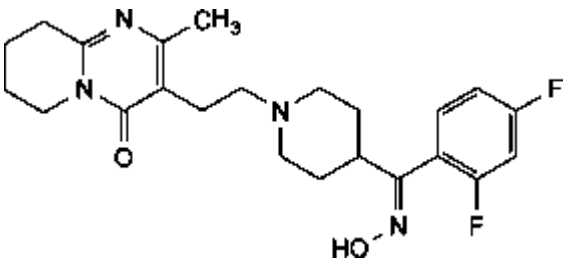
STORAGE

Protected from light.

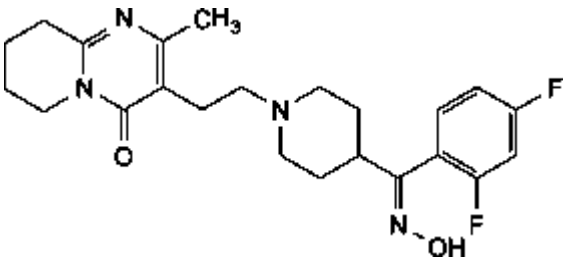
IMPURITIES

Specified impurities *A, B, C, D, E, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F, H, I, J, L, M.*



A. 3-[2-[4-[(*E*)-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



B. 3-[2-[4-[(*Z*)-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,

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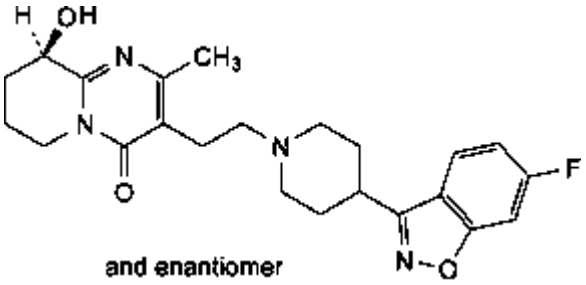
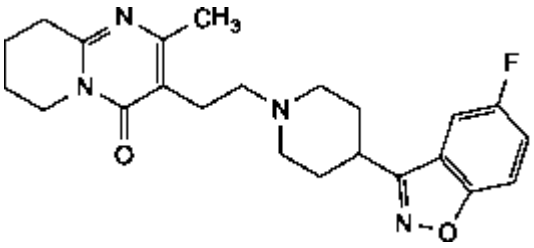
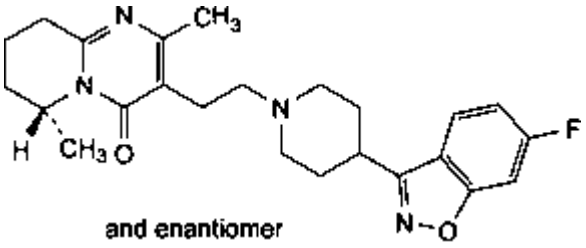


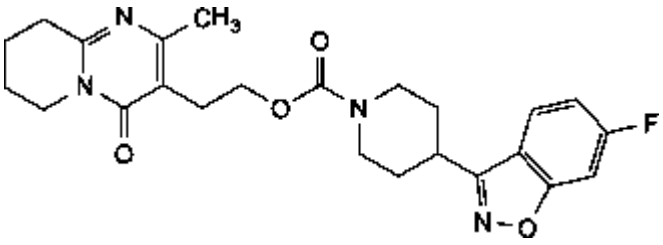
C. (9*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



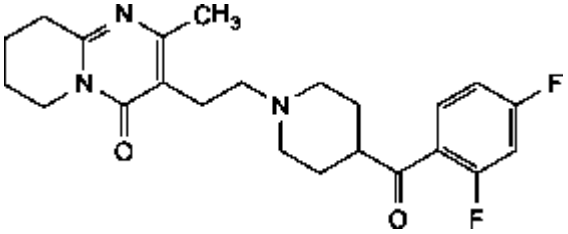
D. 3-[2-[4-(5-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



E. (6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



F. 2-[2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]ethyl 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-carboxylate,



H. 3-[2-[4-(2,4-difluorobenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,

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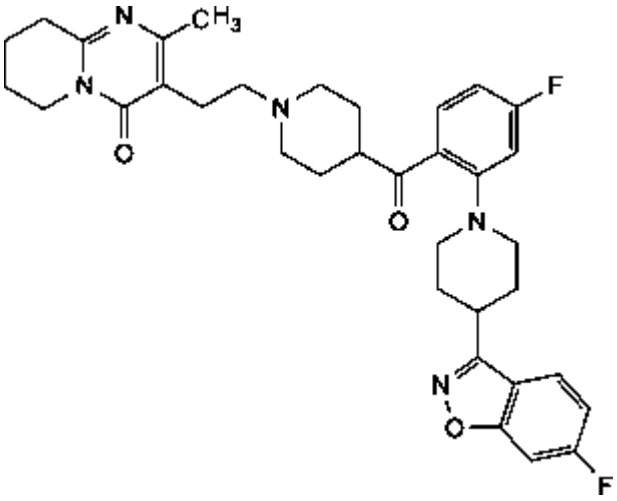
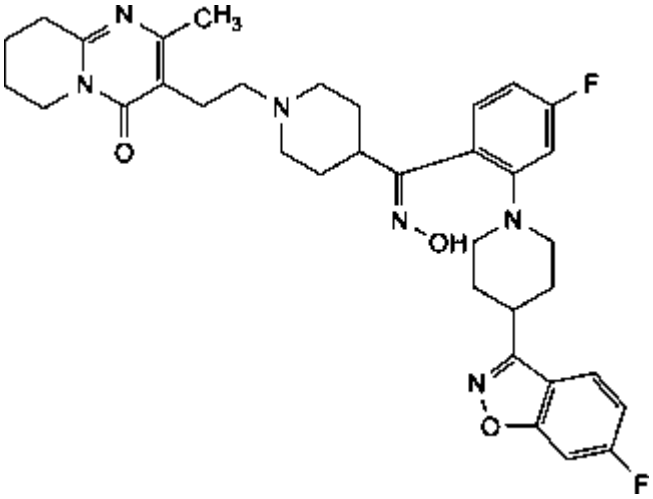
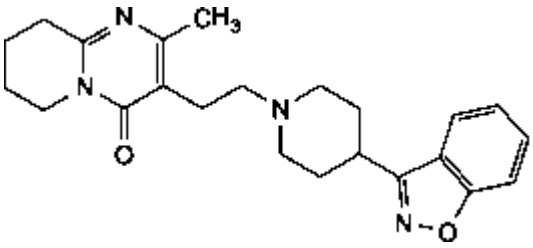


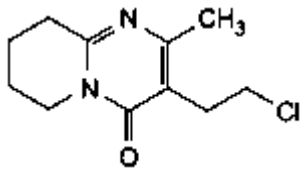
I. 3-[2-[4-[4-fluoro-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]benzoyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



J. 3-[2-[4-[(*Z*)-[4-fluoro-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]phenyl](hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



K. 3-[2-[4-(1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (desfluoro risperidone),



L. 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*pyrido[1,2-*a*]pyrimidin-4-one (piperidopyrimidinone intermediate),

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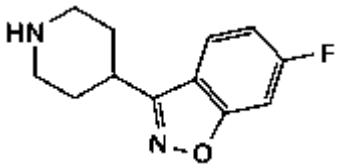

M. 6-fluoro-3-(piperidin-4-yl)-1,2-benzisoxazole.

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Risperidone Dispersible Tablets

General Notices

Dispersible Risperidone Tablets

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

DEFINITION

Risperidone Dispersible Tablets contain Risperidone in a suitable dispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of risperidone, $C_{23}H_{27}FN_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Disperse a quantity of powdered tablets containing 2 mg of Risperidone in 15 mL, mix with the aid of ultrasound and dilute to 20 mL and filter.

(2) 0.01% w/v of *risperidone BPCRS.*

(3) 0.01% w/v each of *risperidone BPCRS* and *trazodone hydrochloride BPCRS.*

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 5 volumes of *water* and 12 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Disintegration

Comply with the requirements for Dispersible Tablets.

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 20 minutes withdraw a sample of the medium and filter. Use the filtered medium, suitably diluted with *0.1M hydrochloric acid* if necessary, expected to contain 0.00005% w/v of Risperidone.

(2) 0.00005% w/v *risperidone BPCRS* in *0.1M hydrochloric acid*.

(3) 0.005% w/v of *risperidone impurity standard BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 237 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusting the pH of the mixture to 3.0 with 13.5M *ammonia*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 10 minutes) are: impurity 2, about 0.65; impurity B, about 0.7 and impurity 1, about 1.6.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of risperidone, $C_{23}H_{27}FN_4O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS.*

LIMITS

The amount of risperidone released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) To a quantity of the powdered tablets containing 5 mg of Risperidone add 10 mL of *0.1M hydrochloric acid* and mix with the aid of ultrasound for 30 minutes. Add 40 mL of *0.1M hydrochloric acid* to the mixture and mix with the aid of ultrasound for a further 15 minutes. Cool and filter through a suitable 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 200 volumes in *0.1M hydrochloric acid*.

(3) 0.005% w/v of *risperidone impurity standard BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusting the pH to 3.05 with 13.5 M *ammonia*.

Mobile phase B 0.1 volumes of *trifluoroacetic acid*, 39 volumes of *methanol* and 61 volumes of *water*, adjusting the pH to 3.05 with 13.5M *ammonia*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-8	100	0	isocratic
8-16	100→0	0→100	linear gradient
16-20	0	100	isocratic
20-21	0→100	100→0	linear gradient
21-30	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 11 minutes) are impurity B, about 0.6; impurity 2, about 0.7 and impurity 1, about 1.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity B and impurity 2 is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any *secondary peak* corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Risperidone comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Place 1 tablet in a 50 mL volumetric flask, add 25 mL of 0.1m hydrochloric acid, mix with the aid of ultrasound for 30 minutes or until completely dispersed, dilute to volume with 0.1M *hydrochloric acid* and filter through a suitable 0.45-µm filter. Dilute a quantity of the filtrate, if necessary, with sufficient 0.1M *hydrochloric acid* to produce a solution expected to contain 0.0005% w/v of Risperidone.

(2) 0.0005% w/v of *risperidone BPCRS* in *0.1M hydrochloric acid*.

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(3) 0.005% w/v of *risperidone impurity standard BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{27}FN_4O_2$ in each tablet from the chromatograms obtained and from the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Risperidone

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w of Risperidone

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 10 mg of Risperidone add 50 mL of 0.1M *hydrochloric acid* and mix with the aid of ultrasound for 30 minutes. Dilute the mixture to 100 mL and filter.

(2) 0.01% w/v of *risperidone BPCRS* in 0.1M *hydrochloric acid*.

(3) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of risperidone, $C_{23}H_{27}FN_4O_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity B, listed under Risperidone and the following:

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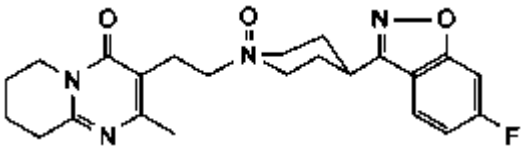
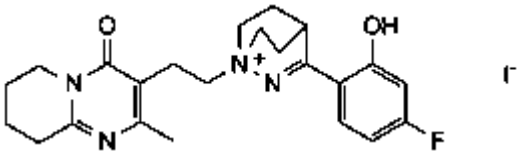


1. *cis*-4-(6-fluoro-1,2-benzoxazol-3-yl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]piperidine *N*-oxide hydrate



2. 3-(4-fluoro-2-hydroxyphenyl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,2-diazabicyclo[2.2.2]oct-2-en-1-ium iodide

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Risperidone Oral Solution

General Notices

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

DEFINITION

Risperidone Oral Solution is a solution of Risperidone in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of risperidone, $C_{23}H_{27}FN_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dilute a volume of the oral solution to contain 0.01% w/v of Risperidone.

(2) 0.01% w/v of *risperidone BPCRS*.

(3) 0.01% w/v each of *risperidone BPCRS* and *trazodone hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 5 volumes of *water* and 12 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.0 to 4.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Dilute a quantity of the oral solution with 0.1M *hydrochloric acid*, if necessary, to contain 0.01% w/v of Risperidone.

(2) Dilute 1 volume of solution (1) to 200 volumes with *0.1M hydrochloric acid*.

(3) Dilute 1 volume of solution (2) to 5 volumes with *0.1M hydrochloric acid*.

(4) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute. Equilibrate the column for at least 30 minutes with *methanol* at the end of each run.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusting the pH of the mixture to 3.0 with 13.5M *ammonia*.

Mobile phase B 0.1 volumes of *trifluoroacetic acid*, 39 volumes of *methanol* and 61 volumes of *water*, adjusting the pH to 3.0 with 13.5M *ammonia*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-8	100	0	isocratic
8-16	100→0	0→100	linear gradient
16-20	0	100	isocratic
20-21	0→100	100→0	linear gradient
21-30	100	0	re-equilibration

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When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 11 minutes) are: impurity B, about 0.6; impurity 2, about 0.7 and impurity 1, about 1.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between impurity B and impurity 2 is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution with 0.1M *hydrochloric acid*, if necessary, to contain 0.01% w/v of Risperidone and filter through a 0.45-µm filter.

(2) 0.01% w/v of *risperidone BPCRS* in 0.1M *hydrochloric acid*.

(3) 0.01% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 237 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water* adjusting the pH of the mixture to 3.0 with 13.5M *ammonia*.

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When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 10 minutes) are: impurity B, about 0.65, impurity 2, about 0.7 and impurity 1, about 1.6.

SYSTEM SUITABILITY

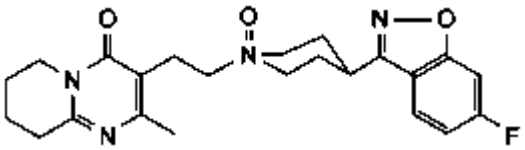
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

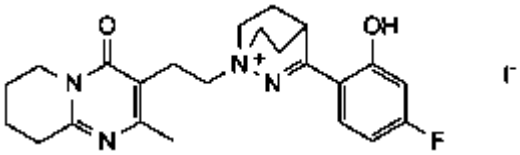
Calculate the total content of risperidone, $C_{23}H_{27}FN_4O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity B, listed under Risperidone and the following:



1. *cis*-4-(6-fluoro-1,2-benzoxazol-3-yl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]piperidine *N*-oxide hydrate



2. 3-(4-fluoro-2-hydroxyphenyl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,2-diazabicyclo[2.2.2]oct-2-en-1-ium iodide

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Risperidone Tablets

General Notices

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

DEFINITION

Risperidone Tablets contain Risperidone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of risperidone, $C_{23}H_{27}FN_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Disperse a quantity of powdered tablets containing 2 mg of Risperidone in 15 mL, mix with the aid of ultrasound and dilute to 20 mL and filter.

(2) 0.01% w/v of *risperidone BPCRS*.

(3) 0.01% w/v each of *risperidone BPCRS* and *trazodone hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 5 volumes of *water* and 12 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, suitably diluted with 0.1M *hydrochloric acid* if necessary, expected to contain 0.00005% w/v of Risperidone.

(2) 0.00005% w/v *risperidone BPCRS* in 0.1M *hydrochloric acid*.

(3) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 237 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusting the pH of the mixture to 3.0 with 13.5M *ammonia*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 10 minutes) are impurity 2, about 0.65, impurity B, about 0.7 and impurity 1, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of risperidone, $C_{23}H_{27}FN_4O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

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LIMITS

The amount of risperidone released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) To a quantity of the powdered tablets containing 5 mg of Risperidone add 10 mL of *water* and mix with the aid of ultrasound for 30 minutes. Add 40 mL of *methanol* to the mixture and mix with the aid of ultrasound for a further 15 minutes. Cool and filter through a suitable 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with 0.1M *hydrochloric acid*.

(3) Dilute 1 volume of solution (2) to 5 volumes with 0.1M *hydrochloric acid*.

(4) 0.01% w/v of *risperidone impurity standard BPCRS* with 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute. Equilibrate the column for at least 30 minutes with *methanol* at the end of each run.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusting the pH of the mixture to 3.0 with 13.5M *ammonia*.

Mobile phase B 0.1 volumes of *trifluoroacetic acid*, 39 volumes of *methanol* and 61 volumes of *water* adjusting the pH to 3.0 with 13.5M *ammonia*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-8	100	0	isocratic
8-16	100→0	0→100	linear gradient
16-20	0	100	isocratic
20-21	0→100	100→0	linear gradient
21-30	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 11 minutes) are impurity B, about 0.6; impurity 2, about 0.7 and impurity 1, about 1.8.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between impurity 2 and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any *secondary peak* corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.4 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Risperidone comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Place 1 tablet in a 50 mL volumetric flask, add 25 mL of 0.1M *hydrochloric acid*, mix with the aid of ultrasound for 30 minutes or until completely dispersed, dilute to volume with 0.1M *hydrochloric acid* and filter through a suitable 0.45-µm filter. Dilute a quantity of the filtrate, if necessary, with sufficient 0.1M *hydrochloric acid* to produce a solution expected to contain 0.0005% w/v of Risperidone.

(2) 0.0005% w/v of *risperidone BPCRS* in 0.1M *hydrochloric acid*.

(3) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{27}FN_4O_2$ in each tablet from the chromatograms obtained and from the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of Risperidone

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Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of Risperidone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 10 mg of Risperidone add 50 mL of 0.1M *hydrochloric acid* and mix with the aid of ultrasound for 30 minutes. Dilute the mixture to 100 mL with 0.1M *hydrochloric acid* and filter. Dilute 1 volume of the resulting solution to 10 volumes with 0.1M *hydrochloric acid*.

(2) 0.001% w/v of *risperidone BPCRS* in 0.1M *hydrochloric acid*.

(3) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

CHROMATOGRAPHIC CONDITIONS

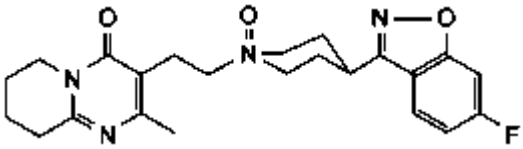
The chromatographic procedure described under Dissolution may be used.

DETERMINATION OF CONTENT

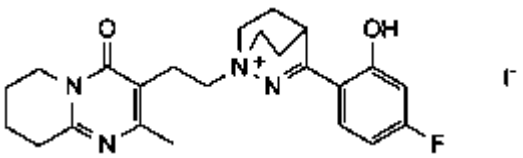
Calculate the total content of Risperidone, $C_{23}H_{27}FN_4O_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity B, listed under Risperidone and the following:



1. *cis*-4-(6-fluoro-1,2-benzoxazol-3-yl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]piperidine *N*-oxide hydrate



2. 3-(4-fluoro-2-hydroxyphenyl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,2-diazabicyclo[2.2.2]oct-2-en-1-ium iodide

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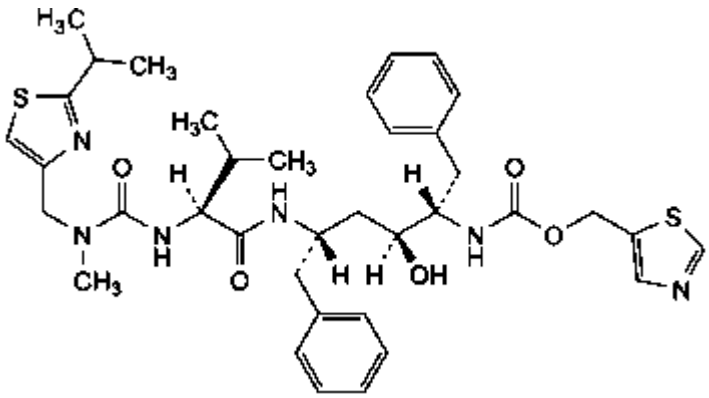
Ritonavir

General Notices

(Ph. Eur. monograph 2136)



$C_{37}H_{48}N_6O_5S_2$ 721 *155213-67-5*

Action and use

Protease inhibitor; antiviral (HIV).

Preparations

Ritonavir Oral Solution

Ritonavir Tablets

Ph Eur

DEFINITION

Thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-2-hydroxy-4-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]carbamate.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

The production method is validated to demonstrate suitable enantiomeric purity of the final product.

CHARACTERS

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Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methanol and in methylene chloride, very slightly soluble in acetonitrile.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *ritonavir CRS*.

If the spectra obtained in the solid state show differences dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mix equal volumes of *acetonitrile R* and a 4.1 g/L solution of *potassium dihydrogen phosphate R*.

Test solution (a) Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Sonicate if necessary.

Test solution (b) Dilute 5.0 mL of test solution (a) to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5.0 mg of *ritonavir for peak identification CRS* (containing impurities E, F, L, O and T) in the solvent mixture and dilute to 5.0 mL with the solvent mixture. Sonicate if necessary.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 10.0 mg of *ritonavir CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Sonicate if necessary. Dilute 5.0 mL of this solution to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (3 µm);

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— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: mix 5 volumes of *butanol R*, 8 volumes of *tetrahydrofuran R*, 18 volumes of *acetonitrile R* and 69 volumes of a 4.1 g/L solution of *potassium dihydrogen phosphate R* filtered through a 0.45 µm nylon membrane;

— *mobile phase B*: mix 5 volumes of *butanol R*, 8 volumes of *tetrahydrofuran R*, 40 volumes of a 4.1 g/L solution of *potassium dihydrogen phosphate R* filtered through a 0.45 µm nylon membrane and 47 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	100	0
60 - 120	100 → 0	0 → 100
120 - 120.1	0 → 100	100 → 0
120.1 - 155	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 50 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *ritonavir for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities E, F, L, O and T.

Relative retention With reference to ritonavir (retention time = about 34 min): impurity E = about 0.39; impurity F = about 0.40; impurity L = about 0.8; impurity O = about 1.1; impurity T = about 2.6.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity F = 1.4; impurity L = 1.9; impurity T = 1.4;

— *impurities E, O*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity T*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

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— *impurities F, L*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{37}H_{48}N_6O_5S_2$ from the declared content of *ritonavir CRS*.

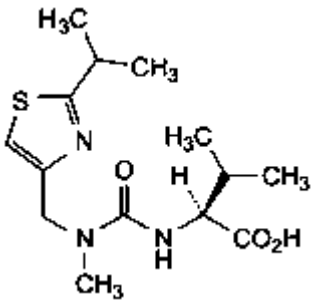
STORAGE

Protected from light.

IMPURITIES

Specified impurities *E, F, L, O, T.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, G, H, I, J, K, M, N, P, Q, R, S, U.*



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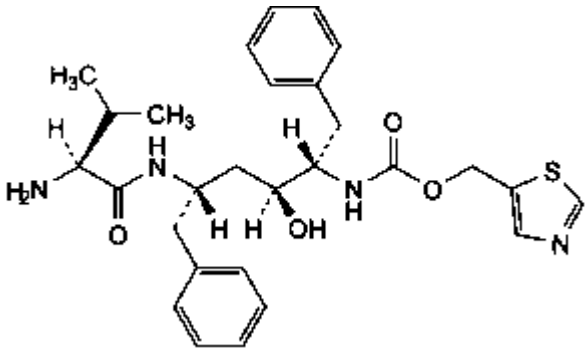
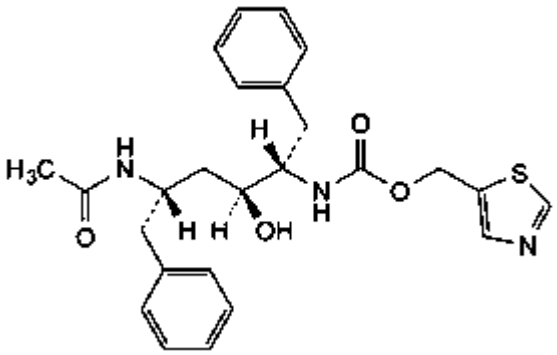
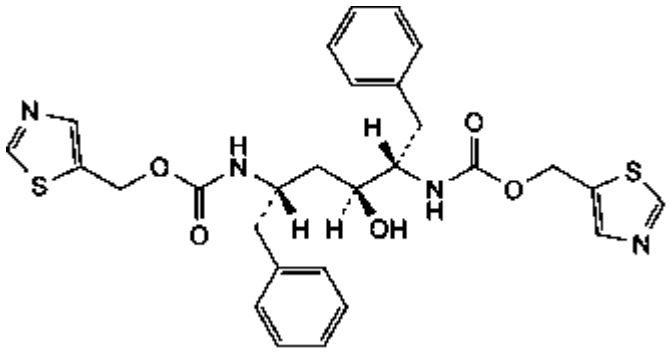
A. (2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoic acid,



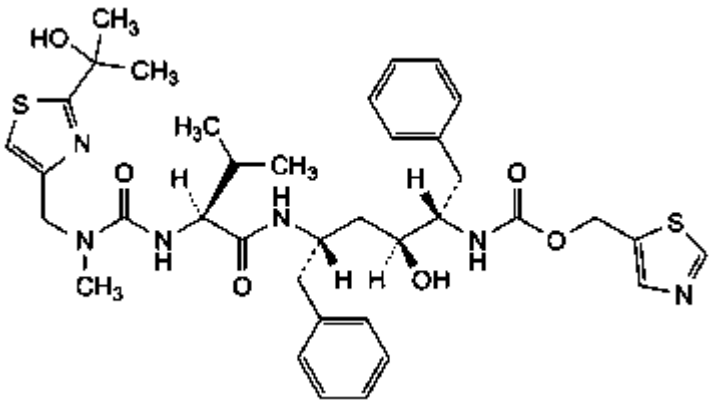
B. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-4-[[(2*S*)-2-amino-3-methylbutanoyl]amino]-1-benzyl-2-hydroxy-5-phenylpentyl]carbamate,



C. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-4-(acetylamino)-1-benzyl-2-hydroxy-5-phenylpentyl]carbamate,



D. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-2-hydroxy-5-phenyl-4-[[(thiazol-5-ylmethoxy)carbonyl]amino]pentyl]carbamate,



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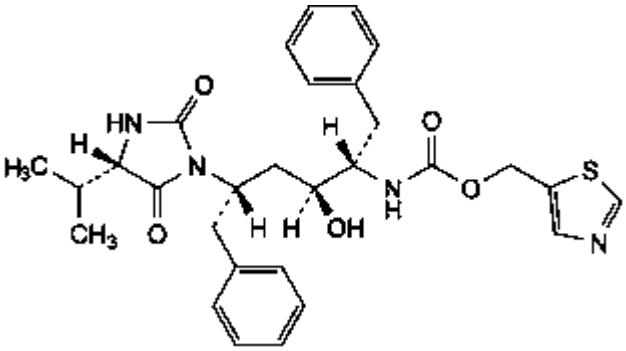
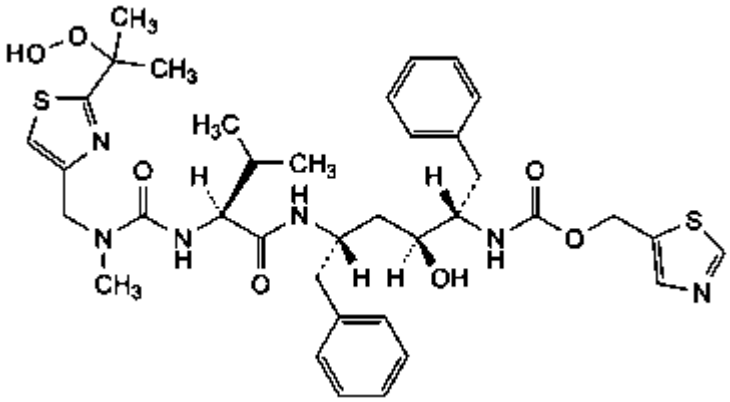
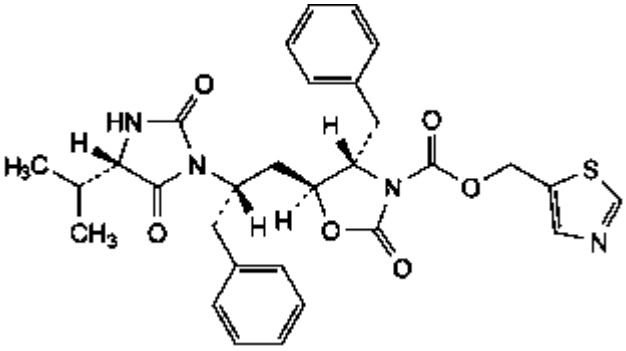
E. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-2-hydroxy-4-[[(2*S*)-2-[[[[2-(1-hydroxy-1-methylethyl)thiazol-4-yl]methyl]methylcarbamoyl]amino]-3-methylbutanoyl]amino]-5-phenylpentyl]carbamate,



F. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-4-[[(2*S*)-1-benzyl-2-hydroxy-4-[(4*S*)-4-(1-methylethyl)-2,5-dioxoimidazolidin-1-yl]-5-phenylpentyl]carbamate,



G. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-4-[[(2*S*)-2-[[[[2-(1-hydroperoxy-1-methylethyl)thiazol-4-yl]methyl]methylcarbamoyl]amino]-3-methylbutanoyl]amino]-2-hydroxy-5-phenylpentyl]carbamate,



H. thiazol-5-ylmethyl (4*S*,5*S*)-4-benzyl-5-[(2*S*)-2-[(4*S*)-4-(1-methylethyl)-2,5-dioxoimidazolidin-1-yl]-3-phenylpropyl]-2-oxooxazolidine-3-carboxylate,

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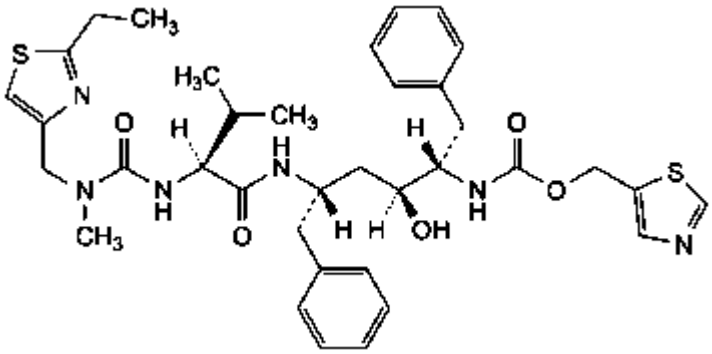
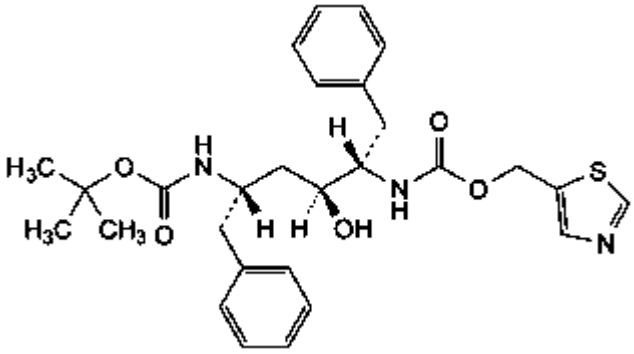
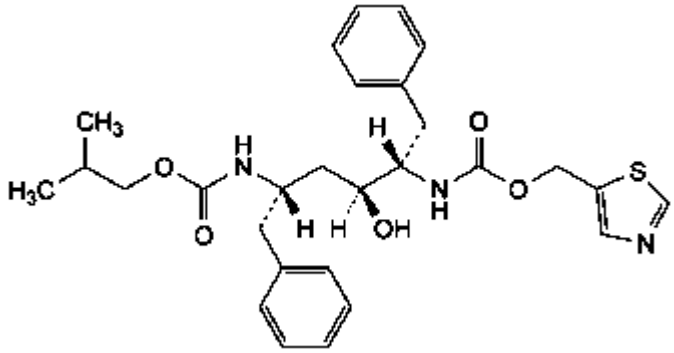


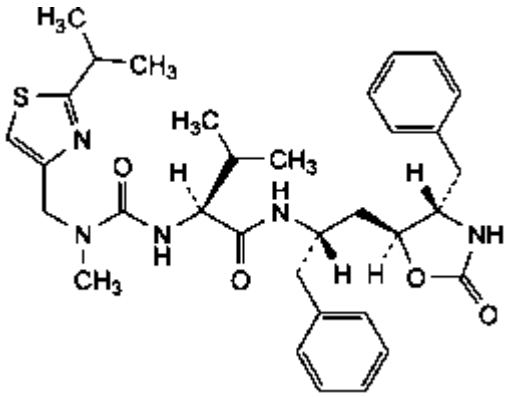
I. thiazol-5-ylmethyl [((1*S*,2*S*,4*S*)-1-benzyl-4-[[(2*S*)-2-[[[[2-ethylthiazol-4-yl]methyl]methylcarbamoyl]amino]-3-methylbutanoyl]amino]-2-hydroxy-5-phenylpentyl]carbamate,



J. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-4-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-5-phenylpentyl]carbamate,



K. thiazol-5-ylmethyl (1*S*,2*S*,4*S*)-1-benzyl-2-hydroxy-4-[[(2-methylpropoxy)carbonyl]amino]-5-phenylpentyl]carbamate,



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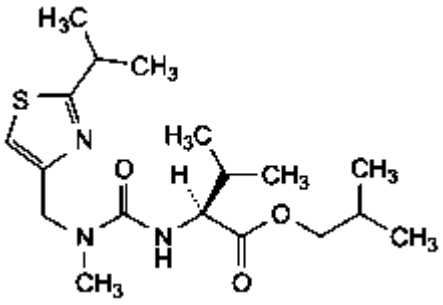
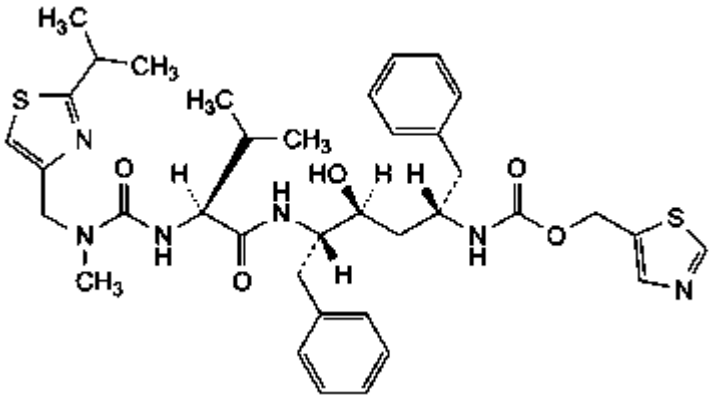
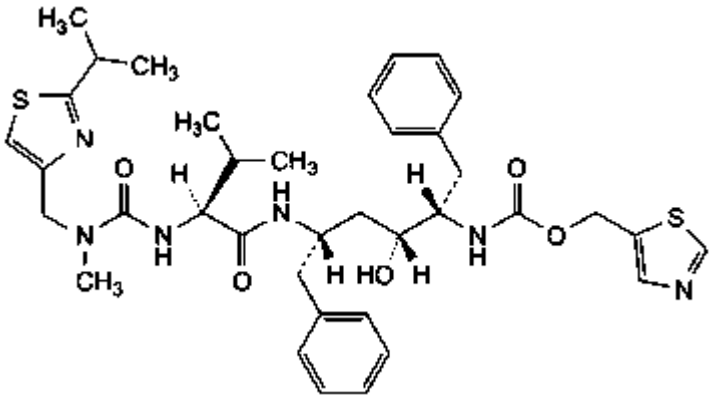
L. (4*S*,5*S*)-4-benzyl-5-[(2*S*)-2-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-3-phenylpropyl]oxazolidin-2-one,



M. 2-methylpropyl (2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoate,



N. thiazol-5-ylmethyl [(1*S*,3*S*,4*S*)-1-benzyl-3-hydroxy-4-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]carbamate,



O. thiazol-5-ylmethyl [(1*S*,2*R*,4*S*)-1-benzyl-2-hydroxy-4-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]carbamate,

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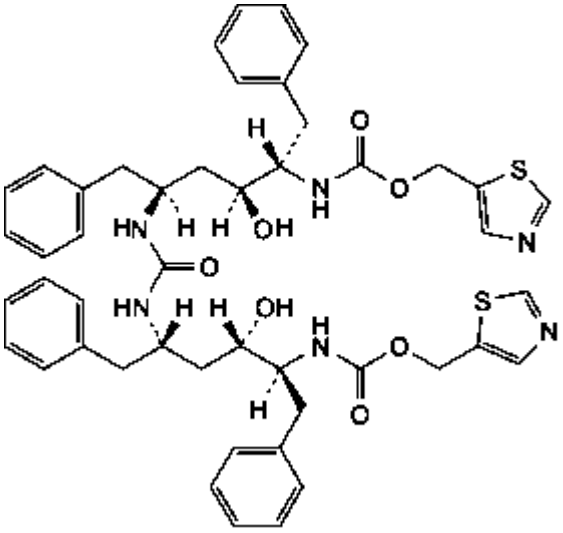
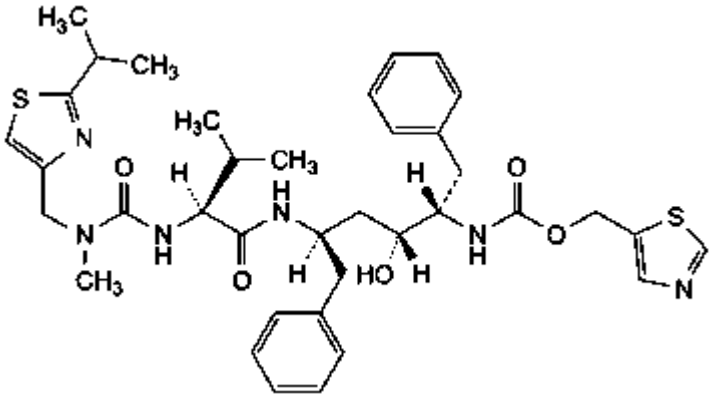
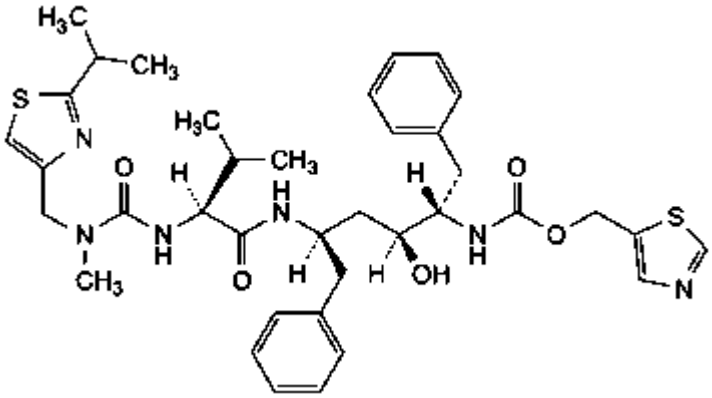


P. bis(thiazol-5-ylmethyl) [carbonylbis[imino[(2*S*,3*S*,5*S*)-3-hydroxy-1,6-diphenylhexane-5,2-diyl]]]dicarbamate,



Q. thiazol-5-ylmethyl [(1*S*,2*R*,4*R*)-1-benzyl-2-hydroxy-4-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]carbamate,



R. thiazol-5-ylmethyl [(1*S*,2*S*,4*R*)-1-benzyl-2-hydroxy-4-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]carbamate,

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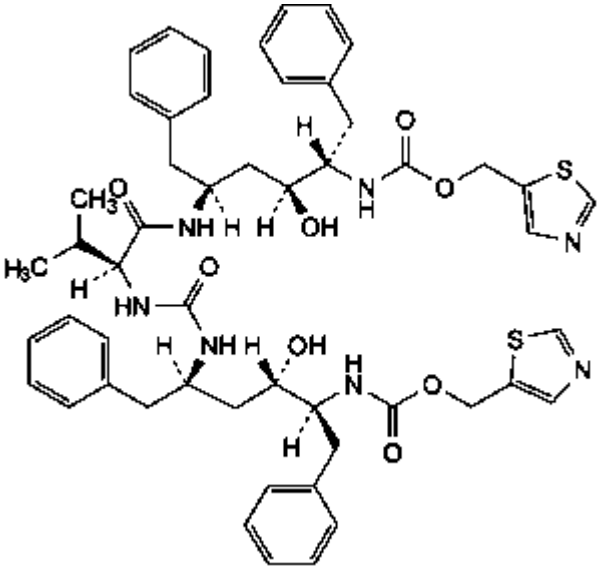
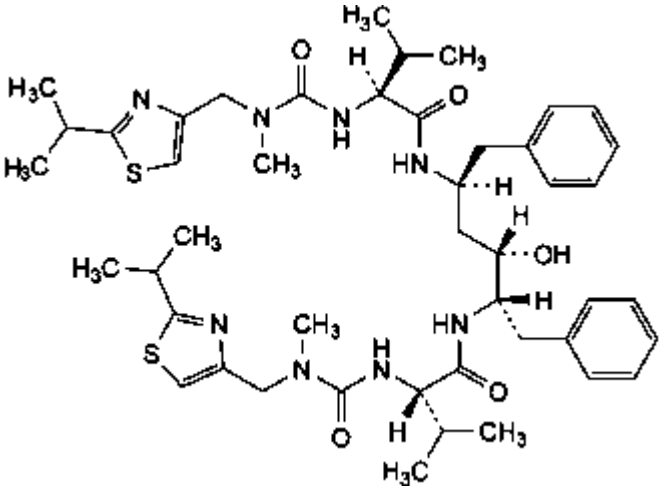


S. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-4-[[(2*S*)-2-[[[(1*S*,3*S*,4*S*)-1-benzyl-3-hydroxy-5-phenyl-4-[[(thiazol-5-ylmethoxy)carbonyl]amino]pentyl]carbamoyl]amino]-3-methylbutanoyl]amino]-2-hydroxy-5-phenylpentyl]carbamate,



T. (2*S*)-*N*-[(1*S*,2*S*,4*S*)-1-benzyl-2-hydroxy-4-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanamide,

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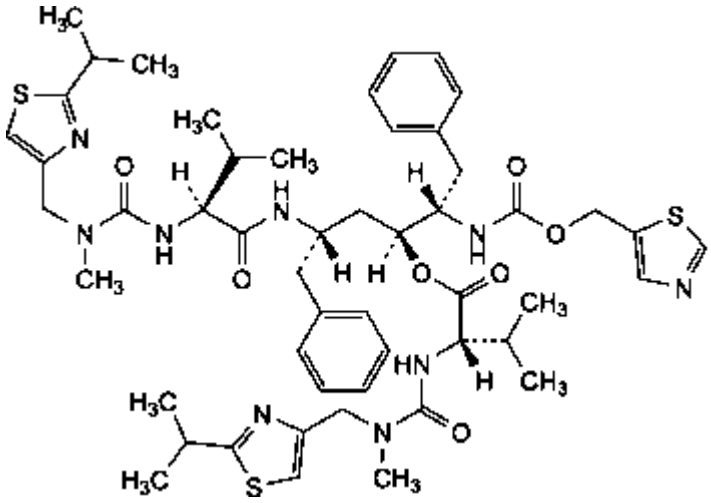

U. (1*S*,3*S*)-3-[[(2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-4-phenyl-1-[(1*S*)-2-phenyl-1-[[(thiazol-5-ylmethoxy)carbonyl]amino]ethyl]butyl (2*S*)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoate.

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Ritonavir Oral Solution

General Notices

Action and use

Protease inhibitor; antiviral (HIV).

DEFINITION

Ritonavir Oral Solution contains Ritonavir.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ritonavir, $C_{37}H_{48}N_6O_5S_2$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared in a mixture of equal volumes of *acetonitrile* and *water*.

(1) Dilute a volume of the oral solution to produce a solution containing 0.2% w/v of Ritonavir.

(2) 0.2% w/v of *ritonavir BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 6 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *glacial acetic acid*, 6 volumes of *n-heptane* and 18 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

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Acidity

pH, 3.7 to 4.7, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Pre-rinse all glassware with *water*.

Solution A Equal volumes of *acetonitrile* and a 0.38% w/v solution of *potassium dihydrogen orthophosphate*.

Solution B 35 volumes of a 0.38% w/v solution of *potassium dihydrogen orthophosphate* and 65 volumes of *acetonitrile*.

Solution C 8 volumes of *butan-1-ol* and 92 volumes of a 0.38% w/v solution of *potassium dihydrogen orthophosphate*.

(1) Dilute a quantity of oral solution containing 0.4 g of Ritonavir to 200 mL with solution B and dilute 1 volume of the resulting solution to 2 volumes with solution C. To 3 volumes of this solution, add 4 volumes of *n-heptane* in a centrifuge tube that has been previously rinsed with *methanol* and dried. Shake the tube vigorously until a uniform emulsion is obtained. Centrifuge the resulting emulsion and remove the clear top layer (heptane) and the viscous white cloudy middle layer, leaving the clear bottom layer in the tube. Repeat the procedure beginning at the words ‘add 4 volumes of *n-heptane*…’ and use the bottom layer.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution C.

(3) Dilute 1 volume of solution (2) to 10 volumes with solution C.

(4) 0.1% w/v of *ritonavir for peak identification EPCRS* in solution A. Dilute 1 volume to 2 volumes with solution C.

(5) To a weighed quantity of oral solution containing 0.8 g of Ritonavir, add 1% w/w of *citric acid* and heat at 70° for 24 hours. Dilute 1 volume to 40 volumes with solution B. To 3 volumes of the resulting solution, add 4 volumes of *n-heptane* in a centrifuge tube that has been previously rinsed with *methanol* and dried. Shake the tube vigorously until a uniform emulsion is obtained. Centrifuge the resulting emulsion and remove the clear top layer (heptane) and the viscous white cloudy middle layer, leaving the clear bottom layer in the tube. Repeat the procedure beginning at the words ‘add 4 volumes of *n-heptane*…’ and use the bottom layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped butylsilyl silica gel for chromatography* (3 µm) (YMC C4 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *butan-1-ol*, 8 volumes of *tetrahydrofuran, stabiliser-free*, 18 volumes of *acetonitrile* and 69 volumes of a solution containing 0.025% w/v of *dipotassium hydrogen orthophosphate* and 0.38% w/v of *potassium dihydrogen orthophosphate*. Adjust to pH 6.3 using 1M *orthophosphoric acid* or 1M *potassium hydroxide*.

Mobile phase B 8 volumes of *butan-1-ol*, 13 volumes of *tetrahydrofuran, stabiliser-free*, 30 volumes of *acetonitrile* and 49 volumes of 0.38% w/v of *potassium dihydrogen orthophosphate*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-80	100	0	isocratic
80-80.1	100→0	0→100	linear gradient
80.1-115	0	100	isocratic column wash
115-115.1	0→100	100→0	linear gradient
115.1-145	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to ritonavir (retention time about 34 minutes) are; impurity B, about 0.1; impurity 3, about 0.25; impurity E, about 0.35; impurity F, about 0.4; impurity 2, about 0.45; impurity 1, about 0.7; impurity L, about 0.9 and impurity O, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *peak to valley ratio* is at least 1.2, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities E, F, L and O using solution (4) and impurities 2 and 3 using solution (5) and multiply the areas of these peaks by the corresponding correction factors: impurity 2, 1.5; impurity 3, 1.7, impurity F, 1.4 and impurity L, 1.9.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity B or impurity E is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity 3 or impurity F is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the area of any peak corresponding to impurity O is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the area of any *secondary peaks* is not greater three times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Pre-rinse all glassware with *water*.

Solution D Equal volumes of *acetonitrile* and 0.03M *potassium dihydrogen orthophosphate*.

(1) Mix a weighed quantity of the oral solution containing 0.25 g of Ritonavir with 80 mL of solution D with the aid of ultrasound, and dilute to 100 mL. Dilute 1 volume to 100 volumes with solution D.

(2) 0.0025% w/v solution of *ritonavir BPCRS* in solution D.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octylsilyl silica gel for chromatography* (5 µm) (Hypersil C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

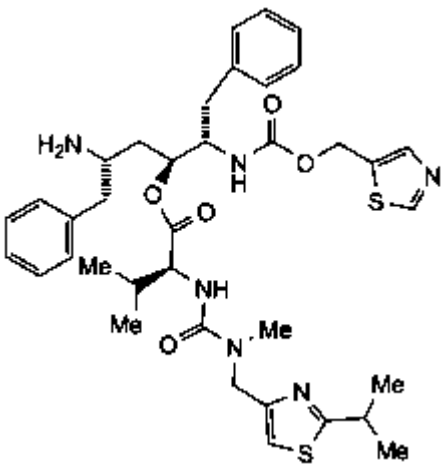
10 volumes of *methanol*, 10 volumes of *tetrahydrofuran, stabiliser-free*, 17.5 volumes of *acetonitrile* and 62.5 volumes of 0.03M *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the Oral Solution, Appendix V G, and calculate the content of ritonavir, $C_{37}H_{48}N_6O_5S_2$, using the declared content of $C_{37}H_{48}N_6O_5S_2$ in *ritonavir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B to S listed under *Ritonavir* and the following:



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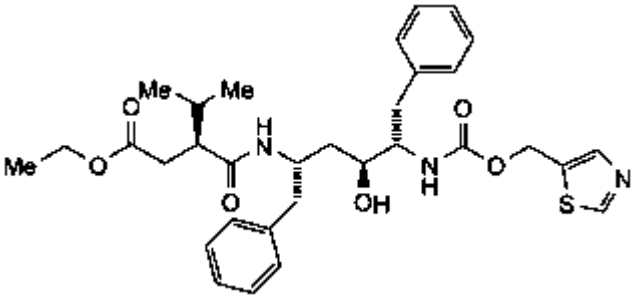
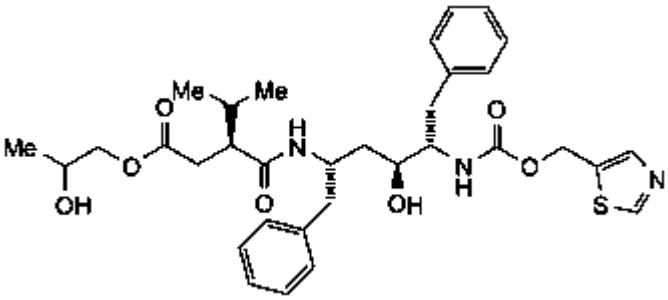
1. (1,3-thiazol-5-yl)methyl (5*S*,8*S*,9*S*)-8-[(2*S*)-2-amino-3-phenylpropyl]-9-benzyl-2-methyl-3,6-dioxo-5-(propan-2-yl)-1-[2-(propan-2-yl)-1,3-thiazol-4-yl]-7-oxa-2,4,10-triazaundecan-11-oate (geo isomer)



2. (1,3-thiazol-5-yl)methyl (3*S*,4*S*,6*S*,9*S*)-3,6-dibenzyl-4-hydroxy-8,11-dioxo-9-(propan-2-yl)-12-oxa-2,7,10-triazatetradecanoate (ethanol adduct)



3. (1,3-thiazol-5-yl)methyl (3*S*,4*S*,6*S*,9*S*,14*RS*)-3,6-dibenzyl-4,14-dihydroxy-8,11-dioxo-9-(propan-2-yl)-12-oxa-2,7,10-triazapentadecanoate (propylene glycol adduct)

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Ritonavir Tablets

General Notices

Action and use

Protease inhibitor; antiviral (HIV).

DEFINITION

Ritonavir Tablets contain Ritonavir.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ritonavir, $C_{37}H_{48}N_6O_5S_2$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared in a mixture of equal volumes of *acetonitrile* and *water*.

(1) Shake a quantity of the powdered tablets containing 20 mg of Ritonavir with 10 mL. Centrifuge and use the supernatant liquid.

(2) 0.2% w/v of *ritonavir BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 6 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *glacial acetic acid*, 6 volumes of *n-heptane* and 18 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.06M *polyoxyethylene 10 lauryl ether*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions

(1) After 120 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with dissolution medium if necessary, expected to contain 0.011% w/v of Ritonavir.

(2) 0.11% w/v of *ritonavir BPCRS* in *methanol R1*. Dilute 1 volume to 10 volumes with dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

45 volumes of 0.03M *potassium dihydrogen orthophosphate*, adjusted to pH 4.0 using *orthophosphoric acid*, and 55 volumes of *acetonitrile R1*.

DETERMINATION OF CONTENT

Calculate the total content of ritonavir, $C_{37}H_{48}N_6O_5S_2$, in the medium from the chromatograms obtained and using the declared content of $C_{37}H_{48}N_6O_5S_2$, in *ritonavir BPCRS*.

LIMITS

The amount of ritonavir released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Pre-rinse all glassware with *water*.

Solution A Equal volumes of *acetonitrile* and a 0.38% w/v solution of *potassium dihydrogen orthophosphate*.

Solution B 10 volumes of a 0.38% w/v solution of *potassium dihydrogen orthophosphate*, 10 volumes of *water*, 15 volumes of *butan-1-ol* and 65 volumes of *acetonitrile*.

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Solution C 5 volumes of *butan-1-ol*, 15 volumes of *acetonitrile* and 80 volumes of a 0.38% w/v solution of *potassium dihydrogen orthophosphate*.

(1) Shake a quantity of powdered tablets containing 0.5 g of Ritonavir with 250 mL of solution B, shake and then mix with the aid of ultrasound. Add sufficient solution B to produce 500 mL and stir. Centrifuge and dilute 1 volume of the supernatant liquid to 2 volumes with solution C. Filter through a 0.2-µm nylon filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution C.

(3) Dilute 1 volume of solution (2) to 10 volumes with solution C.

(4) 0.1% w/v of *ritonavir for peak identification EPCRS* in solution A. Dilute 1 volume to 2 volumes with solution C.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped butylsilyl silica gel for chromatography* (3 µm) (YMC C4 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *butan-1-ol*, 8 volumes of *tetrahydrofuran, stabiliser-free*, 18 volumes of *acetonitrile* and 69 volumes of a solution containing 0.025% w/v of *dipotassium hydrogen orthophosphate* and 0.38% w/v of *potassium dihydrogen orthophosphate*. Adjust to pH 6.3 using 1M *orthophosphoric acid* or 1M *potassium hydroxide*.

Mobile phase B 8 volumes of *butan-1-ol*, 13 volumes of *tetrahydrofuran, stabiliser-free*, 30 volumes of *acetonitrile* and 49 volumes of 0.38% w/v of *potassium dihydrogen orthophosphate*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-80	100	0	isocratic
80-80.1	100→0	0→100	linear gradient
80.1-115	0	100	isocratic column wash
115-115.1	0→100	100→0	linear gradient
115.1-145	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to ritonavir (retention time about 31 minutes) are; impurity E, about 0.39; impurity F, about 0.41; impurity 1, about 0.7; impurity L, about 0.9 and impurity O, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *peak to valley ratio* is at least 1.2, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this

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peak from the peak due to impurity F.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities E, F, L and O using solution (4) and multiply the areas of these peaks by the corresponding correction factors: impurity F, 1.4 and impurity L, 1.9.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than 2.6 times the area of the principal peak in the chromatogram obtained with solution (2) (2.6%)

the area of any peaks corresponding to impurities E, O or L is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the area of any *secondary peaks*, excluding impurity F, is not greater than 0.9 times the area of the principal peak in the chromatogram obtained with solution (2) (0.9%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Pre-rinse all glassware with *water*.

Solution D Equal volumes of *acetonitrile* and 0.03M *potassium dihydrogen orthophosphate*.

Solution E 10 volumes of 0.03M *potassium dihydrogen orthophosphate*, 10 volumes of *water*, 15 volumes of *butan-1-ol* and 65 volumes of *acetonitrile*.

(1) To a number of whole tablets containing 1 g of Ritonavir, add 500 mL of solution E. Add sufficient solution E to produce 1000 mL and stir. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with solution D.
(2) 0.01% w/v solution of *ritonavir BPCRS* in solution D.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octylsilyl silica gel for chromatography* (5 µm) (Hypersil C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

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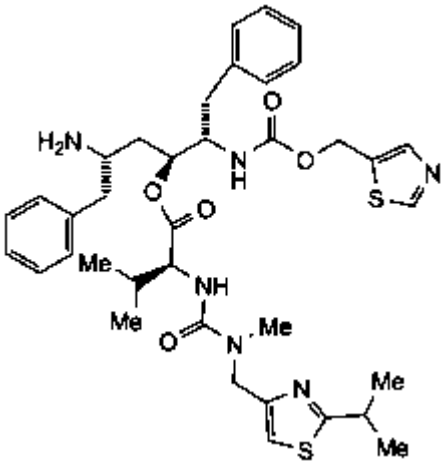
10 volumes of *methanol*, 10 volumes of *tetrahydrofuran, stabiliser-free*, 17.5 volumes of *acetonitrile* and 62.5 volumes of 0.03M *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Calculate the content of ritonavir, $C_{37}H_{48}N_6O_5S_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{37}H_{48}N_6O_5S_2$, in *ritonavir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B to S listed under *Ritonavir* and:



1. (1,3-thiazol-5-yl)methyl (5*S*,8*S*,9*S*)-8-[(2*S*)-2-amino-3-phenylpropyl]-9-benzyl-2-methyl-3,6-dioxo-5-(propan-2-yl)-1-[2-(propan-2-yl)-1,3-thiazol-4-yl]-7-oxa-2,4,10-triazaundecan-11-oate (geo isomer)

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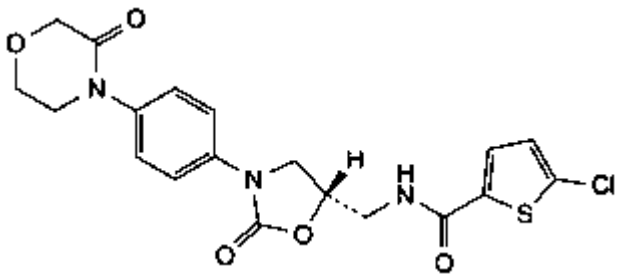
Rivaroxaban

General Notices

(Ph. Eur. monograph 2932)



$C_{19}H_{18}ClN_3O_5S$ 435.9 *366789-02-8*

Action and use

Factor Xa inhibitor; anticoagulant

Preparation

Rivaroxaban Tablets

Ph Eur

DEFINITION

5-Chloro-*N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish powder.

Solubility

Practically insoluble in water, freely soluble in dimethyl sulfoxide, practically insoluble in anhydrous ethanol and in heptane.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *rivaroxaban CRS*.

B. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in 25 mL of *acetonitrile R* and dilute to 50 mL with *anhydrous ethanol R*.

Reference solution (a) Dissolve 1 mg of *rivaroxaban impurity A CRS* in 5 mL of *acetonitrile R* and dilute to 10 mL with *anhydrous ethanol R*.

Reference solution (b) Dissolve 20 mg of the substance to be examined in 25 mL of *acetonitrile R*, add 1 mL of reference solution (a) and dilute to 50 mL with *anhydrous ethanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 2.0 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (10 µm);

— *temperature*: 50 °C.

Mobile phase *anhydrous ethanol R*, *heptane R* (30:70 *V/V*).

Flow rate 0.2 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 3.0 µL of the test solution and reference solution (b).

Run time 1.5 times the retention time of rivaroxaban.

Relative retention With reference to rivaroxaban (retention time = about 17 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and rivaroxaban.

Limit:

— *impurity A*: maximum 0.5 per cent; calculate the ratio of the area of the peak due to impurity A to the sum of the areas of the peaks due to rivaroxaban and impurity A.

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Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 1.36 g of potassium dihydrogen phosphate R in water for chromatography R, add 200 µL of phosphoric acid R and dilute to 1000 mL with water for chromatography R.

Solvent mixture acetonitrile R, solution A (40:60 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of rivaroxaban CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2.5 mg of rivaroxaban for system suitability CRS (containing impurity G) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: mix 5 volumes of methanol R and 95 volumes of a 1.0 g/L solution of sodium hexanesulfonate R in solution A;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	98	2
2 - 8	98 → 84	2 → 16
8 - 25	84 → 64	16 → 36
25 - 37	64 → 20	36 → 80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 3 µL of the test solution and reference solutions (b) and (c).

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Identification of impurities Use the chromatogram supplied with *rivaroxaban for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to rivaroxaban (retention time = about 16 min): impurity G = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 7.0 between the peaks due to impurity G and rivaroxaban.

Calculation of percentage contents:

— for each impurity, use the concentration of rivaroxaban in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.150 g using the evaporation technique at 150 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{19}H_{18}ClN_3O_5S$ taking into account the assigned content of *rivaroxaban CRS*.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E, F, G, H, I, J.*

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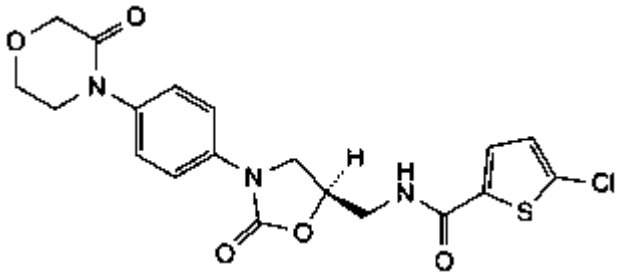
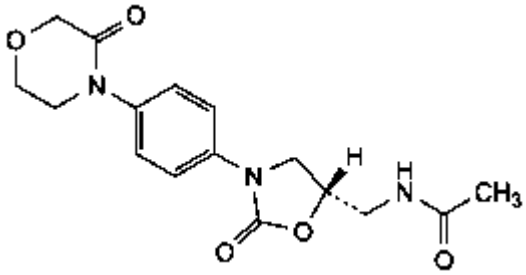
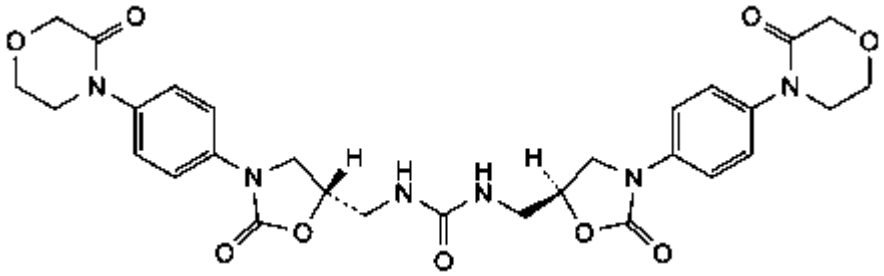


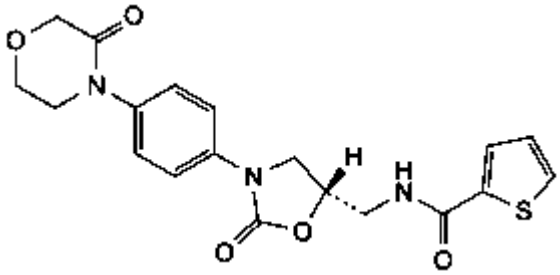
A. 5-chloro-*N*-[[(5*R*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide,



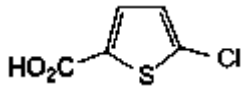
B. *N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]acetamide,



D. *N*,*N*′-bis[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]urea,



E. *N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide,



F. 5-chlorothiophene-2-carboxylic acid,

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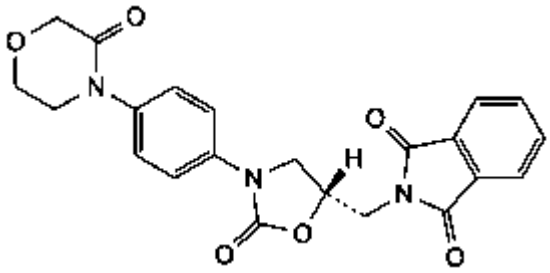
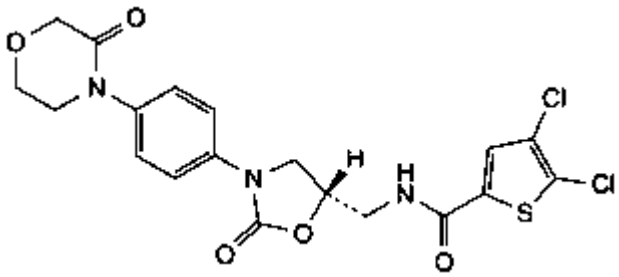
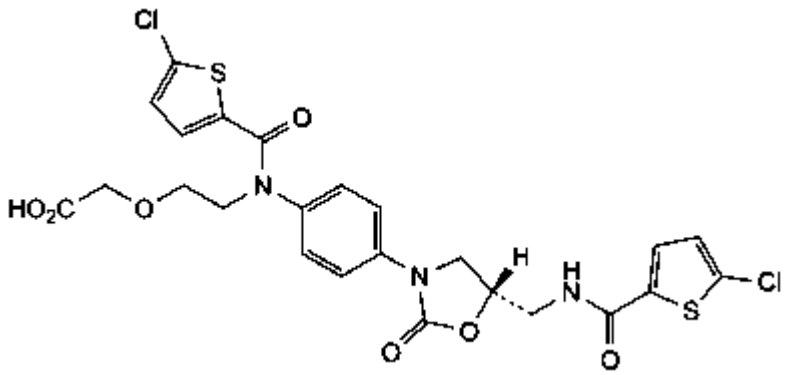


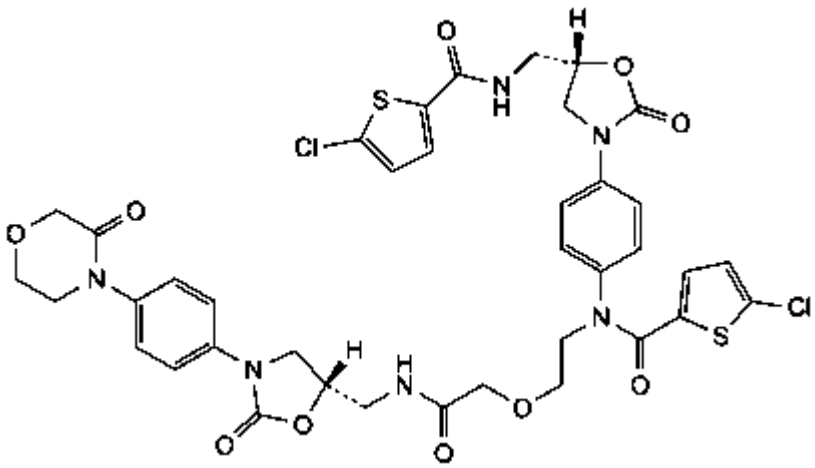
G. 2-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]-2*H*-isoindole-1,3-dione,



H. 4,5-dichloro-*N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide,



I. [2-[1^{5},9^{5}-dichloro-2,5^{2},8-trioxo-3,7-diaza-5(3,5)-1,3-oxazolidina-1,9(2)-dithiophena-4(1,4)-benzenanonaphan-3-yl]ethoxy]acetic acid,



J. 5-chloro-*N*-[4-[(5*S*)-5-[(5-chlorothiophene-2-carboxamido)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl]-*N*-[2-[2-oxo-2-[[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]amino]ethoxy]ethyl]thiophene-2-carboxamide.

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Rivaroxaban Tablets

General Notices

(Ph. Eur. monograph 3021)

Action and use

Factor Xa inhibitor; anticoagulant.

Ph Eur

DEFINITION

Tablets containing *Rivaroxaban (2932)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solution A Dilute 0.67 mL of *phosphoric acid R* to 1000 mL with *water for chromatography R*.

Solvent mixture Solution A, *acetonitrile R* (40:60 *V/V*).

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Test solution To at least 4 whole tablets add a volume of the solvent mixture equivalent to about 2/3 of the final volume. Sonicate for at least 15 min, until the tablets have disintegrated completely. Dilute with the solvent mixture to obtain a concentration of rivaroxaban of 0.2 mg/mL and filter.

Reference solution (a) Dissolve 20.0 mg of *rivaroxaban CRS* in the solvent mixture using sonication and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *rivaroxaban for system suitability CRS* (containing impurity G) in the solvent mixture using sonication and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.055 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, solution A (8:92 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 15	100 → 53	0 → 47

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *rivaroxaban for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to rivaroxaban (retention time = about 9.5 min): impurity G = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity G and rivaroxaban.

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Calculation of percentage contents:

— for each impurity, use the concentration of rivaroxaban in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.1 per cent.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium (2.5 mg tablets) Dissolve 29.9 g of *sodium acetate R* and 16.6 mL of *glacial acetic acid R* in *water R* and dilute to 10 L with the same solvent. Adjust to pH 4.5 with *sodium hydroxide solution R* or *glacial acetic acid R*. Use 900 mL of the medium.

Dissolution medium (10 mg tablets) Dissolve 29.9 g of *sodium acetate R*, 16.6 mL of *glacial acetic acid R* and 20 g of *sodium dodecyl sulfate R* in *water R* and dilute to 10 L with the same solvent. Adjust to pH 4.5 with *sodium hydroxide solution R* or *glacial acetic acid R*. Use 900 mL of the medium.

Dissolution medium (15 mg and 20 mg tablets) Dissolve 29.9 g of *sodium acetate R*, 16.6 mL of *glacial acetic acid R* and 40 g of *sodium dodecyl sulfate R* in *water R* and dilute to 10 L with the same solvent. Adjust to pH 4.5 with *sodium hydroxide solution R* or *glacial acetic acid R*. Use 900 mL of the medium.

Rotation speed 75 r/min.

Time 30 min.

Analysis Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solutions Samples withdrawn from the dissolution vessel and filtered.

Reference solution Dissolve 28.0 mg of *rivaroxaban CRS* in *acetonitrile R* and dilute to 50.0 mL with the same solvent. Dilute a suitable volume of the solution with the dissolution medium to obtain a concentration of rivaroxaban corresponding to the theoretical concentration of rivaroxaban in the test solution, based on the labelled content of the tablets.

Column:

— *size*: *l* = 0.06 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, *water for chromatography R* (40:60 *V/V*).

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 250 nm.

Autosampler Set at 10 °C.

Injection 10 µL.

Run time 3 times the retention time of rivaroxaban.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the amount of dissolved rivaroxaban ($C_{19}H_{18}ClN_3O_5S$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *rivaroxaban CRS*.

Acceptance criterion:

— *Q* = 80 per cent after 30 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

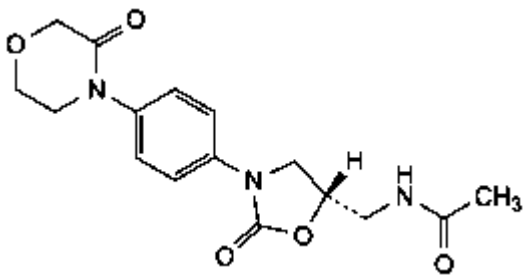
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) taking into account the assigned content of *rivaroxaban CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: B, D, E, G, H, I, J.*



B. *N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]acetamide,

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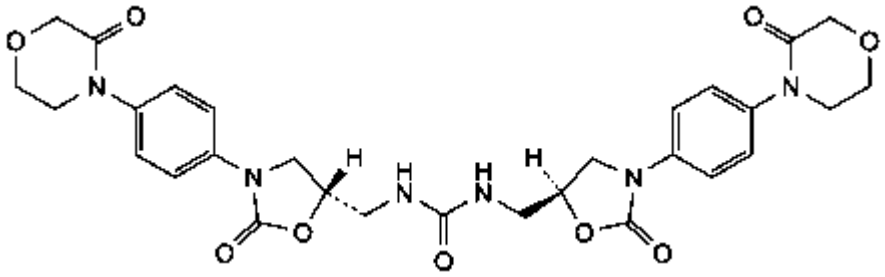
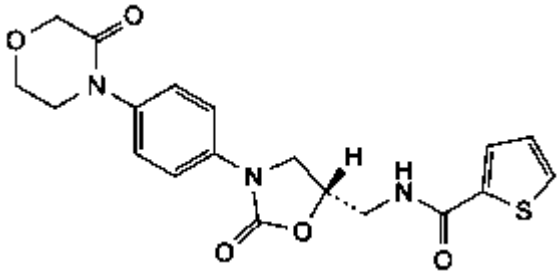
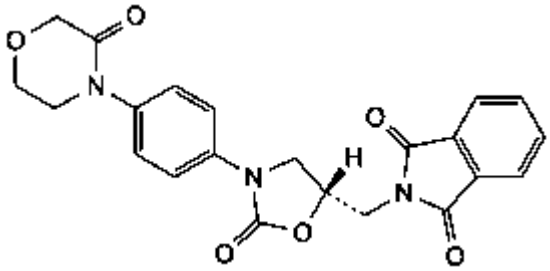


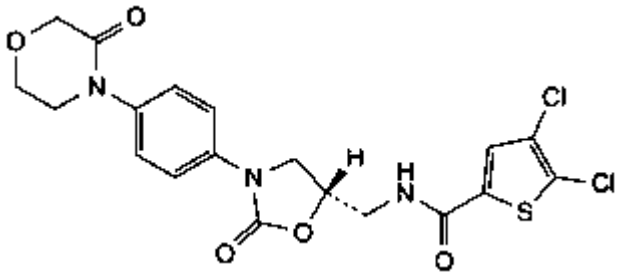
D. *N,N′*-bis[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]urea,



E. *N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide,



G. 2-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]-2*H*-isoindole-1,3-dione,



H. 4,5-dichloro-*N*-[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide,

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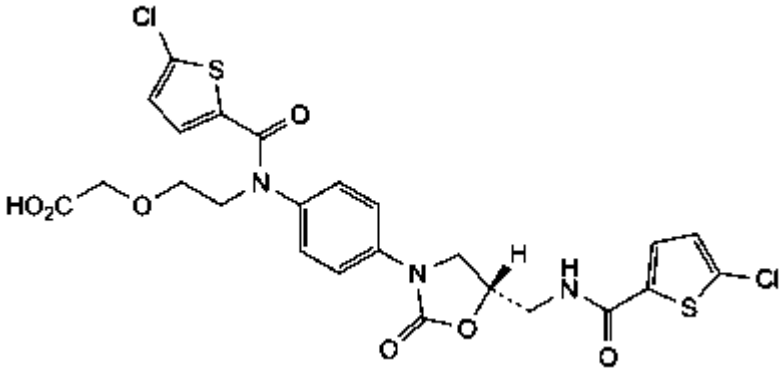
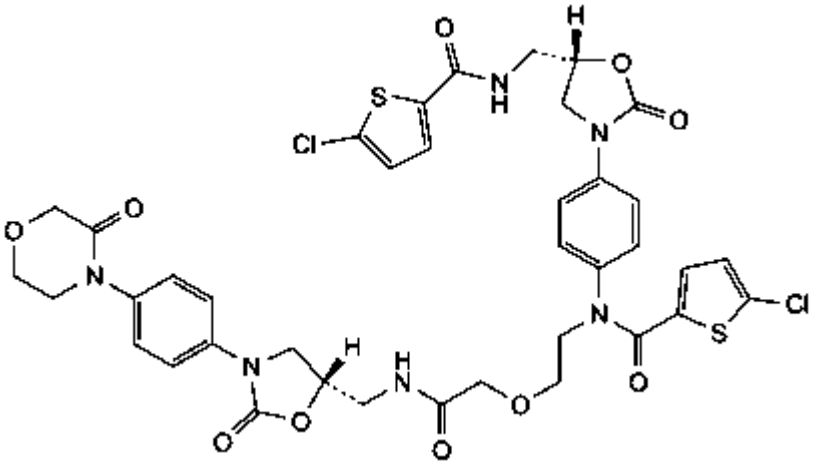


I. [2-[(5^5*S*)-1^5,9^5-dichloro-2,5^2,8-trioxo-3,7-diaza-5(3,5)-1,3-oxazolidina-1,9(2)-dithiophena-4(1,4)-benzenanonaphan-3-yl]ethoxy]acetic acid,



J. 5-chloro-*N*-[4-[(5*S*)-5-[(5-chlorothiophene-2-carboxamido)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl]-*N*-[2-[2-oxo-2-[[[(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]amino]ethoxy]ethyl]thiophene-2-carboxamide.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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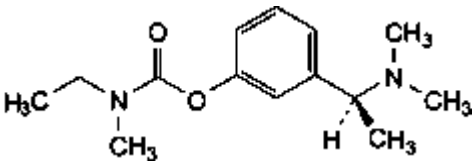
Rivastigmine

General Notices

(Ph. Eur. monograph 2629)



$C_{14}H_{22}N_2O_2$ 250.3 *123441-03-2*

Action and use

Cholinesterase inhibitor; treatment of dementia in Alzheimer's disease and Parkinson's disease.

Preparation

Rivastigmine Transdermal Patches

Ph Eur

DEFINITION

3-[(1*S*)-1-(Dimethylamino)ethyl]phenyl ethyl(methyl)carbamate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Viscous, clear, colourless or yellow or very slightly brown, hygroscopic liquid.

Solubility

Sparingly soluble in water, very soluble in anhydrous ethanol and in heptane.

IDENTIFICATION

Carry out either tests A, B or tests B, C.

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A. Specific optical rotation (2.2.7): -44.0 to -38.0 (anhydrous substance). *Prepare the solution immediately before use.* Dissolve 0.300 g in *ethyl acetate R* and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Film.

Comparison *rivastigmine hydrogen tartrate CRS*, treated as follows: dissolve 0.100 g in 30 mL of *buffer solution pH 11 R*, then add 30 mL of *1,1-dimethylethyl methyl ether R* and shake vigorously for 2 min. Allow the layers to separate. Filter the upper organic layer through *anhydrous sodium sulfate R*. Evaporate the filtrate under reduced pressure at a temperature not exceeding 60 °C to obtain a residue. Record the reference spectrum using this residue.

C. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Solution A Solution containing 1.78 g/L of *disodium hydrogen phosphate dihydrate R* and 1.38 g/L of *sodium dihydrogen phosphate monohydrate R*. Adjust to pH 6.0 with *phosphoric acid R*.

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *rivastigmine impurity D CRS* in the mobile phase and dilute to 200.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 1 mg of *rivastigmine hydrogen tartrate CRS* in reference solution (a) and dilute to 10 mL with reference solution (a).

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *α1-acid-glycoprotein silica gel for chiral separation R* (5 µm).

Mobile phase Mix 205 µL of *N,N-dimethyloctylamine R* and 20.0 mL of *acetonitrile R1* and dilute to 1000 mL with solution A.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Run time Twice the retention time of rivastigmine.

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Relative retention With reference to rivastigmine (retention time = about 9 min): impurity D = about 0.8.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rivastigmine.

Calculation of percentage content:

— use the concentration of impurity D in reference solution (a).

Limit:

— *impurity D*: maximum 0.3 per cent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 62.5 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *rivastigmine for system suitability CRS* (containing impurities A, B and C) in 1 mL of the mobile phase.

Reference solution (c) Dissolve 50.0 mg of *rivastigmine hydrogen tartrate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 42 volumes of an 8.9 g/L solution of *disodium hydrogen phosphate dihydrate R* previously adjusted to pH 7.0 with *phosphoric acid R* and 58 volumes of *methanol R2*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time Twice the retention time of rivastigmine.

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Identification of impurities Use the chromatogram supplied with *rivastigmine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to rivastigmine (retention time = about 10 min): impurity A = about 0.4; impurity C = about 0.6; impurity B = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities C and B.

Calculation of percentage contents:

— for each impurity, use the concentration of rivastigmine in reference solution (a).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.000 g.

Change the solvent after standardisation of the titrant and after every 3rd sample.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (c).

System suitability Reference solution (c):

— *symmetry factor*: maximum 2.5 for the peak due to rivastigmine.

Calculate the percentage content of $C_{14}H_{22}N_2O_2$ taking into account the assigned content of *rivastigmine hydrogen tartrate CRS* and a conversion factor of 0.625.

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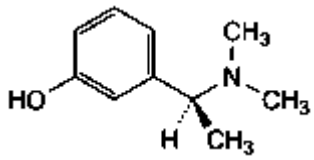
STORAGE

Under an inert gas, in an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

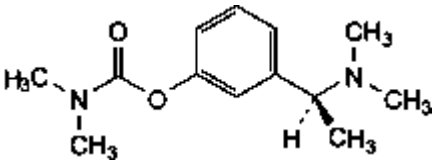
IMPURITIES

Specified impurities A, B, D.

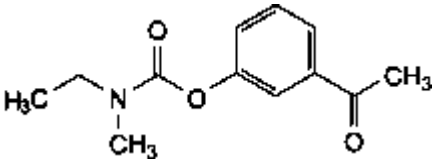
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



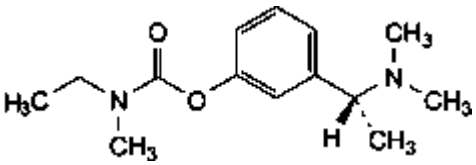
A. 3-[(1*S*)-1-(dimethylamino)ethyl]phenol (dimetol),



B. 3-[(1*S*)-1-(dimethylamino)ethyl]phenyl dimethylcarbamate,



C. 3-acetylphenyl ethyl(methyl)carbamate,



D. 3-[(1*R*)-1-(dimethylamino)ethyl]phenyl ethyl(methyl)carbamate ((*R*)-enantiomer).

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Rivastigmine Capsules

General Notices

Action and use

Cholinesterase inhibitor; treatment of dementia in Alzheimer's disease and Parkinson's disease.

DEFINITION

Rivastigmine Capsules contain Rivastigmine Hydrogen Tartrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of rivastigmine, $C_{14}H_{22}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered capsule contents containing the equivalent of 9 mg of rivastigmine with 15 mL of *methanol* and mix with the aid of ultrasound. Add sufficient *methanol* to produce 25 mL and filter (a 0.45-µm Nylon filter is suitable).

(2) 0.058% w/v of *rivastigmine hydrogen tartrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *formic acid*, 5 volumes of *water*, 30 volumes of *methanol* and 70 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.0003% w/v of rivastigmine.

(2) 0.00048% w/v of *rivastigmine hydrogen tartrate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient a column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile R1*, 15 volumes of *methanol* and 70 volumes of a 0.86% w/v solution of *ammonium dihydrogen orthophosphate* that has been previously adjusted to pH 7.0 with *dilute ammonia solution*.

DETERMINATION OF CONTENT

Calculate the total content of rivastigmine, $C_{14}H_{22}N_2O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$.

LIMITS

The amount of rivastigmine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Shake a quantity of the capsule contents containing the equivalent of 50 mg of rivastigmine with 30 mL. Mix with the aid of ultrasound and add sufficient of the mobile phase to produce 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.

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(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleodur C18 EC Gravity is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of rivastigmine.

MOBILE PHASE

42 volumes of a 0.895% w/v solution of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 7.0 with *orthophosphoric acid* and 58 volumes of *methanol R1*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to rivastigmine (retention time about 9 minutes) are: impurity A, about 0.4; impurity C, about 0.6 and impurity B, about 0.7.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and B is at least 2.0.

LIMITS

Identify any peak corresponding to impurity C in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (3) and multiply the area of any such peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Rivastigmine Hydrogen Tartrate comply with the requirements stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

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(1) Add 5 mL of mobile phase to the contents of one capsule and mix with the aid of ultrasound until completely dispersed. Shake, dilute to produce a solution expected to contain the equivalent of 0.01% w/v of rivastigmine and filter (a 0.45-µm Nylon filter is suitable).

(2) 0.016% w/v of *rivastigmine hydrogen tartrate BPCRS*.

(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of rivastigmine, $C_{14}H_{22}N_2O_2$, in the each capsule from the chromatograms obtained and using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$.

ASSAY

For capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of Rivastigmine Hydrogen Tartrate

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing the equivalent of 2 mg or more and 2% w/w or more of Rivastigmine Hydrogen Tartrate

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Shake a quantity of the capsule contents containing the equivalent of 50 mg of rivastigmine with the mobile phase. Mix with the aid of ultrasound, dilute to 50 mL and filter (a 0.45-µm Nylon filter is suitable). Dilute 1 volume of this solution to 10 volumes.

(2) 0.016% w/v of *rivastigmine hydrogen tartrate BPCRS*.

(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of rivastigmine, $C_{14}H_{22}N_2O_2$, in the capsules from the chromatograms obtained and using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$.

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IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Rivastigmine Hydrogen Tartrate.

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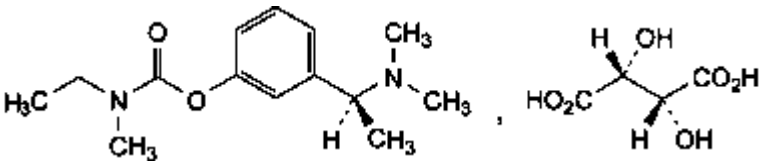
Rivastigmine Hydrogen Tartrate

General Notices

(Ph. Eur. monograph 2630)



$C_{18}H_{28}N_2O_8$ 400.4 *129101-54-8*

Action and use

Cholinesterase inhibitor; treatment of dementia in Alzheimer's disease and Parkinson's disease.

Preparations

Rivastigmine Capsules

Rivastigmine Oral Solution

Ph Eur

DEFINITION

3-[(1*S*)-1-(Dimethylamino)ethyl]phenyl *N*-ethyl-*N*-methylcarbamate hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic, crystalline or fine crystalline powder.

Solubility

Very soluble in water, soluble in methanol, very slightly soluble in ethyl acetate.

It shows polymorphism (*5.9*).

IDENTIFICATION

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IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Specific optical rotation (2.2.7): + 4.2 to + 5.1.

Dissolve 0.600 g in *methanol R* and dilute to 20.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *rivastigmine hydrogen tartrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Solution A Solution containing 1.78 g/L of *disodium hydrogen phosphate dihydrate R* and 1.38 g/L of *sodium dihydrogen phosphate monohydrate R*, adjusted to pH 6.0 with *phosphoric acid R*.

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *rivastigmine impurity D CRS* in the mobile phase and dilute to 200.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 1 mg of *rivastigmine hydrogen tartrate CRS* in reference solution (a) and dilute to 10.0 mL with the same solution.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *α1-acid-glycoprotein silica gel for chiral separation R* (5 µm).

Mobile phase Mix 205 µL of *N,N-dimethyloctylamine R* and 20.0 mL of *acetonitrile R1* and dilute to 1000 mL with solution A.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Run time Twice the retention time of rivastigmine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

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Relative retention With reference to rivastigmine (retention time = about 9 min): impurity D = about 0.8.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rivastigmine.

Calculation of percentage content:

— for impurity D, use the concentration of impurity D in reference solution (a).

Limit:

— *impurity D*: maximum 0.3 per cent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *rivastigmine for system suitability CRS* (containing impurities A, B and C) in 1.0 mL of the mobile phase.

Reference solution (c) Dissolve 50.0 mg of *rivastigmine hydrogen tartrate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 42 volumes of an 8.9 g/L solution of *disodium hydrogen phosphate dihydrate R* previously adjusted to pH 7.0 with *phosphoric acid R* and 58 volumes of *methanol R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time Twice the retention time of rivastigmine.

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Identification of impurities Use the chromatogram supplied with *rivastigmine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention with reference to rivastigmine (retention time = about 10 min): impurity A = about 0.4; impurity C = about 0.6; impurity B = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities C and B.

Calculation of percentage contents:

— for each impurity, use the concentration of rivastigmine hydrogen tartrate in reference solution (a).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to tartaric acid.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (c).

System suitability Reference solution (c):

— *symmetry factor*: maximum 2.5 for the peak due to rivastigmine.

Calculate the percentage content of $C_{18}H_{28}N_2O_8$ taking into account the assigned content of *rivastigmine hydrogen tartrate CRS*.

STORAGE

In an airtight container, protected from light.

IMPURITIES

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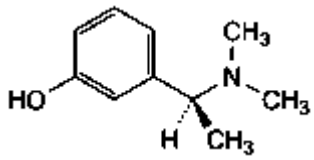
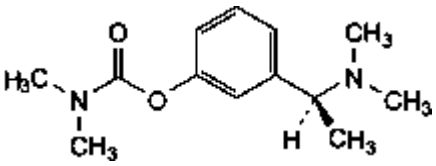
Specified impurities A, D.

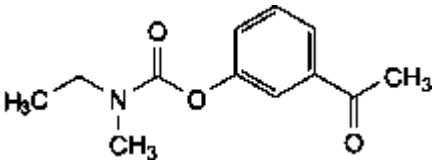
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, E, F, G, H.



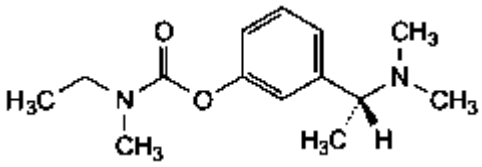
A. 3-[(1*S*)-1-(dimethylamino)ethyl]phenol,



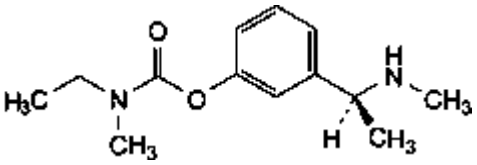
B. 3-[(1*S*)-1-(dimethylamino)ethyl]phenyl *N*,*N*-dimethylcarbamate,



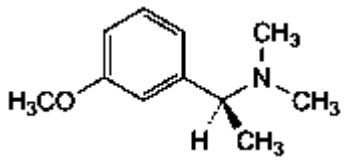
C. 3-acetylphenyl *N*-ethyl-*N*-methylcarbamate,



D. 3-[(1*R*)-1-(dimethylamino)ethyl]phenyl *N*-ethyl-*N*-methylcarbamate,



E. 3-[(1*S*)-1-(methylamino)ethyl]phenyl *N*-ethyl-*N*-methylcarbamate,



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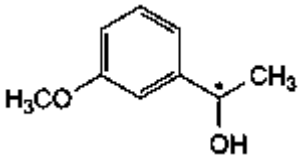
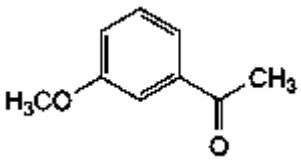
F. (1*S*)-1-(3-methoxyphenyl)-*N*,*N*-dimethylethanamine,



G. 1-(3-methoxyphenyl)ethan-1-ol,



H. 1-(3-methoxyphenyl)ethan-1-one.

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Rivastigmine Oral Solution

General Notices

Action and use

Cholinesterase inhibitor; treatment of dementia in Alzheimer's disease and Parkinson's disease.

DEFINITION

Rivastigmine Oral Solution contains Rivastigmine Hydrogen Tartrate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of rivastigmine, $C_{14}H_{22}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a volume of the oral solution containing the equivalent of 18 mg of rivastigmine with 25 mL of *methanol*. Add sufficient *methanol* to produce 50 mL and filter (a 0.45-µm Nylon filter is suitable).

(2) 0.058% w/v of *rivastigmine hydrogen tartrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *formic acid*, 5 volumes of *water*, 30 volumes of *methanol* and 70 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase. Prepare the solutions immediately before use and protect from light.

(1) Shake a volume of the oral solution containing the equivalent of 25 mg of rivastigmine with 15 mL and add sufficient mobile phase to produce 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra RP C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 217 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 3.5 times the retention time of rivastigmine.

MOBILE PHASE

28 volumes of *acetonitrile R1* and 72 volumes of 0.01M *sodium heptanesulfonate*, adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to rivastigmine (retention time about 7 minutes) are: impurity A, about 0.5; impurity B, about 0.7 and impurity C, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 7.0.

LIMITS

Identify any peak corresponding to impurity C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

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Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Shake a weighed quantity of the oral solution containing the equivalent of 10 mg of rivastigmine with 50 mL of mobile phase. Add sufficient mobile phase to produce 100 mL.

(2) 0.016% w/v of *rivastigmine hydrogen tartrate BPCRS*.

(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 7.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{14}H_{22}N_2O_2$, weight in volume, using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$

STORAGE

Rivastigmine Oral Solution should be protected from light. It should not be refrigerated or allowed to freeze.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Rivastigmine Hydrogen Tartrate.

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Rivastigmine Transdermal Patches

General Notices

Action and use

Cholinesterase inhibitor; treatment of dementia in Alzheimer's disease and Parkinson's disease.

DEFINITION

Rivastigmine Transdermal Patches contain Rivastigmine.

The transdermal patches comply with the requirements stated under Patches and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of rivastigmine.

Content of rivastigmine, $C_{14}H_{22}N_2O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Remove the release liner from an amount of patches containing 18 mg of Rivastigmine and dissolve the contents in 50 mL of *methanol*. Mix with the aid of ultrasound for 60 minutes, allow to cool and centrifuge at 3000 rpm for 10 minutes.

(2) 0.058% w/v of *rivastigmine hydrogen tartrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *formic acid*, 5 volumes of *water*, 30 volumes of *methanol* and 70 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Remove the release liners from the patches. Mix with the aid of ultrasound a quantity of whole patches with sufficient *tetrahydrofuran* to produce a solution containing 0.1% w/v of Rivastigmine, for about 60 minutes. Allow to cool, dilute 1 volume of the solution to 5 volumes and filter (a 0.45-µm PTFE filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra RP C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 217 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 3.5 times the retention time of rivastigmine.

MOBILE PHASE

28 volumes of *acetonitrile R1* and 72 volumes of 0.01M *sodium heptanesulfonate*, adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to rivastigmine (retention time about 7 minutes) are: impurity A, about 0.5; impurity B, about 0.7 and impurity C, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 7.0.

LIMITS

Identify any peak corresponding to impurity C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

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the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Comply with the requirements stated under uniformity of content, Appendix XII C3, Test C, with respect to the individual content of each dosage unit and using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Remove the release liner from one patch and dissolve the contents in sufficient *tetrahydrofuran* to produce a solution containing 0.1% w/v of Rivastigmine. Mix with the aid of ultrasound for 60 minutes. Allow to cool, dilute 1 volume to 10 volumes and filter (a 0.45-µm PTFE filter is suitable).

(2) 0.016% w/v of *rivastigmine hydrogen tartrate BPCRS*.

(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 7.0.

DETERMINATION OF CONTENT

Calculate the content of rivastigmine, $C_{14}H_{22}N_2O_2$, in each patch from the chromatograms obtained and using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of content.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Rivastigmine.

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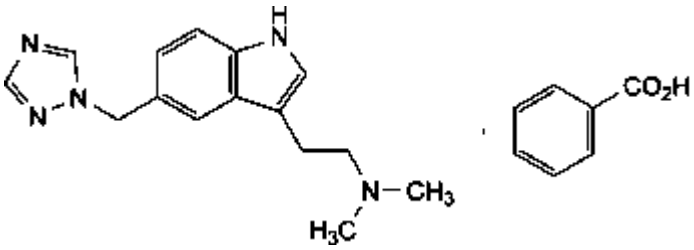
Rizatriptan Benzoate

General Notices

(Ph. Eur. monograph 2585)



$C_{22}H_{25}N_5O_2$ 391.5 *145202-66-0*

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migrane.

Preparations

Rizatriptan Orodispersible Tablets

Rizatriptan Tablets

Ph Eur

DEFINITION

N,*N*-Dimethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine benzoate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder or crystals.

Solubility

Soluble in water, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

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It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *rizatriptan benzoate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Examine the chromatograms obtained in the assay.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time and size to the 2 principal peaks in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Use silanised glass autosampler vials and freshly prepared solutions.*

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 50.0 mg of *rizatriptan benzoate CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *rizatriptan for system suitability CRS* (containing impurity C) in mobile phase A and dilute to 5.0 mL with mobile phase A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 20.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 160 mL of *acetonitrile R* and 840 mL of *water R*, add 1.0 mL of *trifluoroacetic acid R* and mix;

— *mobile phase B*: to 1000 mL of *acetonitrile R* add 1.0 mL of *trifluoroacetic acid R* and mix;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	100	0
8 - 17	100 → 70	0 → 30
17 - 20	70	30
20 - 20.1	70 → 100	30 → 0
20.1 - 23	100	0

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *rizatriptan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to rizatriptan (retention time = about 5 min): impurity C = about 1.3; benzoic acid = about 2.1.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to rizatriptan and impurity C.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *disregard limit*: the area of the peak due to rizatriptan in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard any peak due to benzoic acid.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

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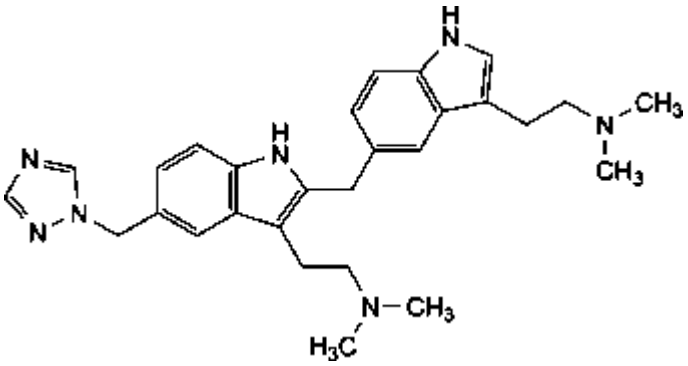
System suitability Reference solution (a):

— *symmetry factor*: maximum 3.5 for the peak due to rizatriptan.

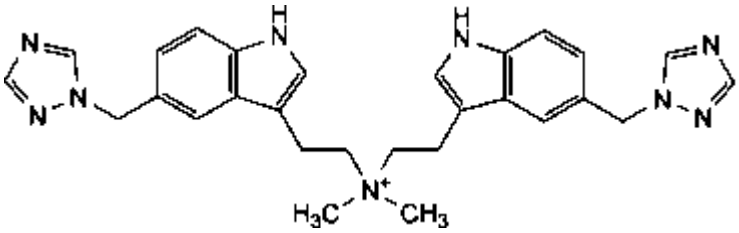
Calculate the percentage content of $C_{22}H_{25}N_5O_2$ from the declared content of *rizatriptan benzoate CRS*.

IMPURITIES

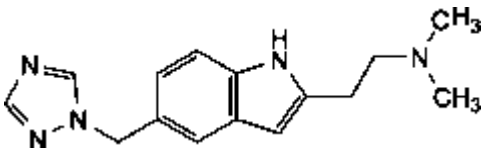
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I.



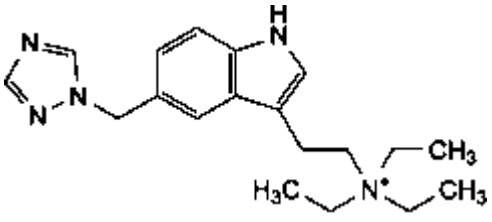
A. 2-[2-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]-*N*,*N*-dimethylethanamine,



B. *N*,*N*-dimethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]-*N*-[2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethyl]ethanaminium,



C. *N*,*N*-dimethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-2-yl]ethanamine,



D. *N*,*N*,*N*-triethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanaminium,

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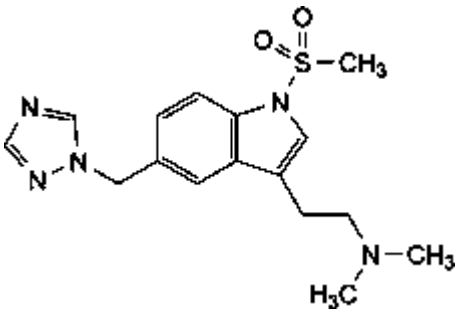
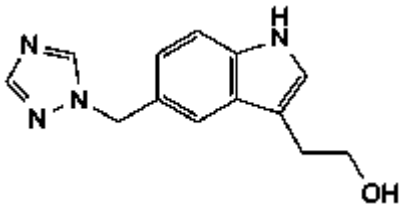
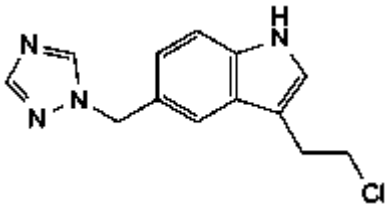


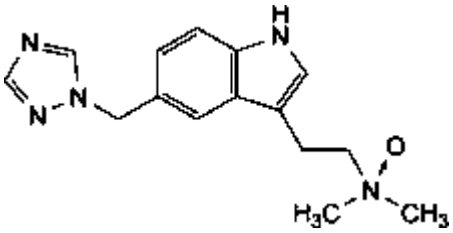
E. *N*,*N*-dimethyl-2-[1-(methylsulfonyl)-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine,



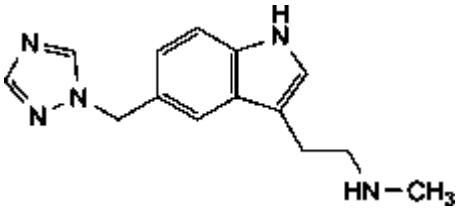
F. 2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanol,



G. 3-(2-chloroethyl)-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole,



H. *N*,*N*-dimethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine *N*-oxide,



I. *N*-methyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine.

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Rizatriptan Orodispersible Tablets

General Notices

Orodispersible Rizatriptan Tablets

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

DEFINITION

Rizatriptan Orodispersible Tablets contain Rizatriptan Benzoate in a suitable orodispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of rizatriptan, $C_{15}H_{19}N_5$

93.4 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol (30%)*.

(1) To a quantity of the powdered tablets containing the equivalent of 68.8 mg of rizatriptan add 7 mL, shake well, filter and dilute to 10 mL.

(2) 1.0% w/v *rizatriptan benzoate BPCRS*.

(3) 1.0% w/v *benzoic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

(f) Expose the plate to iodine vapour until maximum contrast between the spots is obtained and examine in daylight.

MOBILE PHASE

1 volume of 18M *ammonia*, 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) when examined under ultraviolet light corresponds in position to that in the chromatogram obtained with solution (3) (benzoic acid).

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The principal spot in the chromatogram obtained with solution (1) when exposed to iodine vapour corresponds in position to that in the chromatogram obtained with solution (2) (rizatriptan).

B. In the Assay, the principal peaks in the chromatogram obtained with solution (1) have the same retention time as those in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 5 minutes withdraw a 15 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with water if necessary to produce a solution expected to contain the equivalent of about 0.00055% w/v of rizatriptan, at the maximum at 278 nm, Appendix II B, using *water* in the reference cell.
(2) Measure the *absorbance* of a solution of 0.0008% w/v of *rizatriptan benzoate BPCRS* using water in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of rizatriptan $C_{15}H_{19}N_5$ in the medium from the absorbances obtained and using the declared content of $C_{15}H_{19}N_5$, in *rizatriptan benzoate BPCRS*.

LIMITS

The amount of rizatriptan released is not less than 80% (Q) of the stated amount.

Related substances

Prepare a solution containing 1 volume of *acetonitrile R1* and 9 volumes of 0.025M *potassium dihydrogen orthophosphate* (solution A).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 50 mg of rizatriptan add 60 mL of solvent A, mix with the aid of ultrasound, dilute to 100 mL and filter through a 0.4-µm PTFE filter. Dilute 1 volume of the filtrate to 10 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of the resulting solution to 5 volumes with solution A.
(3) Prepare impurity H as follows. To 5 mL of a solution containing 0.0075% w/v of *rizatriptan benzoate BPCRS* in solution A add 0.2 mL of *hydrogen peroxide solution (100 vol)*. Mix, heat in an oven at 60° for 30 minutes and allow to stand for 24 hours before use.
(4) Prepare impurity 1, if aspartame is present, as follows. To a 50-mL round-bottomed flask add 24 mg of *rizatriptan benzoate BPCRS*, 2 mL of *methanol* and 2 mL of *dimethyl carbonate* and mix well. Heat under a reflux condenser for 2 hours at 125°, cool and dilute 1 volume to 100 volumes with solution A. To 1 mL of the resulting solution add 20 µL of 10M *sodium hydroxide*, incubate at room temperature for 2 hours and neutralise to pH 7 with approximately 30 µL of *6M hydrochloric acid*.

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(5) 0.01% w/v of *benzoic acid* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 µm) (YMC Basic is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for twice the retention time of rizatriptan.

MOBILE PHASE

16 volumes of *acetonitrile R1* and 84 volumes of a phosphate buffer solution prepared by weighing 3.4 g of *potassium dihydrogen orthophosphate* and 2.0 g of *sodium hexanesulfonate* into a 1000 mL flask, dissolve in 900 mL of *water*, adjust the pH to 7.5 with 19M *sodium hydroxide* and dilute to volume with *water*.

SYSTEM SUITABILITY

The relative retention times with reference to rizatriptan (retention time about 16 minutes) are: benzoic acid, about 0.2; impurity H, about 0.3; impurity I, about 0.8 and impurity 1, about 0.9.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between benzoic acid and impurity H is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to rizatriptan impurity H is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to rizatriptan impurity I is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak obtained with solution (2) (2%).

Disregard any peaks due to benzoic acid and those with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.1%).

For formulations containing aspartame

SYSTEM SUITABILITY

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The test is not valid unless in the chromatogram obtained with solution (4) the *resolution* between impurity 1 and rizatripan is at least 3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to rizatriptan impurity 1 is not greater than 5.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.1%).

ASSAY

Prepare a solution containing 1 volume of *acetonitrile R1* and 9 volumes of 0.025M *potassium dihydrogen orthophosphate* (solution A).

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 50 mg of rizatriptan add 60 mL of solvent A, mix with the aid of ultrasound, dilute to 100 mL and filter through a 0.4-µm PTFE filter. Dilute 1 volume of the filtrate to 10 volumes with solution A.
(2) 0.0075% w/v of *rizatriptan benzoate BPCRS* in solution A.
(3) Prepare impurity H as follows. Add 0.2 mL of *hydrogen peroxide solution (100 vol)* to 5 mL of solution (1). Mix, heat in an oven at 60° for 30 minutes and allow to stand for 24 hours before use.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3) the *resolution* between benzoic acid and impurity H is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{19}N_5$ in the tablets using the declared content of $C_{15}H_{19}N_5$ in *rizatriptan benzoate BPCRS*.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of rizatriptan.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, H and I listed under Rizatriptan Benzoate and the following:

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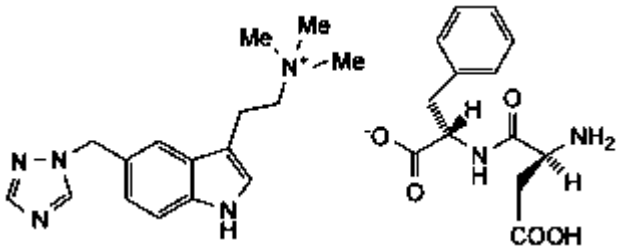

1. *N,N,N*-trimethyl-2-{[(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-indol-3-yl}ethanaminium L-aspartyl-L-phenylalaninate.

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Rizatriptan Tablets

General Notices

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

DEFINITION

Rizatriptan Tablets contain Rizatriptan Benzoate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of rizatriptan, $C_{15}H_{19}N_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Add 10 mL of *methanol* to a quantity of powdered tablets containing the equivalent of 50 mg of rizatriptan, mix with the aid of ultrasound for 5 minutes, filter through a 0.4-µm PTFE filter, evaporate the filtrate and dry under reduced pressure for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of rizatriptan benzoate (*RS 474*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 15 minutes withdraw a 15-mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with *water*, if necessary, to produce a solution expected to contain the equivalent of about 0.0004% w/v of rizatriptan at the maximum at 226 nm, Appendix II B, using *water* in the reference cell.

(2) Measure the *absorbance* of a solution of 0.00058% w/v of *rizatriptan benzoate BPCRS* using *water* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of rizatriptan $C_{15}H_{19}N_5$ in the medium from the absorbances obtained and using the declared content of $C_{15}H_{19}N_5$ in *rizatriptan benzoate BPCRS*.

LIMITS

The amount of rizatriptan released is not less than 80% (Q) of the stated amount.

Related substances

Prepare a solution containing 1 volume of *acetonitrile R1* and 4 volumes of 0.05M *ammonium acetate* (solution A).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 40 mg of rizatriptan add 60 mL of solution A, mix with the aid of ultrasound, dilute to 100 mL with solution A and filter through a 0.4-µm PTFE filter. Dilute 1 volume of the filtrate to 10 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of the resulting solution to 5 volumes with solution A.
(3) To 5 mL of a solution containing 0.0058% w/v of *rizatriptan benzoate BPCRS* in solution A add 0.2 mL of *hydrogen peroxide solution (100 vol)*. Mix, heat in an oven at 60° for 30 minutes and allow to stand for 24 hours before use (preparation of impurity H).
(4) 0.005% w/v of *benzoic acid* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable), fitted with a stainless steel guard column (2 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Sentry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 226 nm.
(f) Inject 10 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for twice the retention time of rizatriptan.

MOBILE PHASE

15 volumes of *acetonitrile R1* and 85 volumes of a phosphate buffer solution prepared as follows: dissolve 1.7 g of *potassium dihydrogen orthophosphate* and 0.94 g of *sodium hexanesulfonate* in 900 mL of *water*, adjust the pH to 6.8 with 19M *sodium hydroxide* and dilute to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to rizatriptan (retention time about 10 minutes) are: benzoic acid, about 0.3 and impurity H, about 0.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between benzoic acid and impurity H is at least 3.0.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

Disregard any peak due to benzoic acid and with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Prepare a solution containing 1 volume of *acetonitrile R1* and 4 volumes of 0.05M *ammonium acetate* (Solution A).

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 40 mg of rizatriptan add 60 mL of solvent A, mix with the aid of ultrasound, dilute to 100 mL with solution A and filter through a 0.4-µm PTFE filter. Dilute 1 volume of the filtrate to 10 volumes.
(2) 0.0058% w/v of *rizatriptan benzoate BPCRS* in solution A.
(3) Prepare impurity H as follows. Add 0.2 mL of *hydrogen peroxide solution (100 vol)* to 5 mL of solution (2). Mix, heat in an oven at 60° for 30 minutes and allow to stand for 24 hours before use.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in solution (3) the *resolution* between the peaks due to benzoic acid and impurity H is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{19}N_5$ in the tablets using the declared content of $C_{15}H_{19}N_5$ in *rizatriptan benzoate BPCRS*.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of rizatriptan.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity H listed under Rizatriptan Benzoate.

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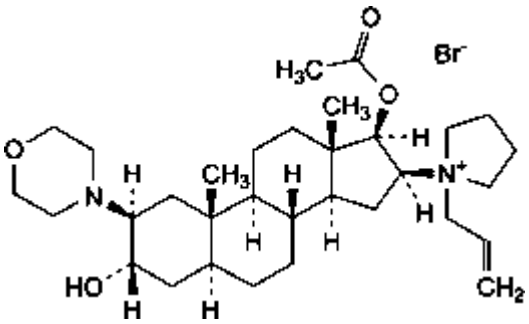
Rocuronium Bromide

General Notices

(Ph. Eur. monograph 1764)



$C_{32}H_{53}BrN_2O_4$ 610 *119302-91-9*

Action and use

Non-depolarizing neuromuscular blocker.

Ph Eur

DEFINITION

1-[17β-Acetoxy-3α-hydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium bromide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Almost white or pale yellow, slightly hygroscopic powder.

Solubility

Freely soluble in water, very soluble in methylene chloride, freely soluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *rocuronium bromide CRS*.

B. Solution S (see Tests) gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

+ 28.5 to + 32.0 (anhydrous substance).

Dissolve 0.250 g in a 5.15 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

pH (*2.2.3*)

8.9 to 9.5 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *water R*, *acetonitrile R1* (10:90 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *rocuronium for peak identification CRS* (containing impurities A, B, C, F, G and H) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 10 volumes of a 4.53 g/L solution of *tetramethylammonium hydroxide R* adjusted to pH 7.4 with *phosphoric acid R* and 90 volumes of *acetonitrile R1*.

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Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 5 µL.

Run time 2.5 times the retention time of rocuronium.

Identification of impurities Use the chromatogram supplied with *rocuronium for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, F, G and H.

Relative retention With reference to rocuronium (retention time = about 9 min): impurity A = about 0.2; impurity G = about 0.4; impurity F = about 0.75; impurity B = about 0.80; impurity H = about 0.95; impurity C = about 1.2.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity H and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rocuronium.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.5; impurity F = 1.3; impurity G = 0.4; impurity H = 0.4;

— *impurities A, B, C*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities F, G, H*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak eluting before impurity A.

Chlorides

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 0.644 g of *sodium bromide R* and 0.824 g of *sodium chloride R* in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *water R*.

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Reference solution (b) Dissolve 0.824 g of *sodium chloride R* in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *water R*. Dilute 2.0 mL of this solution to 50.0 mL with *water R*.

Blank solution *water R*.

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4.0 mm;

— *stationary phase*: *anion-exchange resin R* (13 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *anion-exchange resin R* (13 µm).

Mobile phase A solution containing 0.063 g/L of *sodium hydrogen carbonate R* and 0.212 g/L of *anhydrous sodium carbonate R*.

Flow rate 2.0 mL/min.

Detection Conductivity detector set at 100 µS/V and maintained at 30 °C.

Use a self-regenerating anion suppressor.

Injection 25 µL.

Retention times Chloride = about 1.7 min; bromide = about 2.8 min.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to chloride and bromide.

Limit:

— *chlorides*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

2-Propanol (*2.4.24, System A*)

Maximum 1.0 per cent.

Water (*2.5.12*)

Maximum 4.5 per cent, determined on 0.400 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.400 g in 40 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 60.97 mg of $C_{32}H_{53}BrN_2O_4$.

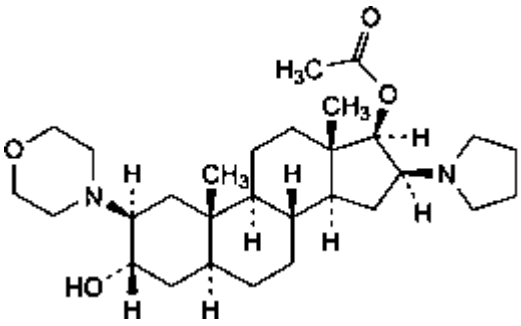
STORAGE

In an airtight container, protected from light, at a temperature below -15 °C.

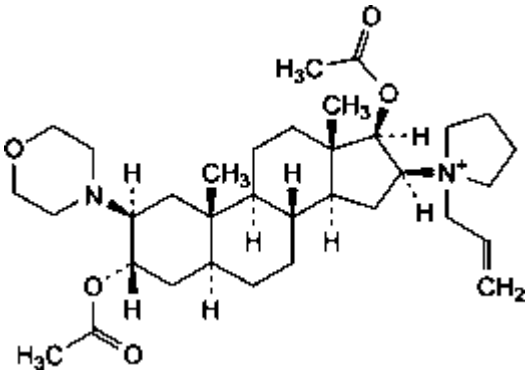
IMPURITIES

Specified impurities *A, B, C, F, G, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E.*



A. 3α-hydroxy-2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-17β-yl acetate,



B. 1-[3α,17β-diacetoxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,

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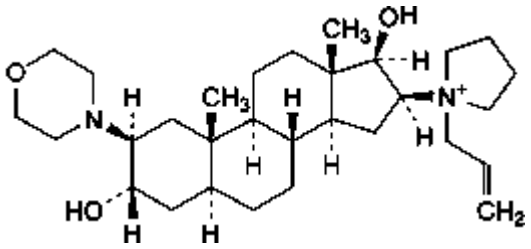
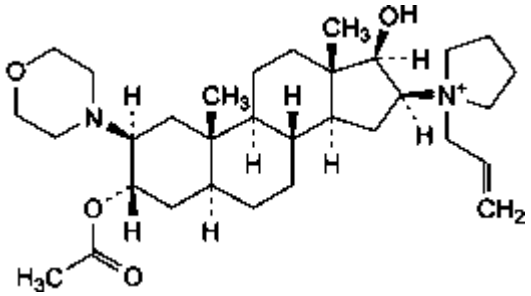
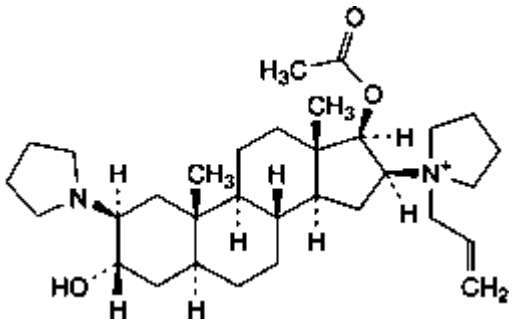


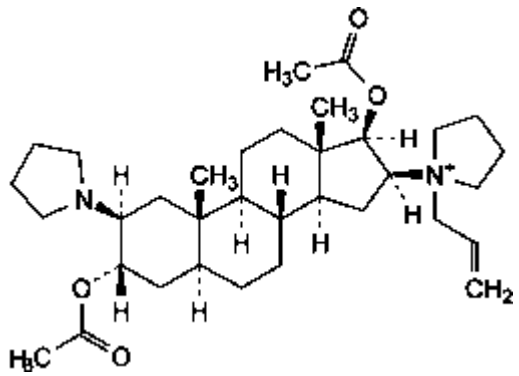
C. 1-[3α,17β-dihydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,



D. 1-[3α-acetoxy-17β-hydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,



E. 1-[17β-acetoxy-3α-hydroxy-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,



F. 1-[3α,17β-acetoxy-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium,

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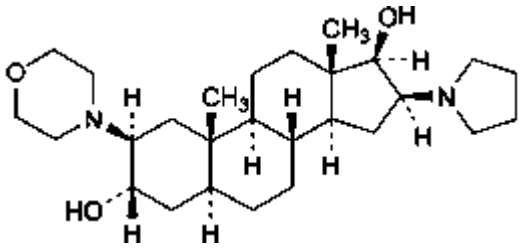
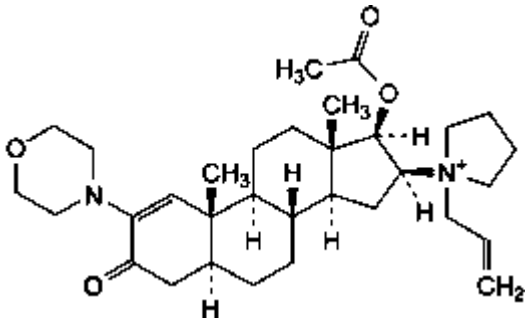


G. 2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstane-3α,17β-diol,



H. 1-[17β-acetoxy-2-(morpholin-4-yl)-3-oxo-5α-androst-1-en-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

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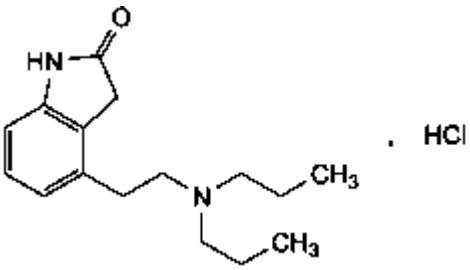
Ropinirole Hydrochloride

General Notices

(Ph. Eur. monograph 2604)



$C_{16}H_{25}ClN_2O$ 296.8 *91374-20-8*

Action and use

Dopamine receptor agonist.

Ph Eur

DEFINITION

4-[2-(Dipropylamino)ethyl]-1,3-dihydro-2*H*-indol-2-one hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Freely soluble in water and in methanol, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ropinirole hydrochloride CRS*.

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B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve, using sonication, 50.0 mg of the substance to be examined in 4 mL of mobile phase B and dilute to 25.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with mobile phase A.

Reference solution (a) Dissolve, using sonication, 7.5 mg of *ropinirole impurity A CRS* and 5.0 mg of the substance to be examined in 16 mL of mobile phase B and dilute to 100.0 mL with mobile phase A.

Reference solution (b) To 1.0 mL of reference solution (a) add 4 mL of mobile phase B and dilute to 25.0 mL with mobile phase A.

Reference solution (c) Dissolve, using sonication, 50.0 mg of *ropinirole hydrochloride CRS* in 4 mL of mobile phase B and dilute to 25.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 20.0 mL with mobile phase A.

Reference solution (d) Dissolve 5.0 mg of *ropinirole for peak identification 1 CRS* (containing impurity D) in mobile phase A and dilute to 5.0 mL with mobile phase A.

Reference solution (e) Dissolve 5.0 mg of *ropinirole for peak identification 2 CRS* (containing impurities G and H) in mobile phase A and dilute to 5.0 mL with mobile phase A.

Reference solution (f) Dissolve 5.0 mg of *ropinirole for peak identification 3 CRS* (containing impurity E) in mobile phase A and dilute to 5.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.85 g of *ammonium acetate R* in 950 mL of *water for chromatography R*, adjust to pH 2.5 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *methanol R*, *acetonitrile R1* (30:70 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	92	8
15 - 30	92 → 80	8 → 20
30 - 50	80 → 60	20 → 40
50 - 75	60	40

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b), (d), (e) and (f).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *ropinirole for peak identification 1 CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity D; use the chromatogram supplied with *ropinirole for peak identification 2 CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities G and H; use the chromatogram supplied with *ropinirole for peak identification 3 CRS* and the chromatogram obtained with reference solution (f) to identify the peak due to impurity E.

Relative retention With reference to ropinirole (retention time = about 30 min): impurity D = about 0.5; impurity A = about 0.9; impurity E = about 1.1; impurity H = about 1.2; impurity G = about 1.4.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to impurity A and ropinirole in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 60 for the peak due to ropinirole in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity G = 2.7; impurity H = 0.5;

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurities other than A, use the concentration of ropinirole hydrochloride in reference solution (b).

Limits:

— *impurities A, D, E, G, H*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

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— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (19:81 *V/V*).

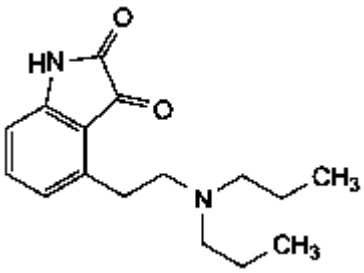
Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{16}H_{25}ClN_2O$ taking into account the assigned content of *ropinirole hydrochloride CRS*.

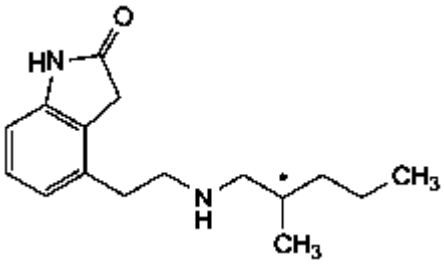
IMPURITIES

Specified impurities *A, D, E, G, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, F.*



A. 4-[2-(dipropylamino)ethyl]-1*H*-indole-2,3-dione,



B. 4-[2-[(2-methylpentyl)amino]ethyl]-1,3-dihydro-2*H*-indol-2-one,

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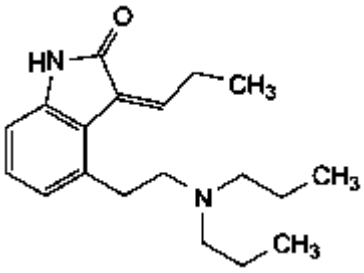
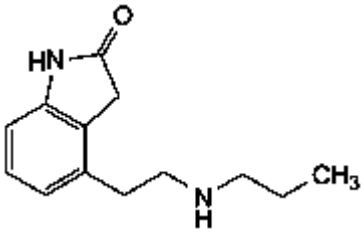
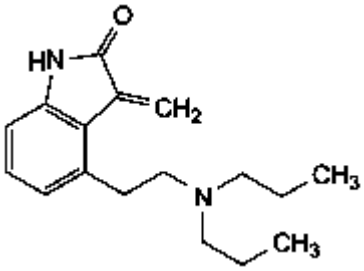


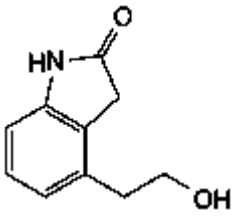
C. (3*Z*)-4-[2-(dipropylamino)ethyl]-3-propylidene-1,3-dihydro-2*H*-indol-2-one,



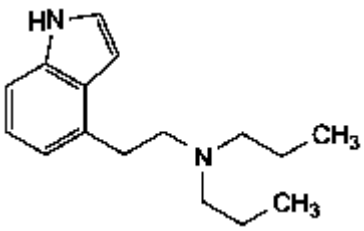
D. 4-[2-(propylamino)ethyl]-1,3-dihydro-2*H*-indol-2-one,



E. 4-[2-(dipropylamino)ethyl]-3-methylidene-1,3-dihydro-2*H*-indol-2-one,



F. 4-(2-hydroxyethyl)-1,3-dihydro-2*H*-indol-2-one,



G. 4-[2-(dipropylamino)ethyl]-1*H*-indole,

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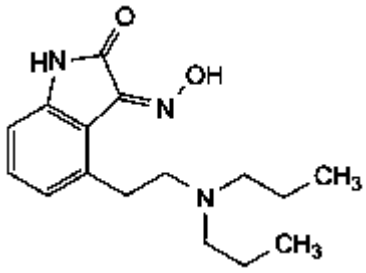

H. (3*Z*)-4-[2-(dipropylamino)ethyl]-3-(hydroxyimino)-1,3-dihydro-2*H*-indol-2-one.

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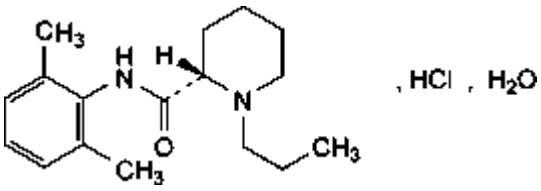
Ropivacaine Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 2335)



$C_{17}H_{27}ClN_2O,H_2O$ 328.9 *132112-35-7*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

(-)-(2*S*)-*N*-(2,6-Dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water and in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

Carry out either tests A, C, D or tests A, B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ropivacaine hydrochloride monohydrate CRS*.

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B. Specific optical rotation (2.2.7): -74.0 to -64.0 (anhydrous substance).

Mix 2 mL of a 200 g/L solution of *sodium hydroxide R* and 30 mL of *water R* and dilute to 100.0 mL with *ethanol (96 per cent) R* (solution A).

Dissolve 0.500 g of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

C. It gives reaction (a) of chlorides (2.3.1).

D. Enantiomeric purity (see Tests).

TESTS

Solution S

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1).

pH (2.2.3)

4.5 to 6.0 for solution S.

Absorbance (2.2.25)

Maximum 0.030 at 405 nm and maximum 0.025 at 436 nm, determined on solution S prepared immediately before use, with a path length of 5 cm and using *water R* as the compensation liquid.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 55 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *bupivacaine hydrochloride CRS* (impurity A) in the mobile phase and dilute to 5 mL with the mobile phase. Dilute 1 mL of this solution to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase Mix 1.3 mL of a 138 g/L solution of *sodium dihydrogen phosphate R* and 32.5 mL of an 89 g/L solution of *disodium hydrogen phosphate dodecahydrate R* and dilute to 1000 mL with *water R*; mix equal volumes of this solution (pH 8.0) and *acetonitrile R*.

Flow rate 1.0 mL/min.

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Injection 20 µL.

Detection Spectrophotometer at 240 nm.

Run time 2.5 times the retention time of ropivacaine.

Relative retention With reference to ropivacaine (retention time = about 6 min): impurity A = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 6.0 between the peaks due to ropivacaine and impurity A.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity H

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 13.0 mg of *2,6-dimethylaniline hydrochloride R* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Retention time Impurity H = about 2-3 min.

Limit:

— *impurity H*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (10 ppm).

Enantiomeric purity

Capillary electrophoresis (2.2.47): use the normalisation procedure.

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 25 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with *water R*.

Reference solution (b) Dissolve 1.5 mg of the substance to be examined and 1.5 mg of *ropivacaine impurity G CRS* in *water R* and dilute to 100 mL with the same solvent.

Capillary:

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— *material*: fused silica;

— *size*: effective length = about 72 cm, total length = 80 cm, Ø = 50 µm.

Temperature 30 °C.

CZE buffer Prepare a 13.3 g/L solution of *dimethyl-β-cyclodextrin R* in an 11.5 g/L solution of *phosphoric acid R* previously adjusted to pH 3.0 with *triethanolamine R*. The CZE buffer is prepared and filtered through a membrane filter (nominal pore size 0.45 µm) immediately before use.

Detection Spectrophotometer at 206 nm.

Preconditioning of the capillary Rinse the capillary at 100 kPa with *water R* for 1 min, with *0.1 M sodium hydroxide* for 10 min and with *water R* for 3 min. If the capillary is new or dry, increase the sodium hydroxide rinse to 30 min.

Between-run rinsing Rinse the capillary at 100 kPa with *water R* for 1 min, with *0.1 M sodium hydroxide* for 4 min, with *water R* for 1 min and with the CZE buffer for 4 min.

Injection Under pressure (5 kPa) for 5 s.

Migration Apply a field strength of 375 V/cm with an initial ramp of 500 V/s and a positive polarity corresponding to a current of 40-45 µA.

Run time 30 min.

System suitability:

— *resolution*: minimum 3.7 between the peaks due to impurity G (1st peak) and (*S*)-ropivacaine in the electropherogram obtained with reference solution (b); if necessary, increase the dimethyl-β-cyclodextrin concentration in the CZE buffer or vary the pH between 2.9 and 3.1 or lower the temperature;

— *signal-to-noise ratio*: minimum 10 for the principal peak in the electropherogram obtained with reference solution (a).

Limit:

— *impurity G*: maximum 0.5 per cent.

Water (*2.5.12*)

5.0 per cent to 6.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 10 mL of *water R* and 40 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

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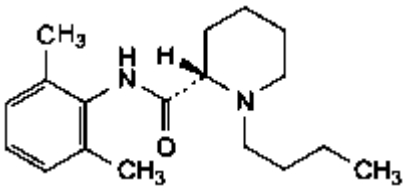
1 mL of *0.1 M sodium hydroxide* is equivalent to 31.09 mg of $C_{17}H_{27}ClN_2O$.

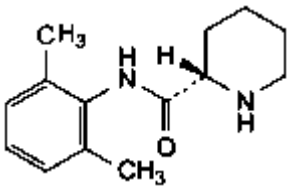
IMPURITIES

Specified impurities *A, G, H.*

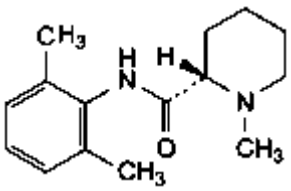
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F.*



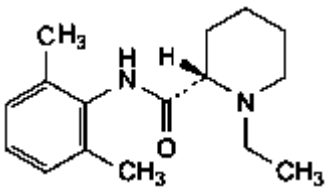
A. (*S*)-bupivacaine,



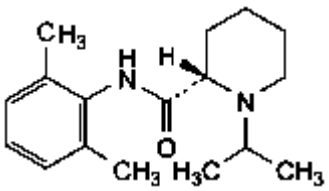
B. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide,



C. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)-1-methylpiperidine-2-carboxamide ((*S*)-mepivacaine),



D. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)-1-ethylpiperidine-2-carboxamide,



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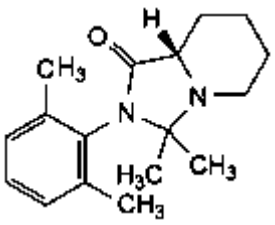
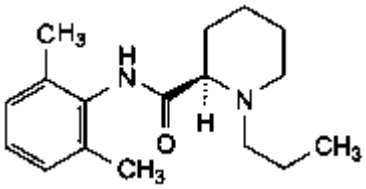
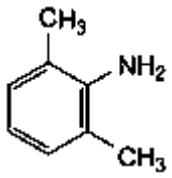
E. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)-1(1-methylethyl)piperidine-2-carboxamide,



F. (8a*S*)-2-(2,6-dimethylphenyl)-3,3-dimethylhexahydroimidazo[1,5-*a*]pyridin-1(5*H*)-one (acetone adduct),



G. (+)-(2*R*)-*N*-(2,6-dimethylphenyl)-1-propylpiperidine-2-carboxamide ((*R*)-ropivacaine),



H. 2,6-dimethylaniline.

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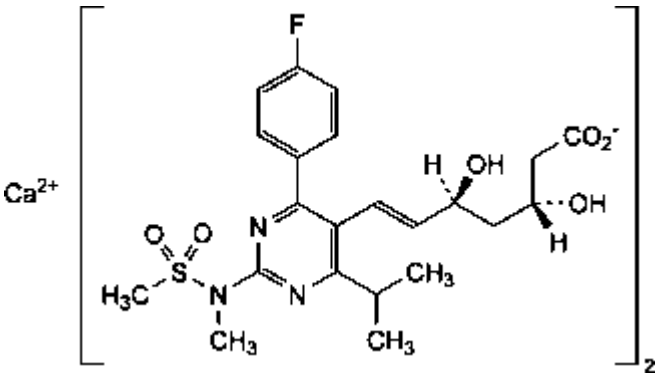
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Rosuvastatin Calcium

General Notices

(Ph. Eur. monograph 2631)



$C_{44}H_{54}CaF_2N_6O_{12}S_2$ 1001 *147098-20-2*

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

Preparation

Rosuvastatin Tablets

Ph Eur

DEFINITION

Calcium bis[(3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate].

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

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Slightly soluble in water, freely soluble in methylene chloride, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *rosuvastatin calcium CRS*.

B. Enantiomeric purity (see Tests).

C. It gives reaction (b) of calcium (2.3.1).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Solvent mixture *acetonitrile R*, *water R* (25:75 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in 6 mL of *acetonitrile R* and dilute to 25.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *rosuvastatin impurity G CRS* in 1 mL of the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 35 °C.

Mobile phase *acetonitrile for chromatography R*, 0.1 per cent *V/V* solution of *trifluoroacetic acid R* (25:75 *V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 10 µL.

Run time 2.6 times the retention time of rosuvastatin.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to rosuvastatin (retention time = about 29 min): impurity G = about 0.9.

System suitability Reference solution (b):

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— *resolution*: minimum 1.5 between the peaks due to impurity G and rosuvastatin.

Calculation of percentage content:

— for impurity G, use the concentration of rosuvastatin calcium in reference solution (a).

Limit:

— *impurity G*: maximum 0.15 per cent.

Impurity L

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 50 mL of acetonitrile R and dilute to 100.0 mL with water R.

Reference solution (a) Dissolve 5 mg of rosuvastatin for impurity L identification CRS in 10 mL of acetonitrile R and dilute to 20 mL with water R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped solid core octylsilyl silica gel for chromatography R (2.7 µm).

Mobile phase To 650 mL of a 0.02 per cent *V/V* solution of trifluoroacetic acid R, add 350 mL of a mixture of 1 volume of ethanol (96 per cent) R and 2 volumes of acetonitrile for chromatography R.

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 243 nm.

Injection 10 µL.

Run time 3 times the retention time of rosuvastatin.

Identification of impurities Use the chromatogram supplied with rosuvastatin for impurity L identification CRS and the chromatogram obtained with reference solution (a) to identify the peak due to impurity L.

Relative retention With reference to rosuvastatin (retention time = about 22 min): impurity L = about 1.1.

System suitability Reference solution (a):

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— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity L and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rosuvastatin.

Calculation of percentage content:

— *correction factor*: multiply the peak area of impurity L by 1.8;

— for impurity L, use the concentration of rosuvastatin calcium in reference solution (b).

Limit:

— *impurity L*: maximum 0.15 per cent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use*.

Solvent mixture acetonitrile R, water R (25:75 *V/V*).

Test solution Dissolve 35.0 mg of the substance to be examined in 12 mL of acetonitrile R and dilute to 50.0 mL with water R.

Reference solution (a) Dissolve 35.0 mg of rosuvastatin calcium CRS in 12 mL of acetonitrile R and dilute to 50.0 mL with water R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 7 mg of rosuvastatin for system suitability CRS (containing impurities A, B and C) in 2.5 mL of acetonitrile R and dilute to 10 mL with water R.

Reference solution (d) Dissolve the contents of a vial of rosuvastatin impurity mixture CRS (impurities D and K) in 1 mL of the solvent mixture.

Reference solution (e) Dissolve 7 mg of rosuvastatin for peak identification CRS (containing impurity M) in 2.5 mL of acetonitrile R and dilute to 10 mL with water R.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1 per cent *V/V* solution of trifluoroacetic acid R, acetonitrile for chromatography R, water for chromatography R (1:29:70 *V/V/V*);

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— *mobile phase B*: 1 per cent *V/V* solution of *trifluoroacetic acid R*, *water for chromatography R*, *acetonitrile for chromatography R* (1:24:75 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100	0
30 - 50	100 → 60	0 → 40
50 - 60	60 → 0	40 → 100
60 - 70	0	100

Flow rate 0.75 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 10 µL of the test solution and reference solutions (b), (c), (d) and (e).

Identification of impurities Use the chromatogram supplied with *rosuvastatin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C; use the chromatogram supplied with *rosuvastatin impurity mixture CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities D and K; use the chromatogram supplied with *rosuvastatin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peak due to impurity M.

Relative retention With reference to rosuvastatin (retention time = about 25 min): impurity M = about 0.8; impurity A = about 0.9; impurity B = about 1.1; impurity C = about 1.5; impurity D = about 1.9; impurity K = about 2.0.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to rosuvastatin and impurity B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 1.4;

— for each impurity, use the concentration of rosuvastatin calcium in reference solution (b).

Limits:

— *impurity C*: maximum 0.8 per cent;

— *impurity B*: maximum 0.5 per cent;

— *impurity A*: maximum 0.2 per cent;

— *impurities D, K, M*: for each impurity, maximum 0.15 per cent;

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— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.2 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 6.1 per cent, determined on 0.100 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{44}H_{54}CaF_2N_6O_{12}S_2$ taking into account the assigned content of *rosuvastatin calcium CRS*.

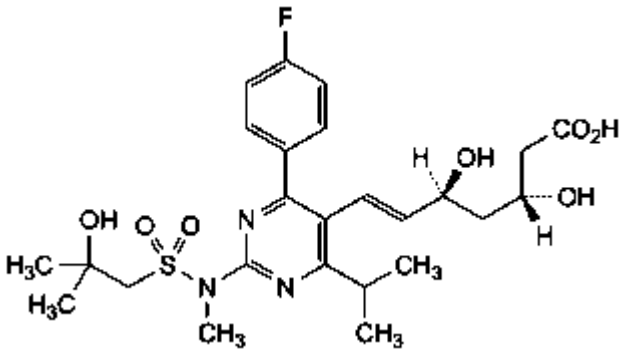
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A, B, C, D, G, K, L, M.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, J, N.*



A. (3*R*,5*S*,6*E*)-7-[2-(2,*N*-dimethyl-2-hydroxypropane-1-sulfonamido)-4-(4-fluorophenyl)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,

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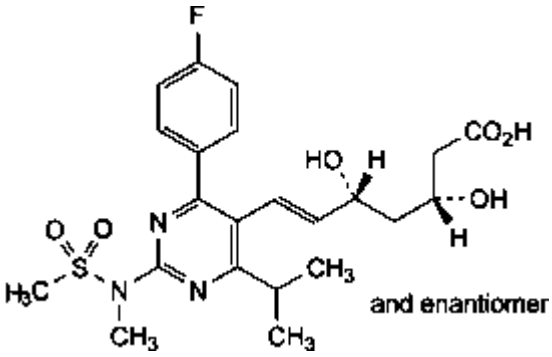
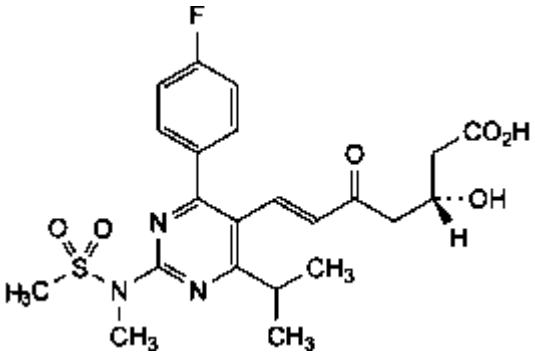
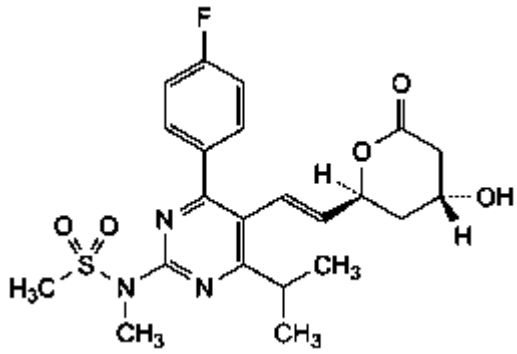


B. (3*RS*,5*RS*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,



C. (3*R*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3-hydroxy-5-oxohept-6-enoic acid,



D. *N*-[4-(4-fluorophenyl)-5-[(1*E*)-2-[(2*S*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethen-1-yl]-6-(propan-2-yl)pyrimidin-2-yl]-*N*-methylmethanesulfonamide,

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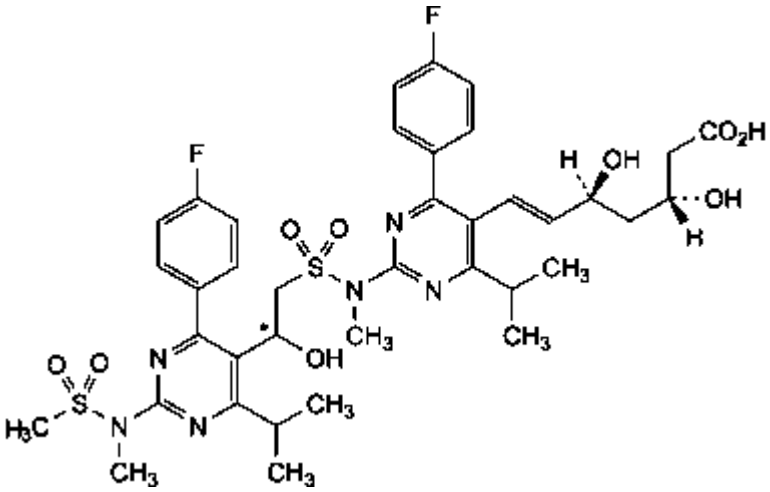
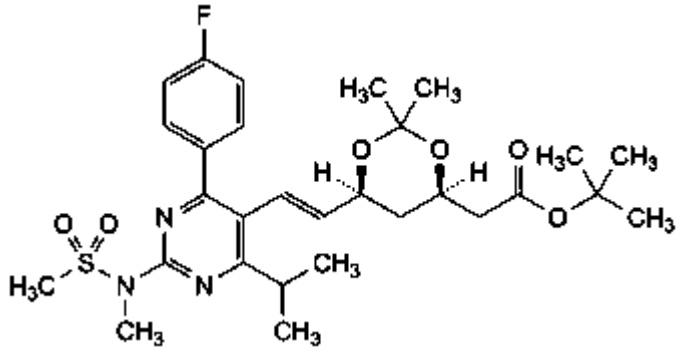
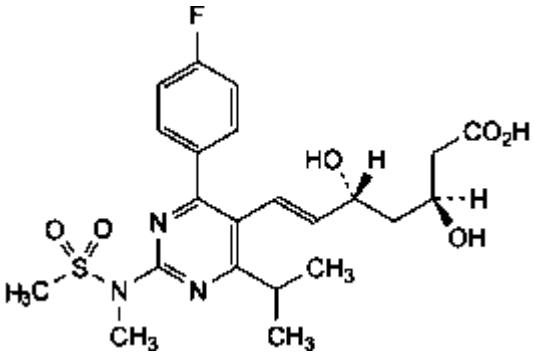


E. (3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-[(2Ξ)-2-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-2-hydroxy-*N*-methylethane-1-sulfonamido]-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,



F. *tert*-butyl[(4*R*,6*S*)-6-[(1*E*)-2-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]ethen-1-yl]-2,2-dimethyl-1,3-dioxan-4-yl]acetate,



G. (3*S*,5*R*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,

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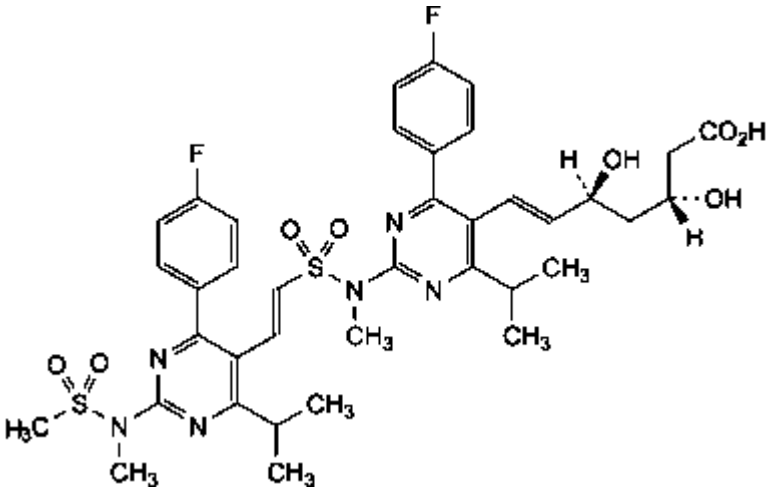
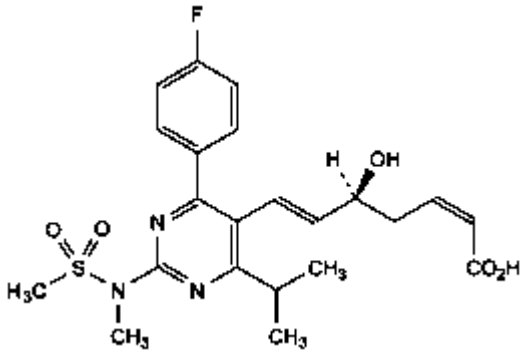
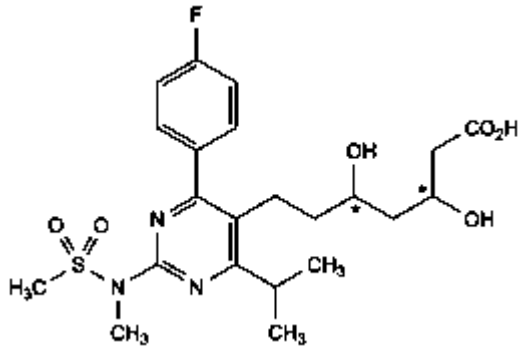


J. (3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-[(1*E*)-2-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-*N*-methylethene-1-sulfonamido]-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,



K. (2*Z*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-5-hydroxyhepta-2,6-dienoic acid,



L. (3Ξ,5Ξ)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyheptanoic acid,

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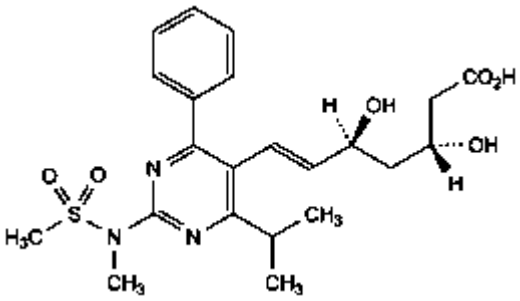
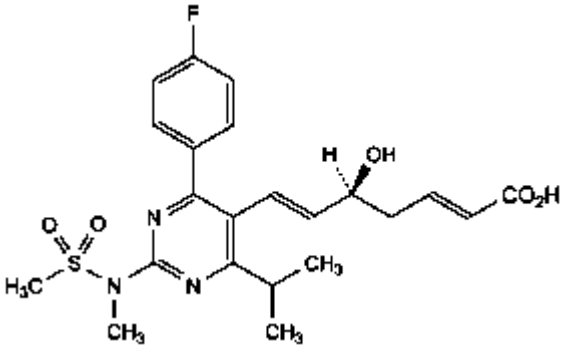


M. (3*R*,5*S*,6*E*)-7-[2-(*N*-methylmethanesulfonamido)-4-phenyl-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,



N. (2*E*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-5-hydroxyhepta-2,6-dienoic acid.

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Rosuvastatin Tablets

General Notices

(Ph Eur. monograph 3008)

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

Ph Eur

DEFINITION

Tablets containing *Rosuvastatin calcium (2631)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

93.0 per cent to 105.0 per cent of the content of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R*, *water R* (25:75 *V/V*).

Test solution To an appropriate number of tablets (at least 6) add at least 50 mL of *water R* and shake vigorously until the tablets have disintegrated completely. Add a suitable volume of *acetonitrile R* and again shake vigorously. Add a suitable volume of *water R* to obtain a

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ratio of acetonitrile to water of 25:75 *V/V*. Filter through a poly(vinylidene difluoride) filter and dilute with the solvent mixture, if necessary, to obtain a concentration of rosuvastatin calcium of 1 mg/mL.

Reference solution (a) To 25.0 mg of *rosuvastatin calcium CRS* add 25 mL of *water R* and allow to stand for at least 10 min. Sonicate for about 30 min until dissolved, shaking every 10 min. Add 12.5 mL of *acetonitrile R*, mix well and dilute to 50.0 mL with *water R*. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dissolve 7 mg of *rosuvastatin for system suitability CRS* (containing impurities A, B and C) in 2.5 mL of *acetonitrile R* and dilute to 10 mL with *water R*.

Reference solution (c) Dissolve the contents of a vial of *rosuvastatin impurity mixture CRS* (containing impurity D) in 1 mL of the solvent mixture.

Reference solution (d) Dissolve 2 mg of *rosuvastatin ethyl ester R* (impurity FP-A) in 20 mL of the solvent mixture. Dilute 1 mL of the solution to 100 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1 per cent *V/V* solution of *trifluoroacetic acid R*, *acetonitrile for chromatography R*, *water for chromatography R* (1:31:68 *V/V/V*);

— *mobile phase B*: 1 per cent *V/V* solution of *trifluoroacetic acid R*, *water for chromatography R*, *acetonitrile for chromatography R* (1:37:66 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 26	100	0
26 - 36	100 → 20	0 → 80
36 - 46	20	80

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 10 µL.

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Identification of impurities Use the chromatogram supplied with *rosuvastatin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C; use the chromatogram supplied with *rosuvastatin impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (d) to identify impurity FP-A.

Relative retention With reference to rosuvastatin (retention time = about 11 min): impurity A = about 0.9; impurity B = about 1.1; impurity C = about 1.7; impurity D = about 2.2; impurity FP-A = about 3.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rosuvastatin.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 1.4;

— for each impurity, use the concentration of rosuvastatin calcium in reference solution (a).

Limits:

— *impurities C, D*: for each impurity, maximum 1.5 per cent;

— *impurity FP-A*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 2.5 per cent;

— *reporting threshold*: 0.1 per cent; disregard the peaks due to impurities A and B.

Dissolution[1] (*2.9.3, Apparatus 2*). *Carry out the test protected from light.*

Dissolution medium (0.05 M citrate buffer solution pH 6.6) Dissolve 147.0 g of *sodium citrate R* in 2 L of *water R*, add 3.3 g of *anhydrous citric acid R* and dilute to 10 L with the same solvent. If necessary, adjust to pH 6.6 ± 0.05 with *sodium citrate R* or *anhydrous citric acid R*. Use 900 mL of the medium.

Rotation speed 50 r/min.

Time 30 min.

Analysis Liquid chromatography (*2.2.29*).

Test solution The samples withdrawn from the dissolution vessel and filtered, using a poly(vinylidene difluoride) filter.

Reference solution To 25.0 mg of *rosuvastatin calcium CRS* add 25 mL of *water R* and allow to stand for at least 10 min. Sonicate for about 30 min until dissolved, shaking every 10 min. Add 12.5 mL of *acetonitrile R*, mix well and dilute to 50.0 mL with *water R*. Dilute a

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suitable volume of the solution with the dissolution medium to obtain a concentration of rosuvastatin corresponding to the theoretical concentration of rosuvastatin in the test solution, based on the labelled content of the tablets.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *phosphoric acid R*, *acetonitrile for chromatography R*, *water for chromatography R* (0.1:40:60 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 20 µL.

Run time 5 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the amount of dissolved rosuvastatin ($C_{22}H_{28}FN_3O_6S$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *rosuvastatin calcium CRS* and applying a conversion factor of 0.96.

Acceptance criterion:

— *Q* = 75 per cent after 30 min.

ASSAY

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture *acetonitrile R*, *water R* (25:75 *V/V*).

Test solution To an appropriate number of tablets (at least 6) add at least 50 mL of *water R* and shake vigorously until the tablets have disintegrated completely. Add a suitable volume of *acetonitrile R* and again shake vigorously. Add a suitable volume of *water R* to obtain a ratio of acetonitrile to water of 25:75 *V/V*. Filter through a poly(vinylidene difluoride) filter and dilute with the solvent mixture, if necessary, to obtain a concentration of rosuvastatin calcium of 0.1 mg/mL.

Reference solution (a) To 25.0 mg of *rosuvastatin calcium CRS* add 25 mL of *water R* and allow to stand for at least 10 min. Sonicate for about 30 min until dissolved, shaking every 10 min. Add 12.5 mL of *acetonitrile R*, mix well and dilute to 50.0 mL with *water R*. Dilute 1.0 mL of the solution to 5.0 mL with the solvent mixture.

Reference solution (b) Dissolve 7 mg of *rosuvastatin for system suitability CRS* (containing impurities A, B and C) in 2.5 mL of *acetonitrile R* and dilute to 10 mL with *water R*.

Column:

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— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1 per cent *V/V* solution of *trifluoroacetic acid R*, *acetonitrile for chromatography R*, *water for chromatography R* (1:31:68 *V/V/V*);

— *mobile phase B*: 1 per cent *V/V* solution of *trifluoroacetic acid R*, *acetonitrile for chromatography R* (1:100 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	100	0
14 - 15	100 → 10	0 → 90

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *rosuvastatin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to rosuvastatin (retention time = about 11 min): impurity B = about 1.1.

System suitability:

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections of reference solution (a);

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rosuvastatin in the chromatogram obtained with reference solution (b).

Calculate the percentage content of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) taking into account the assigned content of *rosuvastatin calcium CRS* and applying a conversion factor of 0.96.

IMPURITIES

Specified impurities *C, D, FP-A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, B, FP-B.*

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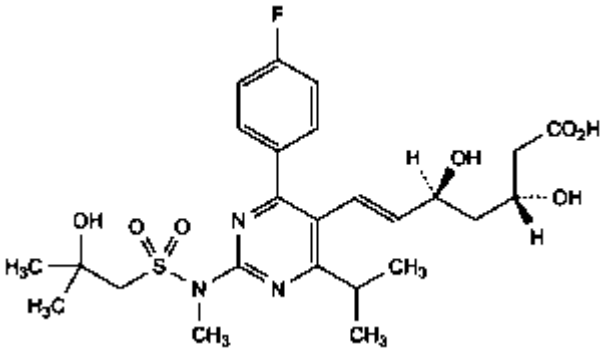
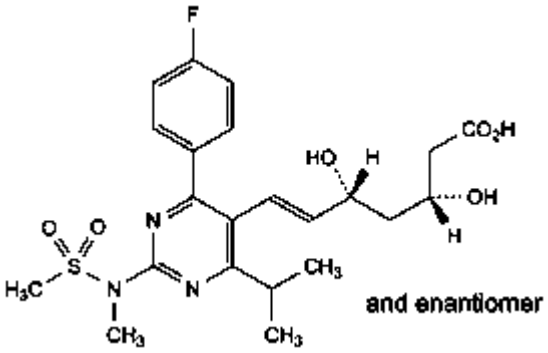
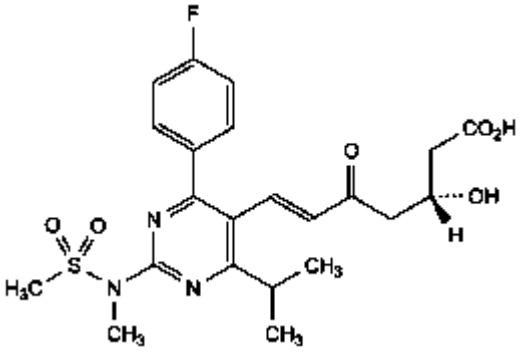


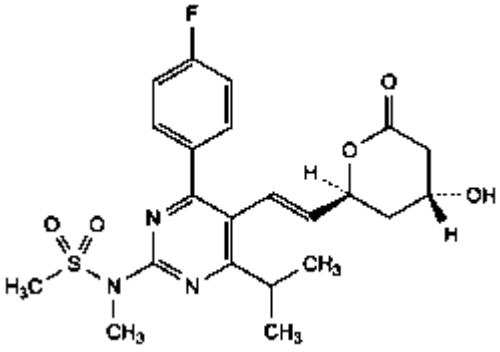
A. (3*R*,5*S*,6*E*)-7-[2-(2,*N*-dimethyl-2-hydroxypropane-1-sulfonamido)-4-(4-fluorophenyl)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,



B. (3*RS*,5*RS*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid,



C. (3*R*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3-hydroxy-5-oxohept-6-enoic acid,



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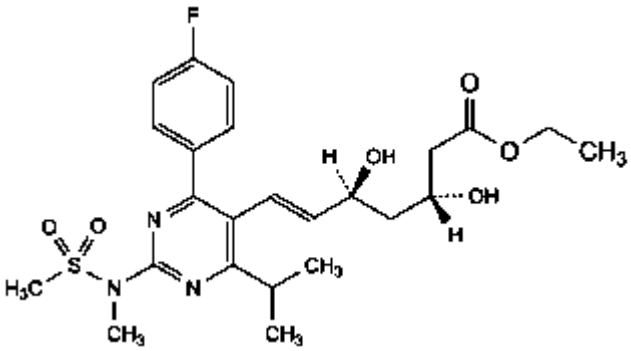
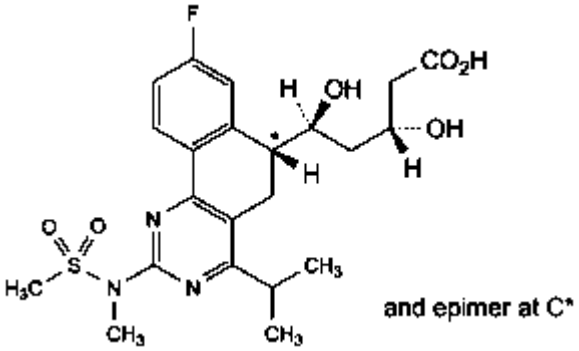
D. *N*-[4-(4-fluorophenyl)-5-[(1*E*)-2-[(2*S*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethen-1-yl]-6-(propan-2-yl)pyrimidin-2-yl]-*N*-methylmethanesulfonamide,



FP-A. ethyl (3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate (rosuvastatin ethyl ester),



FP-B. (3*R*,5*S*)-5-[(6*RS*)-8-fluoro-2-(*N*-methylmethanesulfonamido)-4-(propan-2-yl)-5,6-dihydrobenzo[*h*]quinazolin-6-yl]-3,5-dihydroxypentanoic acid.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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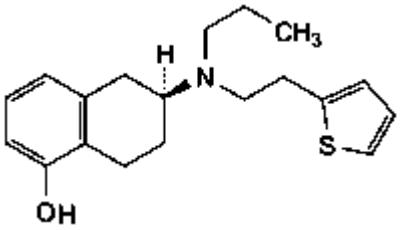
Rotigotine

General Notices

(Ph. Eur. monograph 3014)



$C_{19}H_{25}NOS$ 315.5 *99755-59-6*

Action and use

Dopamine D2 receptor agonist; treatment of Parkinson's disease and restless legs syndrome.

Preparation

Rotigotine Transdermal Patches

Ph Eur

DEFINITION

(6*S*)-6-[Propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or light brown powder.

Solubility

Practically insoluble in water, soluble in anhydrous ethanol, very slightly soluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *rotigotine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

B. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Solution A *methanol R1*, *2-propanol R*, *anhydrous ethanol R* (5:5:90 *V/V/V*).

Solution B 0.1 per cent *V/V* solution of *diethylamine R* in solution A.

Test solution Dissolve 10 mg of the substance to be examined in solution B and dilute to 10 mL with solution B.

Reference solution Dissolve 2 mg of *racemic rotigotine CRS* in 1 mL of solution B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (10 µm).

Mobile phase *diethylamine R*, solution A, *heptane R* (0.1:2:98 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Run time 1.5 times the retention time of rotigotine.

Relative retention With reference to rotigotine (retention time = about 22 min): impurity A = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurity A and rotigotine.

Limit:

— *impurity A*: maximum 0.15 per cent, calculate the ratio of the area of the peak due to impurity A to the sum of the areas of the peaks due to rotigotine and impurity A.

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Related substances

Liquid chromatography (2.2.29).

Solution A 0.1 per cent *V/V* solution of trifluoroacetic acid R.

Solution B 0.1 per cent *V/V* solution of trifluoroacetic acid R in acetonitrile R.

Test solution (a) Suspend 30.0 mg of the substance to be examined in 2.5 mL of solution B and add 20 mL of solution A. Sonicate for at least 20 min, shaking vigorously at 5 min intervals, until dissolution is complete, then dilute to 50.0 mL with solution A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with solution A.

Reference solution (a) Suspend 33.0 mg of rotigotine hydrochloride CRS in 2.5 mL of solution B and add 20 mL of solution A. Sonicate for at least 20 min, shaking vigorously at 5 min intervals, until dissolution is complete, then dilute to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Suspend 3 mg of rotigotine impurity B CRS, 5 mg of rotigotine impurity C CRS, 5 mg of rotigotine impurity G CRS and 3 mg of rotigotine impurity H CRS in 5 mL of solution B and add 40 mL of solution A. Sonicate for at least 20 min, shaking vigorously at 5 min intervals, until dissolution is complete, then dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 50.0 mL with solution A.

Reference solution (c) To 1.0 mL of test solution (a) add 5 mL of solution B and dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped extra-dense bonded octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: trifluoroacetic acid R, water for chromatography R (0.3:1000 *V/V*);

— *mobile phase B*: trifluoroacetic acid R, acetonitrile for chromatography R (0.2:1000 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	82	18
2 - 24	82 → 50	18 → 50

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 220 nm.

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Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, G and H.

Relative retention With reference to rotigotine (retention time = about 10 min): impurity B = about 0.2; impurity C = about 0.6; impurity G = about 1.6; impurity H = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities G and H.

Calculation of percentage contents:

— for each impurity, use the concentration of rotigotine in reference solution (c).

Limits:

— *impurities C, G*: for each impurity, maximum 0.2 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.20 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 2.2 for the principal peak.

Calculate the percentage content of $C_{19}H_{25}NOS$ taking into account the assigned content of *rotigotine hydrochloride CRS* and a conversion factor of 0.8964.

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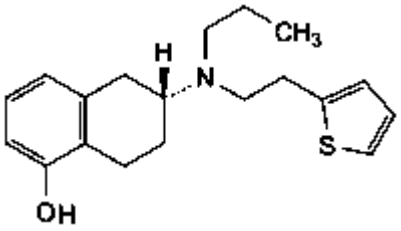
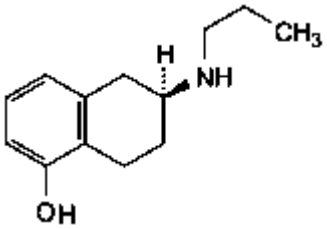
IMPURITIES

Specified impurities A, B, C, G.

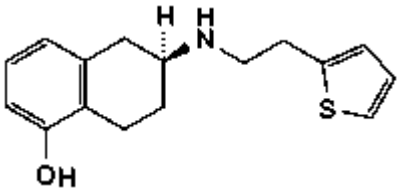
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, E, F, H, I, J, K.



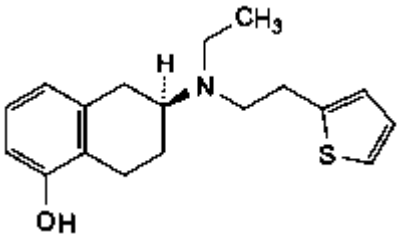
A. (6*R*)-6-[propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((*R*)-rotigotine),



B. (6*S*)-6-(propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (desthienylethyl rotigotine),



C. (6*S*)-6-[[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol (despropyl rotigotine),



D. (6*S*)-6-[ethyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol (ethyl rotigotine),

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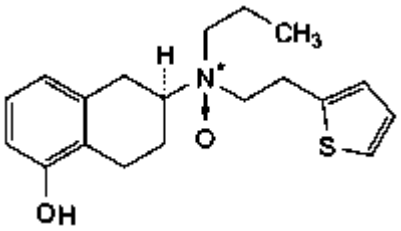
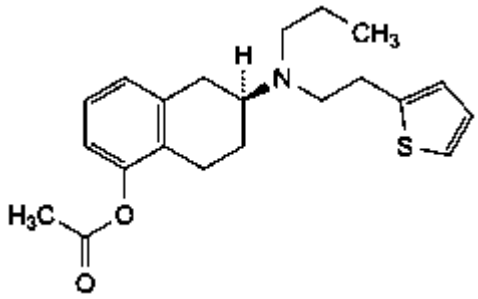
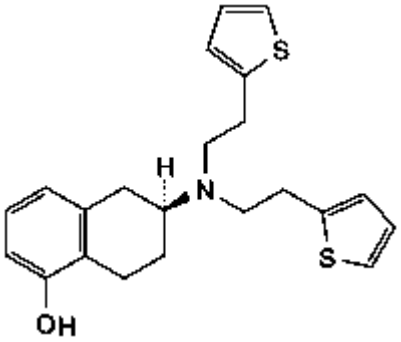


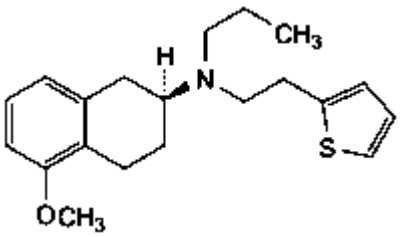
E. (2*S*)-5-hydroxy-*N*-propyl-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine *N*-oxide (rotigotine *N*-oxide),



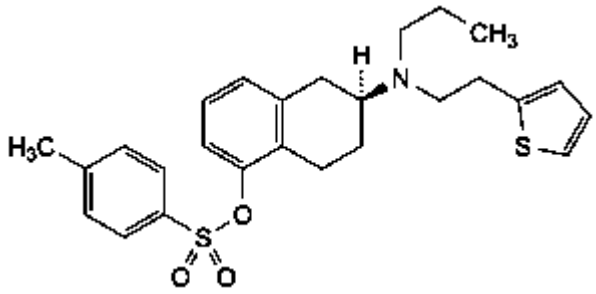
F. (6*S*)-6-[propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-yl acetate (acetyl rotigotine),



G. (6*S*)-6-[*N*,*N*-bis[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol,



H. (2*S*)-5-methoxy-*N*-propyl-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (methoxy rotigotine),



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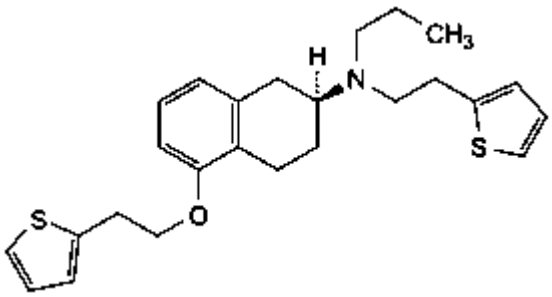
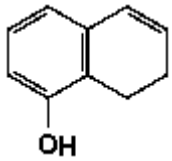
I. (6*S*)-6-[propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-yl 4-methylbenzenesulfonate (rotigotine toluene sulfonic acid ester),



J. (2*S*)-*N*-propyl-5-[2-(thiophen-2-yl)ethoxy]-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (rotigotine thienylethyl ether),



K. 7,8-dihydronaphthalen-1-ol.

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Rotigotine Transdermal Patches

General Notices

Action and use

Dopamine agonist.

DEFINITION

Rotigotine Transdermal Patches contain Rotigotine in a suitable matrix or reservoir presentation.

The transdermal patches comply with the requirements stated under Transdermal Patches and with the following requirements.

PRODUCTION

A suitable test is carried out to demonstrate the appropriate release of rotigotine.

Content of rotigotine, $C_{19}H_{25}NOS$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Remove the release liner and dissolve the contents of one patch in 100 mL of 0.1M *hydrochloric acid* with the aid of ultrasound. Dilute a suitable volume of this solution with 0.1M *hydrochloric acid* to produce a solution expected to contain 0.0025% w/v of Rotigotine. The *light absorption*, Appendix II B, in the range 200 to 300 nm of the final solution obtained exhibits two maxima, at 220 nm and 272 nm.

B. In the test for Uniformity of content, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 1 volume of *methanesulfonic acid*, 200 volumes of *tert-butyl methyl ether* and 800 volumes of *propan-2-ol*.

Solution B 1 volume of *methanesulfonic acid* and 1000 volumes of *water*.

(1) To 3 whole patches, wipe the lacquer off the patches using a solution of 4% *methanolic acetic acid*, dry and dissolve with sufficient Solution A to make a solution expected to contain 0.015% w/v of Rotigotine. To 3 volumes of this solution add 7 volumes of Solution B and mix well (the solution may become turbid). Centrifuge this solution and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with a solution containing 3 volumes of Solution A and 7 volumes of Solution B.

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(3) To 3 volumes of a 0.015% w/v of *rotigotine impurity standard BPCRS* in solution A, add 7 volumes of solution B.

(4) To 3 volumes of a 0.0015% w/v of *rotigotine impurity B EPCRS* in solution A, add 7 volumes of solution B.

(5) Dilute 1 volume of solution (2) to 10 volumes with a solution containing 3 volumes of Solution A and 7 volumes of Solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped Cyanosilyl silica gel for chromatography* (5 µm) (LiChrospher 100 CN is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 80 µL of each solution.

MOBILE PHASE

Mobile phase A 0.5 volumes of *methane sulfonic acid* and 1000 volumes of *water*.

Mobile phase B 0.5 volumes of *methane sulfonic acid* and 1000 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	95	5	isocratic
2-35	95→40	5→60	linear gradient
35-38	40	60	isocratic
38-39	40→95	60→5	linear gradient
39-45	95	5	re-equilibration

When the chromatograms are run under the prescribed conditions, the retention times relative to rotigotine (retention time, about 16 minutes) are: impurity B, about 0.3; impurity K, about 0.6; impurity C, about 0.7; impurity D, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to rotigotine impurity K and impurity C is at least 2.0;

the *resolution* between the peaks due to rotigotine impurity D and rotigotine is at least 1.5.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity K using the chromatogram obtained with solution (3) and multiply the area of this peak by a correction factor of 3.7. Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity B using the chromatogram obtained with solution (4).

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity C is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity B is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

Uniformity of content

Comply with the requirements stated under uniformity of content, Appendix XII C3, Test C, with respect to the individual content of each dosage unit and using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 4 volumes of *propan-2-ol*, 1 volume of *tert-butyl methyl ether* and 0.005 volumes of *methanesulfonic acid*.

Solution B 1000 volumes *water* and 1 volume *methanesulfonic acid*.

(1) Remove the release liner and backing foil from 10 patches and dissolve each patch in a sufficient volume of Solution A to produce a solution expected to contain 0.045 % w/v of Rotigotine. Dilute 3 volumes of this solution to 10 volumes with Solution B and mix well (the solution may become turbid). Centrifuge this solution and use the supernatant liquid.
(2) 0.0135 % w/v of *rotigotine BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Superspher 60 RP select B is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 272 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

650 volumes of *water*, 350 volumes of *acetonitrile* and 0.5 volumes of *methanesulfonic acid*.

When the chromatograms are run under the prescribed conditions, the retention time of the peak due to Rotigotine is about 1.5 minutes.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to rotigotine is in the range 0.8 to 2.8.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{25}NOS$ in the transdermal patch using the declared content of $C_{19}H_{25}NOS$ in *rotigotine BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Rotigotine*.

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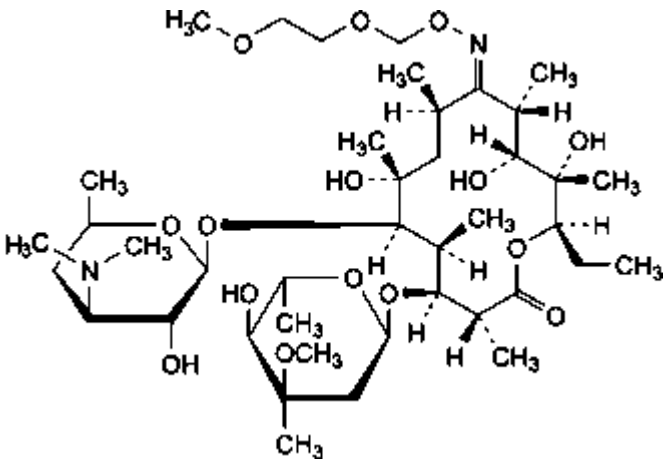
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Roxithromycin

General Notices

(Ph. Eur. monograph 1146)



$C_{41}H_{76}N_2O_{15}$ 837 *80214-83-1*

Action and use

Antibacterial.

Ph Eur

DEFINITION

(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*S*,12*R*,13*S*,14*R*)-4-[(2,6Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-10-[(*E*)[(2-methoxyethoxy)methoxy]imino]-3,5,7,9,11,13hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*hexopyranosyl]oxy]oxacyclotetradecan-2-one(erythromycin 9-(*E*)-[*O*-[(2-methoxyethoxy)methyl]oxime]).

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in acetone, in ethanol (96 per cent) and in methylene chloride. It is slightly soluble in dilute hydrochloric acid.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *roxithromycin CRS*.

If the spectra obtained shows differences, prepare further spectra using 90 g/L solutions in *methylene chloride R*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.2 g in *methanol R* and dilute to 20 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-93 to -96 (anhydrous substance).

Dissolve 0.500 g in *acetone R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solution A Mix 30 volumes of *acetonitrile R* and 70 volumes of a 48.6 g/L solution of *ammonium dihydrogen phosphate R*, adjusted to pH 5.3 with *dilute sodium hydroxide solution R*.

Test solution Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 25.0 mL with solution A.

Reference solution (a) Dissolve 50.0 mg of *roxithromycin CRS* in solution A and dilute to 25.0 mL with solution A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with solution A.

Reference solution (c) Dissolve 2.0 mg of *roxithromycin for system suitability CRS* in solution A and dilute to 1.0 mL with solution A.

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Reference solution (d) Dilute 1.0 mL of *toluene R* to 100.0 mL with *acetonitrile R*. Dilute 0.2 mL of this solution to 200.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a 10 nm pore size and a carbon loading of about 19 per cent,

— *temperature*: 15 °C.

Mobile phase:

— *mobile phase A*: mix 26 volumes of *acetonitrile R* and 74 volumes of a 59.7 g/L solution of *ammonium dihydrogen phosphate R*, adjusted to pH 4.3 with *dilute sodium hydroxide solution R*,

— *mobile phase B*: *water R*, *acetonitrile R* (30:70 *V/V*),

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100	0
50 - 51	100 → 90	0 → 10
51 - 80	90	10
80 - 81	90 → 100	10 → 0
81 - 100	100	0

Flow rate 1.1 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL, using an injector maintained at 8 °C, of the test solution and reference solutions (b), (c) and (d).

Relative retention With reference to roxithromycin (retention time = about 22 min): impurity A = about 0.28; impurity B = about 0.31; impurity C = about 0.33; impurity D = about 0.62; impurity E = about 0.67; impurity F = about 0.83; impurity G = about 1.15; impurity K = about 1.7; impurity H = about 1.85; impurity J = about 2.65; impurity I = about 3.1.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to roxithromycin.

Limits:

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— *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),

— *impurities A, B, C, D, E, F, H, I, J*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent). Disregard any peak due to toluene (use reference solution (d) to identify it).

Water (2.5.12)

Maximum 3.0 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances, with the following modifications.

Column:

— *size*: *l* = 0.25 m.

Mobile phase Mix 307 volumes of *acetonitrile R* and 693 volumes of a 49.1 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 5.3 with *dilute sodium hydroxide solution R*.

Flow rate 1.5 mL/min.

Injection Test solution and reference solutions (a) and (c).

Retention time Roxithromycin = about 12 min.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to roxithromycin.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J.*

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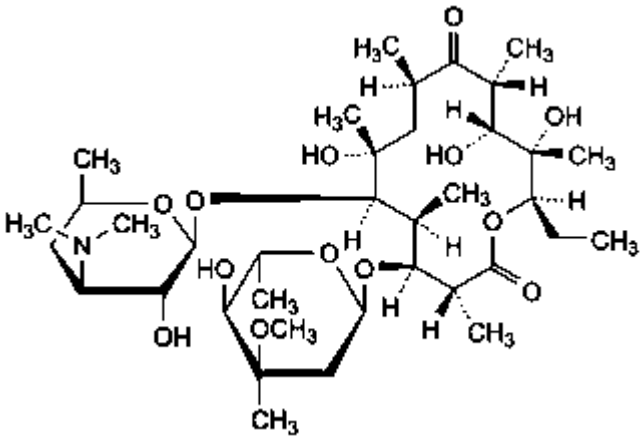
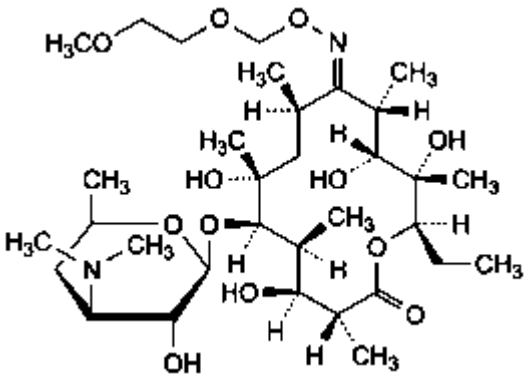
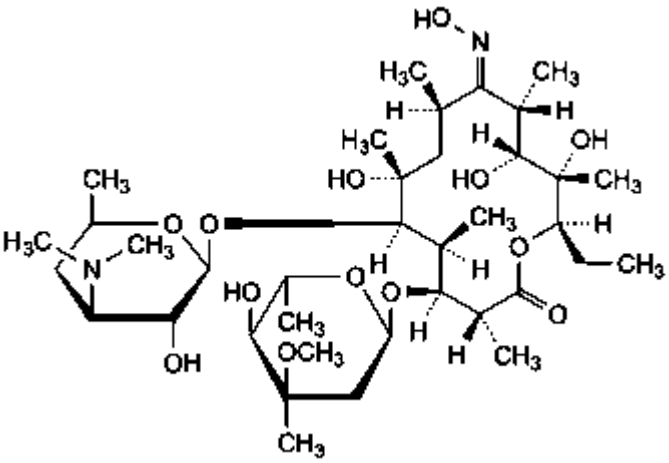
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) K.



A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin A),



B. 3-*O*-de(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)erythromycin 9-(*E*)-[*O*-[(2-methoxyethoxy)methyl]oxime],



C. erythromycin 9-(*E*)-oxime,

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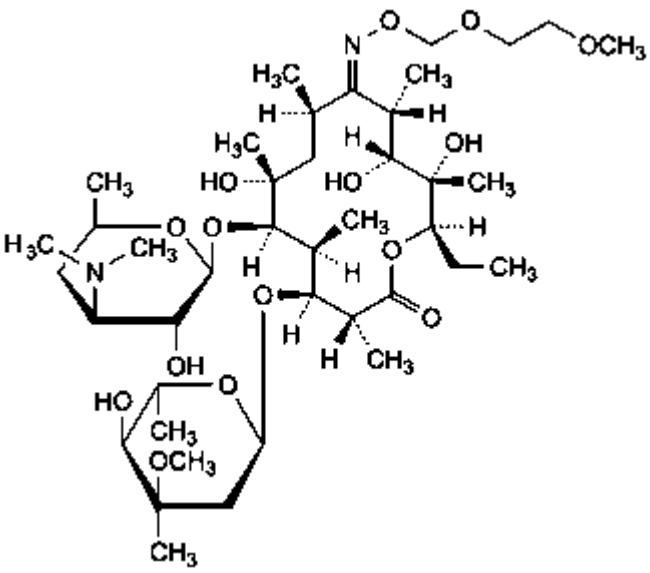
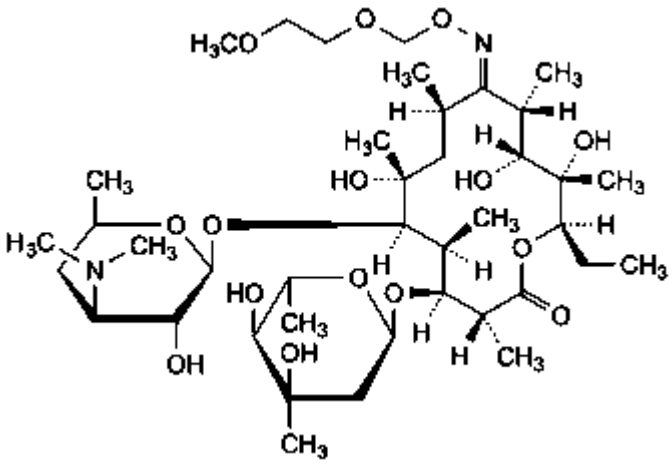
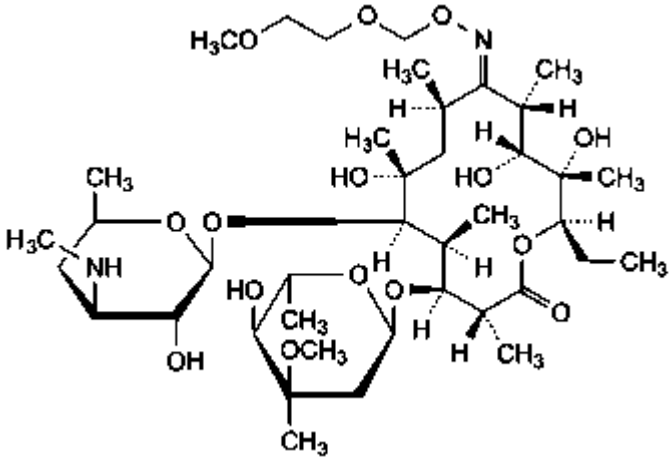


D. erythromycin 9-(*Z*)-[*O*-[(2-methoxyethoxy)methyl]oxime],



E. 3″-*O*-demethylerythromycin 9-(*E*)-[*O*-[(2-methoxyethoxy)methyl]oxime],



F. 3′-*N*-demethylerythromycin 9-(*E*)-[*O*-[(2-methoxyethoxy)methyl]oxime],

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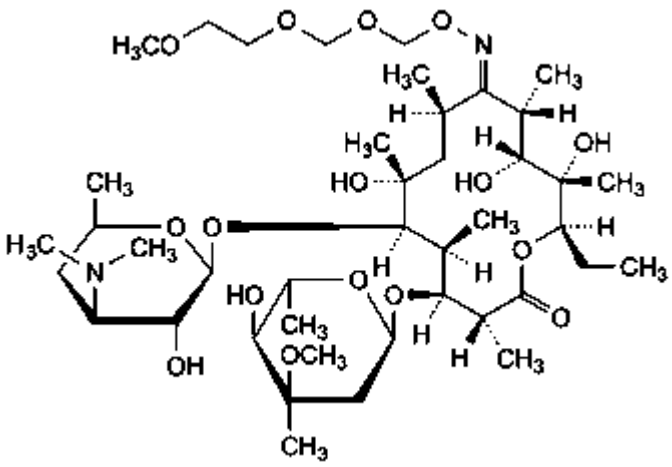
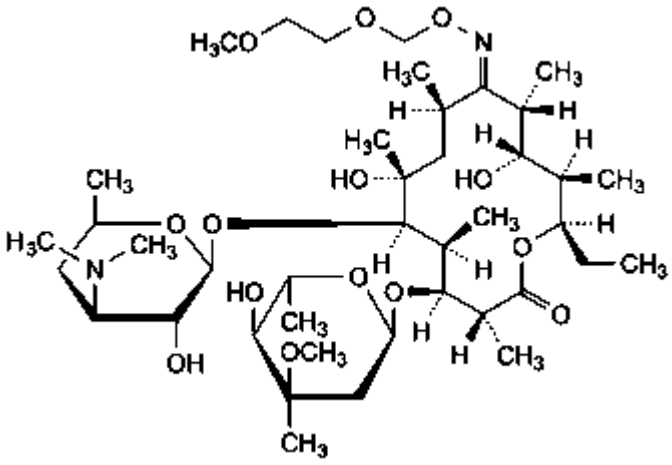
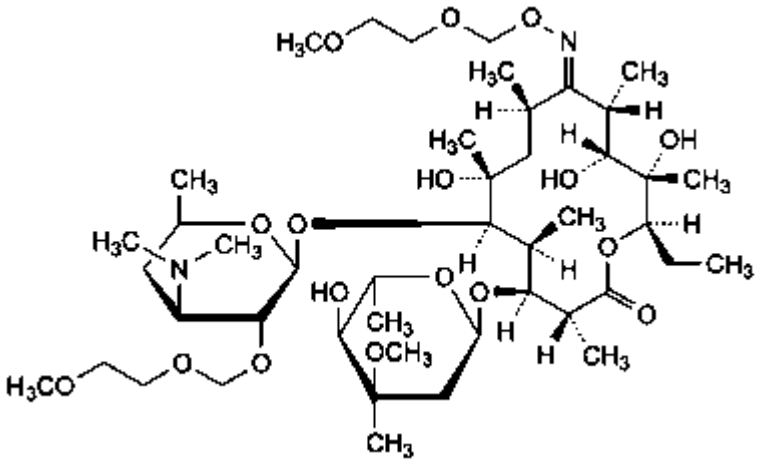


G. erythromycin 9-(*E*)-[*O*-[[(2-methoxyethoxy)methoxy]methyl]oxime],



H. 12-deoxyerythromycin 9-(*E*)-[*O*-[(2-methoxyethoxy)methyl]oxime],



I. 2′-*O*-[(2-methoxyethoxy)methyl]erythromycin 9-(*E*)-[*O*-[(2-methoxyethoxy)methyl]oxime],

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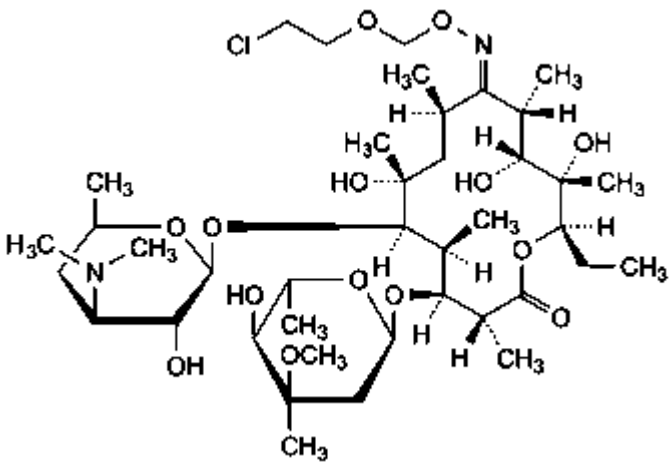
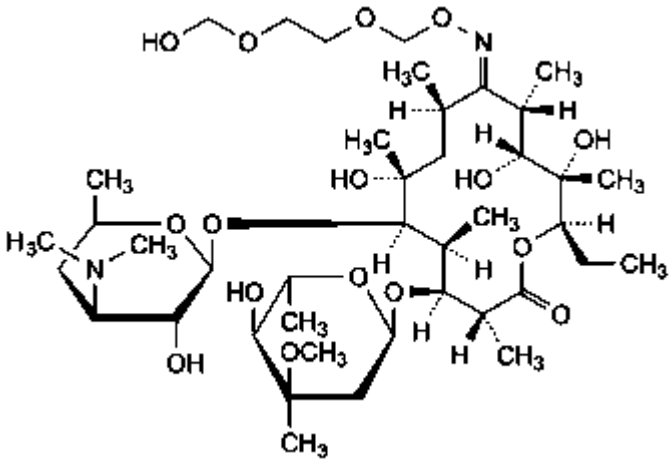


J. erythromycin 9-(*E*)-[*O*-[(2-chloroethoxy)methyl]oxime],



K. erythromycin 9-(*E*)-[*O*-[[2-(hydroxymethoxy)ethoxy]methyl]oxime].

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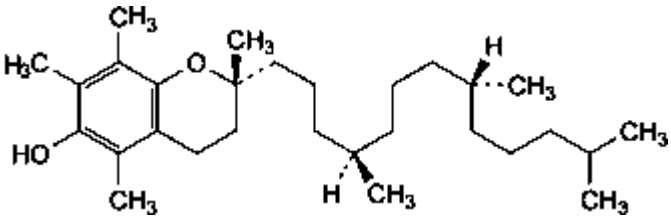
RRR-Alpha-Tocopherol

General Notices

(RRR-α-Tocopherol, Ph. Eur. monograph 1256)



$C_{29}H_{50}O_2$ 430.7 *59-02-9*

Action and use

Used in prevention and treatment of vitamin E deficiencies.

Ph Eur

DEFINITION

(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol.

Content

94.5 per cent to 102.0 per cent.

CHARACTERS

Appearance

Clear, colourless or yellowish-brown, viscous, oily liquid.

Solubility

Practically insoluble in water, freely soluble in acetone, in anhydrous ethanol, in methylene chloride and in fatty oils.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Optical rotation (2.2.7): + 0.05° to + 0.10°.

Dissolve 2.50 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *α-tocopherol CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 2 mL of *cyclohexane R*.

Reference solution Dissolve 10 mg of *α-tocopherol CRS* in 2 mL of *cyclohexane R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution Dissolve 1.0 g of *squalane R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Test solution (a) Dissolve 0.100 g of the substance to be examined in 10.0 mL of the internal standard solution.

Test solution (b) Dissolve 0.100 g of the substance to be examined in 10.0 mL of *cyclohexane R*.

Reference solution (a) Dissolve 0.100 g of *α-tocopherol CRS* in 10.0 mL of the internal standard solution.

Reference solution (b) Dissolve 10 mg of *α-tocopherol R* and 10 mg of *α-tocopheryl acetate R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

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— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 15	280
Injection port		290
Detector		290

Detection Flame ionisation.

Injection 1 µL of test solution (b) and reference solution (b).

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to α-tocopherol and α-tocopheryl acetate.

Limits:

— *total*: maximum 4.0 per cent;

— *disregard limit*: 0.1 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Gas chromatography (*2.2.28*) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: minimum 0.6 for the principal peak.

Calculate the percentage content of $C_{29}H_{50}O_2$ taking into account the assigned content of *α-tocopherol CRS*.

STORAGE

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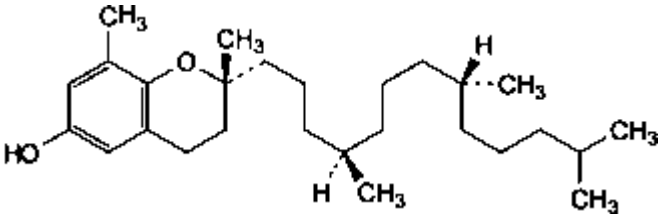
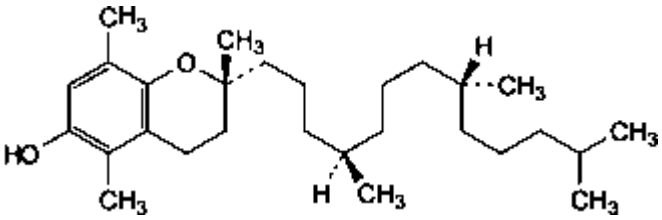
Under an inert gas, protected from light.

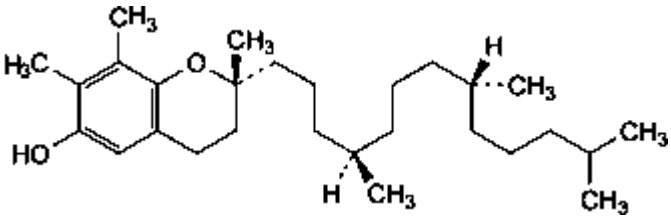
IMPURITIES



A. (2*R*)-2,8-dimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol (*RRR*-δ-tocopherol),



B. (2*R*)-2,5,8-trimethyl-2-[(4*R*,8*R*)4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol (*RRR*-β-tocopherol),



C. (2*R*)-2,7,8-trimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol (*RRR*-γ-tocopherol).

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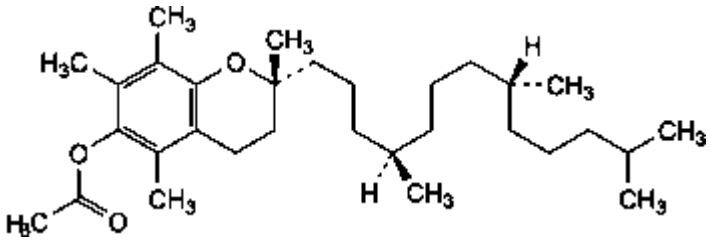
RRR-Alpha-Tocopheryl Acetate

General Notices

(RRR-α-Tocopheryl Acetate, Ph. Eur. monograph 1257)



$C_{31}H_{52}O_3$ 472.7

Action and use

Used in prevention and treatment of vitamin E deficiencies.

Ph Eur

DEFINITION

(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yl acetate.

Content

95.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

Clear, colourless or slightly greenish-yellow, viscous, oily liquid.

Solubility

Practically insoluble in water, freely soluble in acetone, in anhydrous ethanol and in fatty oils, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Optical rotation (2.2.7): + 0.25° to + 0.35°.

Dissolve 2.50 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *α-tocopheryl acetate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 10 mg of the substance to be examined in 2 mL of *cyclohexane R*.

Test solution (b) In a ground-glass stoppered tube, dissolve about 10 mg of the substance to be examined in 2 mL of *2.5 M alcoholic sulfuric acid R*. Heat on a water-bath for 5 min. Cool and add 2 mL of *water R* and 2 mL of *cyclohexane R*. Shake for 1 min. Use the upper layer.

Reference solution (a) Dissolve 10 mg of *α-tocopheryl acetate CRS* in 2 mL of *cyclohexane R*.

Reference solution (b) Prepare as described for test solution (b), using *α-tocopheryl acetate CRS* instead of the substance to be examined.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with test solution (a) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). In the chromatograms obtained with test solution (b) and reference solution (b), there may be 2 spots depending on the degree of hydrolysis: the spot with the higher R_F value is due to α-tocopheryl acetate and corresponds to the spot in the chromatogram obtained with reference solution (a); the spot with the lower R_F value is due to α-tocopherol.

TESTS

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution Dissolve 1.0 g of *squalane R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Test solution (a) Dissolve 0.100 g of the substance to be examined in 10.0 mL of the internal standard solution.

Test solution (b) Dissolve 0.100 g of the substance to be examined in 10.0 mL of *cyclohexane R*.

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Reference solution (a) Dissolve 0.100 g of *α-tocopheryl acetate CRS* in 10.0 mL of the internal standard solution.

Reference solution (b) Dissolve 10 mg of *α-tocopherol R* and 10 mg of *α-tocopheryl acetate R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 15	280
Injection port		290
Detector		290

Detection Flame ionisation.

Injection 1 µL of test solution (b) and reference solutions (a) and (b); inject directly onto the column or via a sufficiently inert, glass-lined injection port using an automatic injection device or other reproducible injection method.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to α-tocopherol and α-tocopheryl acetate in the chromatogram obtained with reference solution (b);

— in the chromatogram obtained with reference solution (a), the area of the peak due to α-tocopherol is not greater than 0.2 per cent of the area of the peak due to α-tocopheryl acetate.

Limits:

— *total*: maximum 4.0 per cent;

— *disregard limit*: 0.1 per cent.

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The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Gas chromatography (*2.2.28*) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

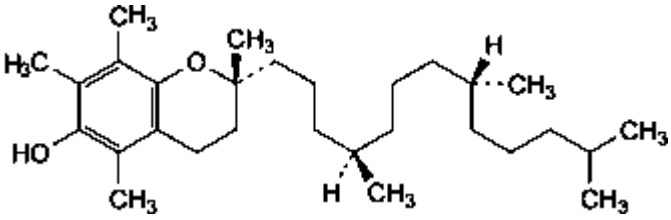
— *symmetry factor*: minimum 0.6 for the principal peak.

Calculate the percentage content of $C_{31}H_{52}O_3$ taking into account the assigned content of *α-tocopheryl acetate CRS*.

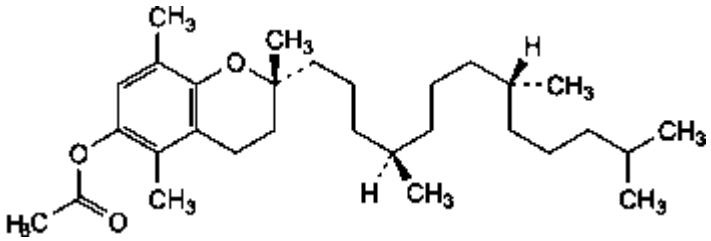
STORAGE

Protected from light.

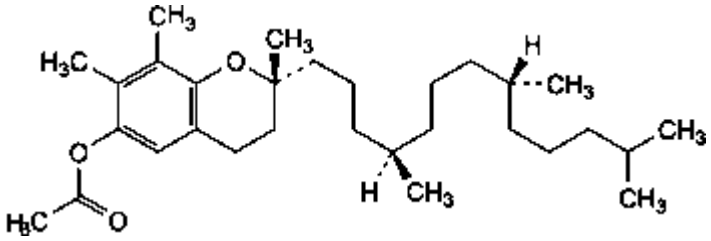
IMPURITIES



A. (2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol (*RRR*-α-tocopherol),



B. (2*R*)-2,5,8-trimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yl acetate (*RRR*-β-tocopheryl acetate),



C. (2*R*)-2,7,8-trimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yl acetate (*RRR*-γ-tocopheryl acetate),

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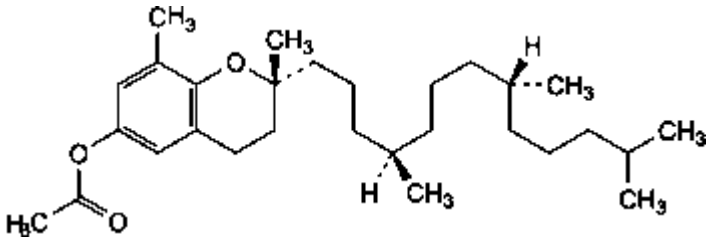

D. (2*R*)-2,8-dimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yl acetate (*RRR*-δ-tocopheryl acetate).

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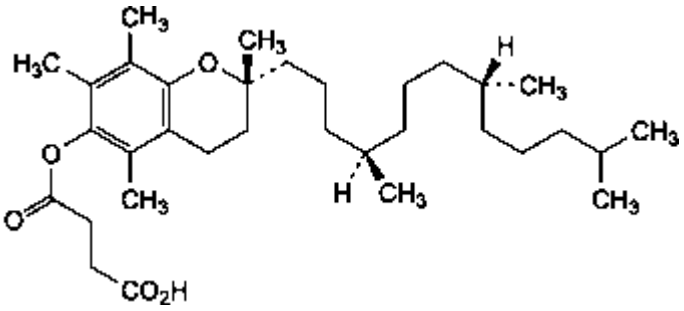
RRR-Alpha-Tocopheryl Hydrogen Succinate

General Notices

(RRR-α-Tocopheryl Hydrogen Succinate, Ph. Eur. monograph 1259)



$C_{33}H_{54}O_5$ 530.8 *4345-03-3*

Action and use

Used in prevention and treatment of vitamin E deficiencies.

Ph Eur

DEFINITION

(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yl hydrogen succinate.

Content

96.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, soluble in acetone and in anhydrous ethanol.

IDENTIFICATION

Fi

Processing math: 100%

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Second identification: A, C, D.

A. Absorbance (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *RRR-α-tocopheryl hydrogen succinate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 10 mg of the substance to be examined in 2 mL of *cyclohexane R*.

Test solution (b) In a ground-glass-stoppered tube, dissolve 10 mg of the substance to be examined in 2 mL of *2.5 M alcoholic sulfuric acid R*. Heat on a water-bath for 5 min. Cool and add 2 mL of *water R* and 2 mL of *cyclohexane R*. Shake for 1 min. Use the upper layer.

Reference solution (a) Dissolve 10 mg of *RRR-α-tocopheryl hydrogen succinate CRS* in 2 mL of *cyclohexane R*.

Reference solution (b) Prepare as described for test solution (b), using *RRR-α-tocopheryl hydrogen succinate CRS* instead of the substance to be examined.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *ether R*, *cyclohexane R* (0.2:20:80 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In a current of air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with test solution (a) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). In the chromatograms obtained with test solution (b) and reference solution (b), there are 2 spots: the spot with the higher R_F value is due to α-tocopherol, the spot with the lower R_F value is due to *RRR*-α-tocopheryl hydrogen succinate and corresponds to the spot obtained with reference solution (a). Depending on the degree of hydrolysis, the lower spot may be weak or even absent.

Detection B Spray with a mixture of 10 volumes of *hydrochloric acid R*, 40 volumes of a 2.5 g/L solution of *ferric chloride R* in *ethanol (96 per cent) R* and 40 volumes of a 10 g/L solution of *phenanthroline hydrochloride R* in *ethanol (96 per cent) R*.

Results B In the chromatograms obtained with test solution (b) and reference solution (b), the spot due to α-tocopherol is orange.

D. After saponification, the resulting *RRR*-α-tocopherol is dextrorotatory (2.2.7). The specific optical rotation after oxidation to the quinone form is not less than + 24.

Carry out the test avoiding exposure to actinic light Transfer 1.0 g to a round bottomed, ground-glass-stoppered, 250 mL flask, dissolve in 30 mL of *ethanol R* and heat under reflux for 3 min. While the solution is boiling, add, through the condenser, 20 mL of *2 M*

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alcoholic potassium hydroxide R. Continue heating under reflux for 20 min and, without cooling, add 4.0 mL of *hydrochloric acid R* dropwise through the condenser. Cool, rinse the condenser with 10 mL of *anhydrous ethanol R*, transfer the contents of the flask to a 500 mL separating funnel, and rinse the flask with 4 quantities, each of 25 mL, of *water R* and 4 quantities, each of 25 mL, of *ether R*. Add the rinsings to the separating funnel. Shake vigorously for 2 min, allow the layers to separate and collect each of the 2 layers in individual separating funnels. Shake the aqueous layer with 2 quantities, each of 50 mL, of *ether R* and add these extracts to the main ether extract. Wash the combined ether extracts with 4 quantities, each of 100 mL, of *water R* and discard the washings.

To the ether solution add 40 mL of a 100 g/L solution of *potassium ferricyanide R* in an 8 g/L solution of *sodium hydroxide R* and shake for 3 min. Wash the ether solution with 4 quantities, each of 50 mL, of *water R*, discard the washings and dry the ether layer over *anhydrous sodium sulfate R*. Evaporate the ether on a water-bath under reduced pressure or in an atmosphere of nitrogen until a few millilitres remain, then complete the evaporation removing the last traces of ether without the application of heat. Immediately dissolve the residue in 25.0 mL of *trimethylpentane R* and determine the optical rotation.

Calculate the specific optical rotation of the substance in the test solution using as *c* the number of grams equivalent to α-tocopherol (factor 0.811) in 1000 mL.

TESTS

Absorbance (*2.2.25*)

Solution A Dissolve 0.150 g in *anhydrous ethanol R* and dilute to 100 mL with the same solvent.

Test solution (a) Dilute 10.0 mL of solution A to 100.0 mL with *anhydrous ethanol R*.

Test solution (b) Dilute 20.0 mL of solution A to 50.0 mL with *anhydrous ethanol R*.

Absorption maximum At 284 nm for test solution (a).

Absorption minimum At 254 nm for test solution (b).

Specific absorbance at the absorption maximum 36 to 39 for test solution (a).

Specific absorbance at the absorption minimum 6.0 to 8.0 for test solution (b).

Acid value (*2.5.1*)

101 to 108, determined on 1.00 g.

Free tocopherol

Maximum 1.0 per cent.

Dissolve 0.500 g in 100 mL of *0.25 M alcoholic sulfuric acid R*. Add 20 mL of *water R* and 0.1 mL of a 2.5 g/L solution of *diphenylamine R* in *sulfuric acid R*. Titrate with *0.01 M ammonium and cerium sulfate* until a blue colour is obtained that persists for at least 5 s. Carry out a blank titration.

1 mL of *0.01 M ammonium and cerium sulfate* is equivalent to 2.154 mg of free tocopherol.

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Related substances

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 0.300 g of *dotriacontane R* in *hexane R* and dilute to 100.0 mL with the same solvent.

Test solution Weigh 30.0 mg of the substance to be examined into a 20 mL vial. Add 2.0 mL of *methanol R*, 1.0 mL of *dimethoxypropane R* and 0.1 mL of *hydrochloric acid R*. Cap tightly and sonicate. Allow to stand in the dark for 1 h ± 5 min. Remove from the dark, uncap and evaporate just to dryness on a steam bath with the aid of a stream of nitrogen. Add 10.0 mL of the internal standard solution. Vortex into solution.

Reference solution Weigh 30.0 mg of *RRR-α-tocopheryl hydrogen succinate CRS* into a 20 mL vial. Add 2.0 mL of *methanol R*, 1.0 mL of *dimethoxypropane R* and 0.1 mL of *hydrochloric acid R*. Cap tightly and sonicate. Allow to stand in the dark for 1 h ± 5 min. Remove from the dark, uncap and evaporate just to dryness on a steam bath with the aid of a stream of nitrogen. Add 10.0 mL of the internal standard solution. Vortex into solution.

Column:

— *material*: fused silica;

— *size*: *l* = 15 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 3-6 mL/min.

Split ratio 1:10 to 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	200 → 250
	10 - 20	250
I		300

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	Time (min)	Temperature (°C)
Detector		330

Detection Flame ionisation.

Injection 1 µL; inject directly onto the column or via a glass-lined injection port using an automatic injection device or some other reproducible injection method.

System suitability Reference solution:

— *resolution*: minimum 12.0 between the peaks due to dotriacontane and *RRR*-α-tocopheryl hydrogen succinate.

Interference test Dissolve 0.100 g of the substance to be examined in *hexane R* and dilute to 50.0 mL with the same solvent. Inject 1 µL of the solution and record the chromatogram. If a peak is detected with the same retention time as that of the peak due to dotriacontane, calculate the area of this peak relative to the peak area of the substance to be examined. If the relative peak area is greater than 0.5 per cent, use the corrected peak area $S'_{D(corr)}$ for the final calculation.

$$S'_{D(corr)} = S'_{D} - \frac{S_I \times S'_T}{S_{TI}}$$

S'_D = area of the peak due to dotriacontane in the chromatogram obtained with the test solution;

S_I = area of the peak with the same retention time as that of the peak due to dotriacontane in the chromatogram obtained in the interference test;

S'_T = area of the peak due to *RRR*-α-tocopheryl hydrogen succinate in the chromatogram obtained with the test solution;

S_{TI} = area of the peak due to *RRR*-α-tocopheryl hydrogen succinate in the chromatogram obtained in the interference test.

Measure the areas of the peaks due to *RRR-α-tocopheryl hydrogen succinate CRS* (S_T) and dotriacontane (S_D) in the chromatogram obtained with the reference solution and the areas of the peaks due to *RRR*-α-tocopheryl hydrogen succinate (S'_T) and dotriacontane (S'_D) in the chromatogram obtained with the test solution.

Determine the response factor (RF) for *RRR*-α-tocopheryl hydrogen succinate from the areas of the peaks due to *RRR-α-tocopheryl hydrogen succinate CRS* and dotriacontane in the chromatogram obtained with the reference solution, using the following expression:

$$\frac{S_D \times m_T}{S_T \times m_D}$$

Calculate the percentage content of *RRR*-α-tocopheryl hydrogen succinate using the following expression:

$$\frac{100 \times S'_T \times m_D \times RF}{S'_{D(corr)} \times m}$$

S area of the peak due to dotriacontane in the chromatogram obtained with the reference solution;

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$S'_{D(corr)}$	=	corrected area of the peak due to dotriacontane in the chromatogram obtained with the test solution;
S_T	=	area of the peak due to *RRR-α-tocopheryl hydrogen succinate CRS* in the chromatogram obtained with the reference solution;
S'_T	=	area of the peak due to *RRR*-α-tocopheryl hydrogen succinate in the chromatogram obtained with the test solution;
m_D	=	mass of dotriacontane in the test solution and in the reference solution, in milligrams;
m_T	=	mass of *RRR-α-tocopheryl hydrogen succinate CRS* in the reference solution, in milligrams;
m	=	mass of the substance to be examined in the test solution, in milligrams.

STORAGE

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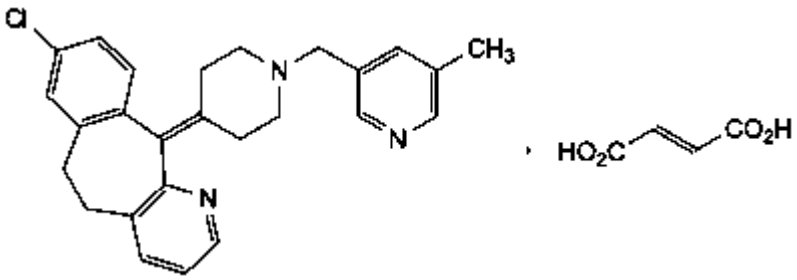
Rupatadine Fumarate

General Notices

(Ph. Eur. monograph 2888)



$C_{30}H_{30}ClN_3O_4$ 532.0 *182349-12-8*

Ph Eur

DEFINITION

8-Chloro-11-[1-[(5-methylpyridin-3-yl)methyl]piperidin-4-ylidene]-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (2*E*)-but-2-enedioate.

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or slightly pinkish powder.

Solubility

Very slightly soluble in water, slightly soluble in anhydrous ethanol, very slightly soluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *rupatadine fumarate CRS*.

TESTS

Related substances

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Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture acetonitrile R, mobile phase A (20:80 *V/V*).

Test solution Dissolve 32.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 3 mg of rupatadine for system suitability CRS (containing impurities A and B) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 7.0 g/L solution of sodium dihydrogen phosphate monohydrate R in water for chromatography R;

— *mobile phase B*: acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 27	80 → 50	20 → 50

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram supplied with rupatadine for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to rupatadine (retention time = about 17 min): fumaric acid = about 0.1; impurity A = about 0.6; impurity B = about 0.7.

System suitability Reference solution (b):

— resolution: minimum 5.0 between the peaks due to impurities A and B.

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Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 1.3;

— for each impurity, use the concentration of rupatadine fumarate in reference solution (a).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.7 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to fumaric acid.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* in an oven at 80 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 17.73 mg of $C_{30}H_{30}ClN_3O_4$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.

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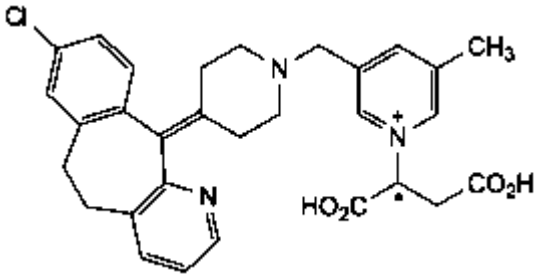
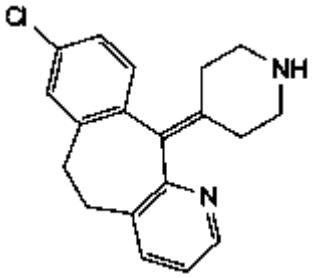
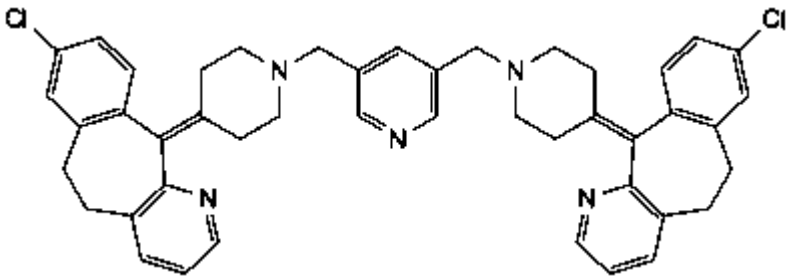


A. 3-[[4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidin-1-yl]methyl]-1-(1,2-dicarboxyethyl)-5-methylpyridin-1-ium,



B. 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine,



C. 11,11′-[pyridine-3,5-diylbis(methylenepiperidin-1-yl-4-ylidene)]bis(8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine).

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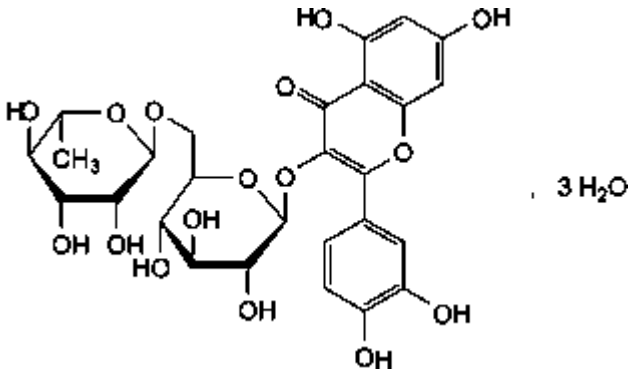
Rutoside Trihydrate

General Notices

(Ph. Eur. monograph 1795)



$C_{27}H_{30}O_{16},3H_2O$ 665 *250249-75-3*

Action and use

Bioflavinoid.

Ph Eur

DEFINITION

3-[[6-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-1-benzopyran-4-one trihydrate.

Content

95.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow or greenish-yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in solutions of alkali hydroxides.

IDENTIFICATION

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First identification: *B*.

Second identification: *A, C, D*.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *methanol R*, dilute to 250.0 mL with the same solvent and filter if necessary. Dilute 5.0 mL of the solution to 50.0 mL with *methanol R*.

Spectral range 210-450 nm.

Absorption maxima At 257 nm and 358 nm.

Specific absorbance at the absorption maximum at 358 nm 305 to 330 (anhydrous substance).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *rutoside trihydrate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 25 mg of *rutoside trihydrate CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *butanol R*, *anhydrous acetic acid R*, *water R*, *methyl ethyl ketone R*, *ethyl acetate R* (5:10:10:30:50 *V/V/V/V/V*).

Application 10 µL.

Development Over a path of 10 cm.

Drying In air.

Detection Spray with a mixture of 2.5 mL of *ferric chloride solution R1* and 7.5 mL of a 10 g/L solution of *potassium ferricyanide R* and examine for 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 10 mg in 5 mL of *ethanol (96 per cent) R*, add 1 g of *zinc R* and 2 mL of *hydrochloric acid R1*. A red colour develops.

TESTS

Light-absorbing impurities

The absorbance (2.2.25) is not greater than 0.10 at wavelengths between 450 nm and 800 nm.

Dissolve 0.200 g in 40 mL of *2-propanol R*. Stir for 15 min, dilute to 50.0 mL with *2-propanol R* and filter.

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Substances insoluble in methanol

Maximum 3 per cent.

Shake 2.5 g of the substance to be examined for 15 min in 50 mL of *methanol R* at 20-25 °C. Filter under reduced pressure through a sintered-glass filter (1.6) (2.1.2) previously dried for 15 min at 100-105 °C, allowed to cool in a desiccator and tared. Wash the filter 3 times with 20 mL of *methanol R*. Dry the filter for 30 min at 100-105 °C. Allow to cool and weigh. The residue weighs a maximum of 75 mg.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.10 g of the substance to be examined in 20 mL of *methanol R* and dilute to 100.0 mL with mobile phase B.

Reference solution (a) Dissolve 10.0 mg of *rutoside trihydrate CRS* in 2.0 mL of *methanol R* and dilute to 10.0 mL with mobile phase B.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 5 volumes of *tetrahydrofuran R* and 95 volumes of a 15.6 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: mix 40 volumes of *tetrahydrofuran R* and 60 volumes of a 15.6 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	50 → 0	50 → 100
10 - 15	0	100
15 - 16	0 → 50	100 → 50
16 - 20	50	50

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

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Relative retention With reference to rutoside (retention time = about 7 min): impurity B = about 1.1; impurity A = about 1.2; impurity C = about 2.5.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to rutoside and impurity B.

Limits Locate the impurities by comparison with the chromatogram provided with *rutoside trihydrate CRS*:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.8; impurity C = 0.5;

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (4.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Water (*2.5.12*)

7.5 per cent to 9.5 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 20 mL of *dimethylformamide R*. Titrate with 0.1 M tetrabutylammonium hydroxide, determining the end-point potentiometrically (*2.2.20*).

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 30.53 mg of $C_{27}H_{30}O_{16}$.

STORAGE

Protected from light.

IMPURITIES

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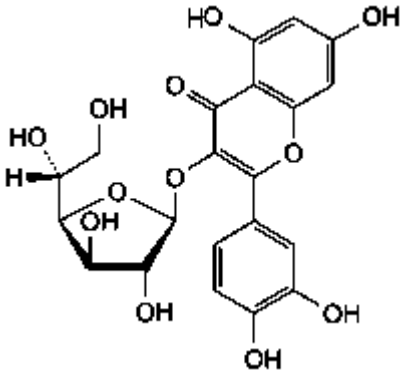
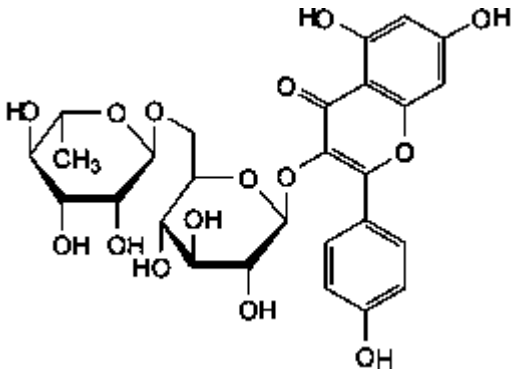
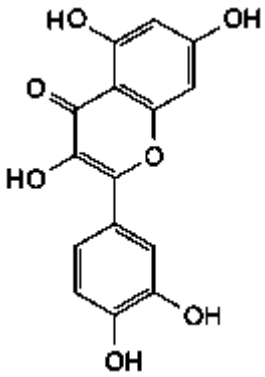


A. 2-(3,4-dihydroxyphenyl)-3-(β-D-glucofuranosyloxy)-5,7-dihydroxy-4*H*-1-benzopyran-4-one (isoquercitroside),



B. 3-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5,7-dihydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one (kaempferol 3-rutinoside),



C. 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one (quercetin).

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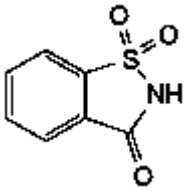
Saccharin

General Notices

(Ph. Eur. monograph 0947)



$C_7H_5NO_3S$ 183.2 *81-07-2*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

1,2-Benzisothiazol-3(2*H*)-one 1,1-dioxide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Sparingly soluble in boiling water and in ethanol (96 per cent), slightly soluble in cold water. It dissolves in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: C.

Second identification: A, B, D, E.

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A. A saturated solution, prepared without heating, turns *blue litmus paper R* red.

B. Melting point (*2.2.14*): 226 °C to 230 °C.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison *saccharin CRS*.

D. Mix about 10 mg with about 10 mg of *resorcinol R*, add 0.25 mL of *sulfuric acid R* and carefully heat the mixture over a naked flame until a dark green colour is produced. Allow to cool, add 10 mL of *water R* and *dilute sodium hydroxide solution R* until an alkaline reaction is produced. An intense green fluorescence develops.

E. To 0.2 g add 1.5 mL of *dilute sodium hydroxide solution R*, evaporate to dryness and heat the residue carefully until it melts, avoiding carbonisation. Allow to cool, dissolve the mass in about 5 mL of *water R*, add *dilute hydrochloric acid R* until a weak acid reaction is produced and filter, if necessary. To the filtrate add 0.2 mL of *ferric chloride solution R2*. A violet colour develops.

TESTS

Solution S

Dissolve 5.0 g in 20 mL of a 200 g/L solution of *sodium acetate R* and dilute to 25 mL with the same solution.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

o- and *p*-Toluenesulfonamide

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 25 mg of *caffeine R* in *methylene chloride R* and dilute to 100 mL with the same solvent.

Test solution Suspend 10.0 g of the substance to be examined in 20 mL of *water R* and dissolve using 5-6 mL of *strong sodium hydroxide solution R*. If necessary adjust the solution to pH 7-8 with *1 M sodium hydroxide* or *1 M hydrochloric acid* and dilute to 50 mL with *water R*. Shake the solution with 4 quantities, each of 50 mL, of *methylene chloride R*. Combine the lower layers, dry over *anhydrous sodium sulfate R* and filter. Wash the filter and the sodium sulfate with 10 mL of *methylene chloride R*. Combine the solution and the washings and evaporate almost to dryness in a water-bath at a temperature not exceeding 40 °C. Using a small quantity of *methylene chloride R*, quantitatively transfer the residue into a suitable 10 mL tube, evaporate to dryness in a current of nitrogen and dissolve the residue in 1.0 mL of the internal standard solution.

Blank solution Evaporate 200 mL of *methylene chloride R* to dryness in a water-bath at a temperature not exceeding 40 °C. Dissolve the residue in 1 mL of *methylene chloride R*.

Reference solution Dissolve 20.0 mg of *o-toluenesulfonamide R* and 20.0 mg of *toluenesulfonamide R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *methylene chloride R*. Evaporate 5.0 mL of the final solution to dryness in a current of nitrogen. Dissolve the residue in 1.0 mL of the internal standard solution.

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Column:

— *material*: fused silica;

— *size*: *l* = 10 m, Ø = 0.53 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 2 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 10 mL/min.

Split ratio 1:2.

Temperature:

— *column*: 180 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL.

Order of elution *o*-toluenesulfonamide, *p*-toluenesulfonamide, caffeine.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to *o*-toluenesulfonamide and *p*-toluenesulfonamide in the chromatogram obtained with the reference solution;

— the chromatogram obtained with the blank solution does not show any peak with the same retention times as the internal standard, *o*-toluenesulfonamide and *p*-toluenesulfonamide.

Limits:

— *o-toluenesulfonamide*: the ratio of its area to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the reference solution (10 ppm);

— *p-toluenesulfonamide*: the ratio of its area to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the reference solution (10 ppm).

Readily carbonisable substances

Dissolve 0.20 g in 5 mL of *sulfuric acid R* and keep at 48-50 °C for 10 min. When viewed against a white background, the solution is not more intensely coloured than a solution prepared by mixing 0.1 mL of red primary solution, 0.1 mL of blue primary solution and 0.4 mL of yellow primary solution (*2.2.2*) with 4.4 mL of *water R*.

Loss on drying (*2.2.32*)

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Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 40 mL of *ethanol (96 per cent) R*. Add 40 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, using a 10 g/L solution of *phenolphthalein R* in *ethanol (96 per cent) R* as indicator. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.32 mg of $C_7H_5NO_3S$.

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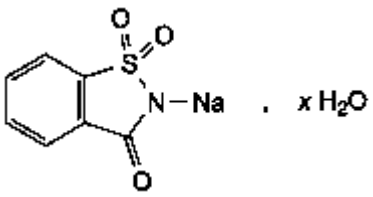
Saccharin Sodium

General Notices

Soluble Saccharin

(Ph. Eur. monograph 0787)



$C_7H_4NNaO_3S,xH_2O$ 205.2 (anhydrous substance)

Anhydrous saccharin sodium *128-44-9*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

2-Sodio-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

It may be anhydrous or contain a variable quantity of water.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, efflorescent in dry air.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

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First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 226 °C to 230 °C.
To 5 mL of solution S (see Tests) add 3 mL of *dilute hydrochloric acid R*. A white precipitate is formed. Filter and wash with *water R*. Dry the precipitate at 100-105 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs; dry the substances to constant mass at 105 °C before use.

Comparison *saccharin sodium CRS*.

C. Mix about 10 mg with about 10 mg of *resorcinol R*, add 0.25 mL of *sulfuric acid R* and carefully heat the mixture over a naked flame until a dark green colour is produced. Allow to cool, add 10 mL of *water R* and *dilute sodium hydroxide solution R* until an alkaline reaction is produced. An intense green fluorescence develops.
D. To 0.2 g add 1.5 mL of *dilute sodium hydroxide solution R*, evaporate to dryness and heat the residue carefully until it melts, avoiding carbonisation. Allow to cool, dissolve the mass in about 5 mL of *water R*, add *dilute hydrochloric acid R* until a weak acid reaction is produced and filter, if necessary. To the filtrate add 0.2 mL of *ferric chloride solution R2*. A violet colour develops.
E. Solution S gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 2.0 g in 10 mL of *water R*.

Acidity or alkalinity

To 10 mL of solution S add about 0.05 mL of a 10 g/L solution of *phenolphthalein R* in *ethanol (96 per cent) R*. The solution is neither pink nor red. Add 0.05 mL of *0.1 M sodium hydroxide*. The solution becomes pink or red.

o- and *p*-Toluenesulfonamide

Gas chromatography (2.2.28).

Internal standard solution Dissolve 25 mg of *caffeine R* in *methylene chloride R* and dilute to 100 mL with the same solvent.

Test solution Dissolve 10.0 g of the substance to be examined in 50 mL of *water R*. If necessary adjust the solution to pH 7-8 by addition of *1 M sodium hydroxide* or *1 M hydrochloric acid*. Shake the solution with 4 quantities, each of 50 mL, of *methylene chloride R*. Combine

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the lower layers, dry over *anhydrous sodium sulfate R* and filter. Wash the filter and the sodium sulfate with 10 mL of *methylene chloride R*. Combine the solution and the washings and evaporate almost to dryness in a water-bath at a temperature not exceeding 40 °C. Using a small quantity of *methylene chloride R*, quantitatively transfer the residue into a suitable 10 mL tube, evaporate to dryness in a current of *nitrogen R* and add 1.0 mL of the internal standard solution.

Blank solution Evaporate 200 mL of *methylene chloride R* to dryness in a water-bath at a temperature not exceeding 40 °C. Dissolve the residue in 1 mL of *methylene chloride R*.

Reference solution Dissolve 20.0 mg of *o-toluenesulfonamide R* and 20.0 mg of *toluenesulfonamide R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *methylene chloride R*. Evaporate 5.0 mL of the final solution to dryness in a current of *nitrogen R*. Take up the residue using 1.0 mL of the internal standard solution.

Column:

— *material*: fused silica;

— *size*: *l* = 10 m, Ø = 0.53 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 2 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 10 mL/min.

Split ratio 1:2.

Temperature:

— *column*: 180 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL.

Elution order *o*-toluenesulfonamide, *p*-toluenesulfonamide, caffeine.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to *o*-toluenesulfonamide and *p*-toluenesulfonamide in the chromatogram obtained with the reference solution;

— the chromatogram obtained with the blank solution does not show any peak with the same retention times as the internal standard, *o*-toluenesulfonamide and *p*-toluenesulfonamide.

Limits:

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— *o-toluenesulfonamide*: the ratio of its area to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the reference solution (10 ppm);

— *p-toluenesulfonamide*: the ratio of its area to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the reference solution (10 ppm).

Readily carbonisable substances

Dissolve 0.200 g in 5 mL of *sulfuric acid R* and keep at 48-50 °C for 10 min. When viewed against a white background, the solution is not more intensely coloured than a solution prepared by mixing 0.1 mL of red primary solution, 0.1 mL of blue primary solution and 0.4 mL of yellow primary solution (*2.2.2*) with 4.4 mL of *water R*.

Water (*2.5.12*)

Maximum 15.0 per cent, determined on 0.200 g.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*, with slight heating if necessary. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 20.52 mg of $C_7H_4NNaO_3S$.

STORAGE

In an airtight container.

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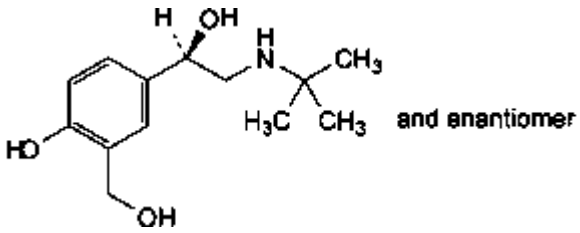
Salbutamol

General Notices

(Ph. Eur. monograph 0529)



$C_{13}H_{21}NO_3$ 239.3 *18559-94-9*

Action and use

Beta2-adrenoceptor agonist; bronchodilator.

Preparations

Salbutamol Pressurised Inhalation

Salbutamol Prolonged-release Capsules

Ph Eur

DEFINITION

(1*RS*)-2-[(1,1-Dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in ethanol (96 per cent).

mp

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About 155 °C, with decomposition.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 80.0 mg in a 10 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of the solution to 100.0 mL with a 10 g/L solution of *hydrochloric acid R*.

Spectral range 230-350 nm.

Absorption maximum At 276 nm.

Specific absorbance at the absorption maximum 66 to 75.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *salbutamol CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 50 mL with the same solvent.

Reference solution Dissolve 10 mg of *salbutamol CRS* in *methanol R* and dilute to 50 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *water R*, *ethyl acetate R*, *2-propanol R*, *methyl isobutyl ketone R* (3:18:35:45:50 *V/V/V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a 1 g/L solution of *methylbenzothiazolone hydrazone hydrochloride R* in a 90 per cent *V/V* solution of *methanol R*, followed by a 20 g/L solution of *potassium ferricyanide R* in a mixture of 1 volume of *concentrated ammonia R1* and 3 volumes of *water R*, followed by a further spraying with a 1 g/L solution of *methylbenzothiazolone hydrazone hydrochloride R* in a 90 per cent *V/V* solution of *methanol R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in 50 mL of a 20 g/L solution of *disodium tetraborate R*. Add 1 mL of a 30 g/L solution of *4-aminoantipyrine R*, 10 mL of *methylene chloride R* and 10 mL of a 20 g/L solution of *potassium ferricyanide R*. Shake and allow to separate. An orange-red

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colour develops in the methylene chloride layer.

TESTS

Solution S

Dissolve 0.50 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *salbutamol CRS*, 2 mg of *salbutamol impurity B CRS*, 3.0 mg of *salbutamol impurity D CRS*, 3.0 mg of *salbutamol impurity F CRS* and 3.0 mg of *salbutamol impurity G CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *salbutamol impurity I CRS* in 1.0 mL of the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 335 m^2/g, a pore size of 10 nm and a carbon loading of 11.7 per cent.

Mobile phase Mix 22 volumes of *acetonitrile R1* and 78 volumes of a solution containing 2.87 g/L of *sodium heptanesulfonate R* and 2.5 g/L of *potassium dihydrogen phosphate R* previously ajusted to pH 3.65 with *dilute phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 25 times the retention time of salbutamol.

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Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, D, F and G; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity I.

Relative retention With reference to salbutamol (retention time = about 2 min): impurity B = about 1.3; impurity A = about 1.7; impurity C = about 2.0; impurity D = about 2.7; impurity H = about 3.0; impurity E = about 3.1; impurity G = about 4.1; impurity F = about 6.2; impurity I = about 23.2.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to salbutamol and impurity B.

Limits:

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity G*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities A, B, C, E, H, I*: for each impurity, not more than 1.5 times the area of the peak due to salbutamol in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to salbutamol in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 1.0 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Impurity J

Maximum 0.2 per cent.

Dissolve 50.0 mg in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solvent. The absorbance (2.2.25) of the solution measured at 310 nm is not greater than 0.10.

Boron

Maximum 50 ppm.

Test solution To 50 mg of the substance to be examined add 5 mL of a solution containing 13 g/L of *anhydrous sodium carbonate R* and 17 g/L of *potassium carbonate R*. Evaporate to dryness on a water-bath and dry at 120 °C. Ignite the residue rapidly until the organic matter has been destroyed, allow to cool and add 0.5 mL of *water R* and 3.0 mL of a freshly prepared 1.25 g/L solution of *curcumin R* in *glacial acetic acid R*. Warm gently to effect solution, allow to cool and add 3.0 mL of a mixture prepared by adding 5 mL of *sulfuric acid R*, slowly

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and with stirring, to 5 mL of *glacial acetic acid R*. Mix and allow to stand for 30 min. Dilute to 100.0 mL with *ethanol (96 per cent) R*, filter and use the filtrate.

Reference solution Dissolve 0.572 g of *boric acid R* in 1000.0 mL of *water R*. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. To 2.5 mL of this solution add 5 mL of a solution containing 13 g/L of *anhydrous sodium carbonate R* and 17 g/L of *potassium carbonate R*, and treat this mixture in the same manner as the test solution.

Measure the absorbance (*2.2.25*) of the test solution and of the reference solution at the absorption maximum at about 555 nm. The absorbance of the test solution is not greater than that of the reference solution.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

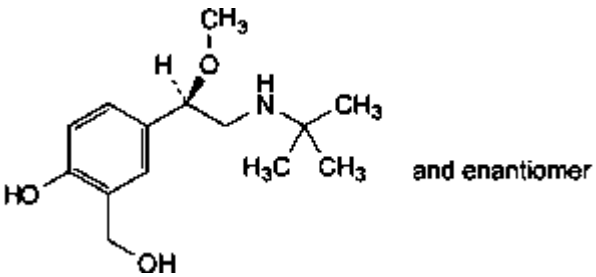
1 mL of *0.1 M perchloric acid* is equivalent to 23.93 mg of $C_{13}H_{21}NO_3$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J.*



A. 5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-methoxyethyl]-2-hydroxyphenyl]methanol,

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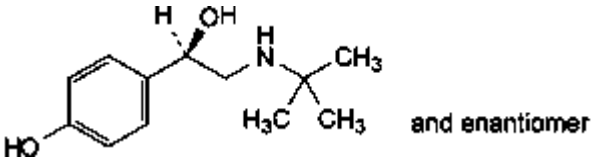
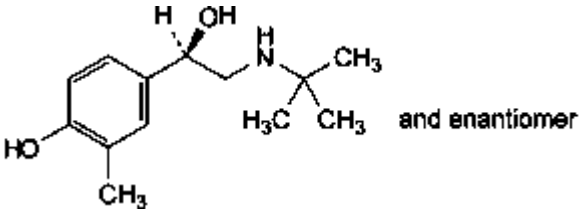
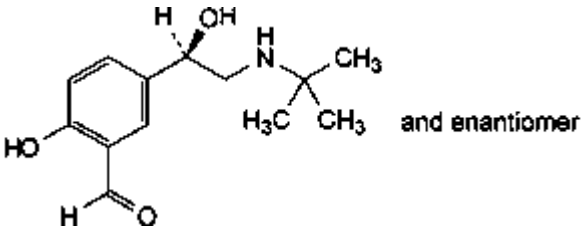


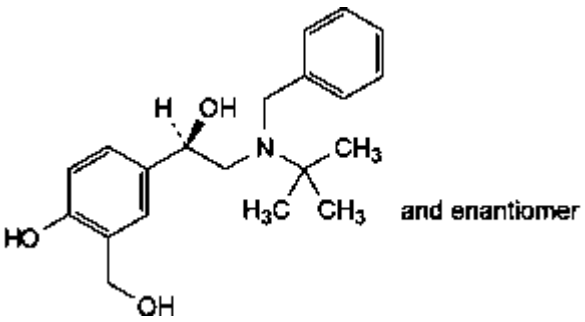
B. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxyphenyl)ethanol,



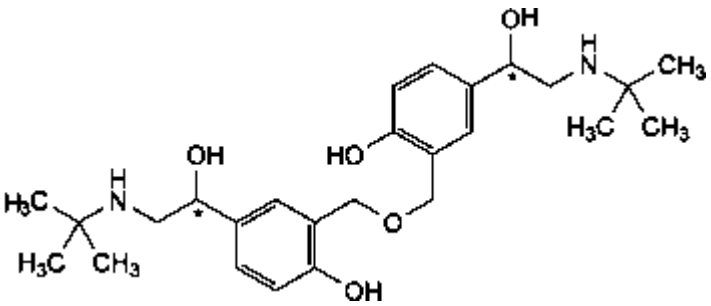
C. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxy-3-methylphenyl)ethanol,



D. 5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxybenzaldehyde,



E. (1*RS*)-2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol,



F. 1,1′-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol],

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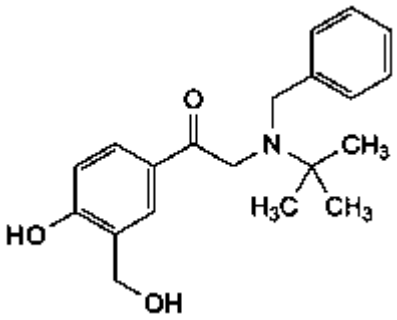
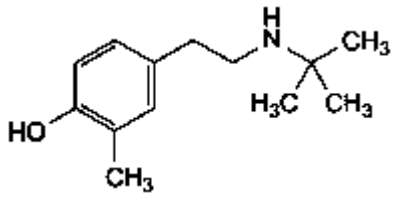
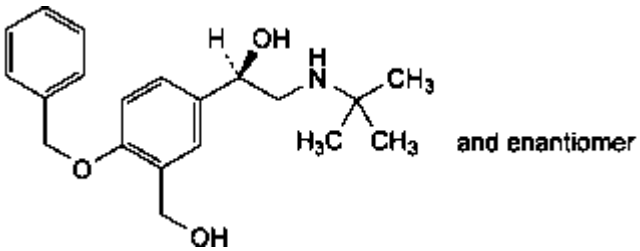


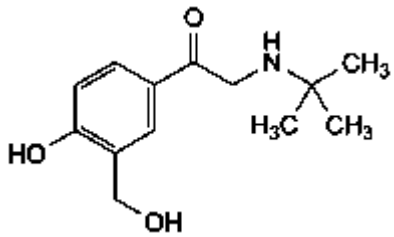
G. 2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone,



H. 4-[2-[(1,1-dimethylethyl)amino]ethyl]-2-methylphenol,



I. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]ethanol,



J. 2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (salbutamone).

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Salbutamol Inhalation Powder

General Notices

Salbutamol Powder for Inhalation, metered-dose powder inhalers

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Inhalation Powder consists of Salbutamol Sulfate in *microfine powder* either alone or combined with a suitable carrier. It is administered by a dry-powder inhaler.

The inhalation powder complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of salbutamol, $C_{13}H_{21}NO_3$

80.0 to 120.0% of the stated amount.

IDENTIFICATION

For inhalation powders containing salbutamol sulfate

Complies with Identification tests A, B and D stated below.

For inhalation powders containing salbutamol sulfate admixed with lactose

Complies with Identification tests A, B, C and D stated below.

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the powder for inhalation containing the equivalent of 1 mg of salbutamol in 10 mL of *water*.

(2) 0.010% w/v of *salbutamol sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use as the coating *silica gel* (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) Remove the plate, allow it to dry in air, spray with a 0.1% w/v solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride* in *methanol (90%)* and dry in air for 10 minutes. Spray the plate with a 2% w/v solution of *potassium hexacyanoferrate(III)* in a mixture of 1 volume of 18M *ammonia* and 3 volumes of *water* and spray again with the 0.1% w/v solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride* in *methanol (90%)*.

MOBILE PHASE

4 volumes of 13.5M *ammonia*, 16 volumes of *water*, 30 volumes of *propan-2-ol* and 50 volumes of *ethyl acetate*.

CONFIRMATION

The spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (2) has the same retention time as the principal peak in the chromatogram obtained with solution (3).

C. Dissolve 0.25 g of the powder in 5 mL of *water*. Add 5 mL of 6M *ammonia* and heat in a water bath at 80° for 10 minutes. An orange-red colour is produced.

D. Dissolve about 45 mg of the powder in 5 mL of *water*. The resulting solution yields reaction A characteristic of *sulfates*, Appendix VI.

TESTS

Related Substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dissolve a quantity of the inhalation powder in sufficient mobile phase to produce a solution containing the equivalent of 0.020% w/v salbutamol and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 3 volumes of this solution to 10 volumes.

(3) 0.00004% w/v of *salbutamol sulfate BPCRS*.

(4) 0.00016% w/v of *salbutamol impurity F EPCRS*.

(5) 0.00004% w/v of each of *salbutamol sulfate BPCRS* and *salbutamol impurity B BPCRS*.

(6) 0.00006% w/v of *salbutamol impurity D EPCRS*.

(7) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume of this solution to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *spherical end-capped octylsilyl silica gel for chromatography* (5 µm) (Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

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(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 25 times the retention time of salbutamol.

MOBILE PHASE

22 volumes of *acetonitrile* and 78 volumes of a solution containing 0.287% w/v of *sodium heptanesulfonate* and 0.25% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.7 with 2M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention of impurity D with reference to salbutamol (retention time, about 2 minutes) is about 2.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salbutamol impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.8%);

the area of any peak corresponding to salbutamol impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (6) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

The total impurity content is not greater than 2.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (7) (0.05%).

Uniformity of delivered dose

Complies with the requirements for Inhalation Powders stated under Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient *water* to produce a solution containing the equivalent of 0.0001% w/v of salbutamol.

(2) 0.00012% w/v of *salbutamol sulfate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of salbutamol, $C_{13}H_{21}NO_3$, per delivered dose using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*. Repeat the procedure as described for reservoir systems under Inhalation Powders, Uniformity of delivered dose.

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ASSAY

Where the label states delivered dose, use the average of the individual results determined in the test for Uniformity of delivered dose.

Where the label states metered dose, carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the powder in sufficient *water* to produce a solution containing the equivalent of 0.0001% w/v of salbutamol.

(2) 0.00012% w/v of *salbutamol sulfate BPCRS* in *water*.

(3) 0.0001% w/v of *salbutamol sulfate BPCRS* and 0.0001% w/v of *salbutamol impurity B BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of salbutamol, $C_{13}H_{21}NO_3$, using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

LABELLING

The label states the content of active ingredient in terms of the equivalent metered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Salbutamol Sulfate.

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Salbutamol Inhalation Powder, pre-metered

General Notices

Salbutamol Inhalation Powder, pre-dispensed

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Inhalation Powder, pre-metered consists of Salbutamol Sulfate in *microfine powder* either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of salbutamol, $C_{13}H_{21}NO_3$

95.0 to 105.0% of the stated amount per pre-metered unit.

IDENTIFICATION

For inhalation powders, pre-metered containing salbutamol sulfate

Complies with Identification tests A, B and D stated below.

For inhalation powders, pre-metered containing salbutamol sulfate admixed with lactose

Complies with Identification tests A, B, C and D stated below.

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the powder containing the equivalent of 1 mg of salbutamol in 10 mL of *water*.

(2) 0.010% w/v of *salbutamol sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use as the coating *silica gel* (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) Remove the plate, allow it to dry in air, spray with a 0.1% w/v solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride* in *methanol (90%)* and dry in air for 10 minutes. Spray the plate with a 2% w/v solution of *potassium hexacyanoferrate(III)* in a mixture of 1 volume of 18M *ammonia* and 3 volumes of *water* and spray again with the 0.1% w/v solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride* in *methanol (90%)*.

MOBILE PHASE

4 volumes of 13.5M *ammonia*, 16 volumes of *water*, 30 volumes of *propan-2-ol* and 50 volumes of *ethyl acetate*.

CONFIRMATION

The spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (2) has the same retention time as the principal peak in the chromatogram obtained with solution (3).

C. Dissolve 0.25 g of the powder in 5 mL of *water*. Add 5 mL of 6M *ammonia* and heat in a water bath at 80° for 10 minutes. An orange-red colour is produced.

D. Dissolve about 45 mg of the powder in 5 mL of *water*. The resulting solution yields reaction A characteristic of *sulfates*, Appendix VI.

TESTS

Related Substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dissolve a quantity of the powder in sufficient mobile phase to produce a solution containing the equivalent of 0.020% w/v of salbutamol and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 3 volumes to 10 volumes.

(3) 0.00004% w/v of *salbutamol sulfate BPCRS*.

(4) 0.00016% w/v of *salbutamol impurity F EPCRS*.

(5) 0.00004% w/v of each of *salbutamol sulfate BPCRS* and *salbutamol impurity B BPCRS*.

(6) 0.00006% w/v of *salbutamol impurity D EPCRS*.

(7) Dilute 1 volume of solution (1) to 100 volumes and further, dilute 1 volume to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *spherical end-capped octylsilyl silica gel for chromatography* (5 µm) (Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

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(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 25 times the retention time of salbutamol.

MOBILE PHASE

22 volumes of *acetonitrile* and 78 volumes of a solution containing 0.287% w/v of *sodium heptanesulfonate* and 0.25% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.7 with 2M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to salbutamol (retention time, about 2 minutes) are: impurity D, about 2.7; impurity F, about 6.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.8%);

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (6) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

The total impurity content is not greater than 2.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (7) (0.05%).

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient mobile phase to produce a solution containing the equivalent of 0.00008% w/v of salbutamol.

(2) 0.0001% w/v of *salbutamol sulfate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of salbutamol, $C_{13}H_{21}NO_3$, per delivered dose using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*. Repeat the procedure as described for pre-metered systems under Inhalation Powders, Uniformity of delivered dose.

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of the pre-metered units in sufficient *water* to produce a solution containing the equivalent of 0.0001% w/v of salbutamol.

(2) 0.00012% w/v of *salbutamol sulfate BPCRS* in *water*.

(3) 0.0001% w/v of *salbutamol sulfate BPCRS* and 0.0001% w/v of *salbutamol impurity B BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of salbutamol, $C_{13}H_{21}NO_3$, using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

LABELLING

The label states the content of active ingredient in terms of the equivalent metered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Salbutamol Sulfate.

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Salbutamol Injection

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Injection is a sterile solution of Salbutamol Sulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of salbutamol, $C_{13}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or very pale yellow solution.

IDENTIFICATION

A. Dilute a volume of the injection with sufficient *0.1M hydrochloric acid* to produce a solution containing the equivalent of 0.004% w/v of salbutamol. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum only at 276 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Evaporate a suitable volume of the injection to dryness using a rotary evaporator, wash the residue with four 5-mL quantities of *absolute ethanol*, filter, evaporate the filtrate to dryness and dissolve the residue in sufficient *water* to produce a solution containing the equivalent of 0.1% w/v of salbutamol.

(2) 0.12% w/v of *salbutamol sulfate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, place it in an atmosphere saturated with *diethylamine* for a few minutes and spray with *diazotised nitroaniline solution*.

MOBILE PHASE

4 volumes of 13.5M *ammonia*, 16 volumes of *water*, 30 volumes of *propan-2-ol* and 50 volumes of *ethyl acetate*.

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CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

C. Dilute a volume containing the equivalent of 0.5 mg of salbutamol to 50 mL with *water*, add 1 mL of 5M *ammonia*, 1 mL of a 3% w/v solution of *4-aminoantipyrine*, 10 mL of a 2% w/v solution of *potassium hexacyanoferrate(III)* and 10 mL of *chloroform*, shake and allow to separate. An orange-red colour is produced in the *chloroform* layer.

D. A volume containing the equivalent of 1 mg of salbutamol yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

pH, 3.4 to 5.0, Appendix V L.

Salbutamol ketone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.050% w/v of salbutamol.

(2) 0.00025% w/v of *salbutamol ketone impurity BPCRS* (impurity J) in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1.5 volumes of *propan-2-ol* and 98.5 volumes of 0.1M *ammonium acetate* adjusted to pH 4.5 with *glacial acetic acid*.

Mobile phase B *propan-2-ol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-20	100→86	0→14	linear gradient
20-30	86	14	isocratic
30-31	86→100	14→0	linear gradient

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
31-45	100	0	re-equilibration

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salbutamol ketone (impurity J) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dilute a volume of the injection, if necessary, with the mobile phase to produce a solution containing the equivalent of 0.005% w/v of salbutamol.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.0004% w/v of *salbutamol impurity B BPCRS* and 0.0005% w/v of *salbutamol sulfate BPCRS*.

(4) 0.000025% w/v of *salbutamol impurity D EPCRS*.

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with spherical *end-capped octylsilyl silica gel for chromatography* (5 µm) with a specific surface area of 335 m^2 per g, a pore size of 10 nm and a carbon loading of 11.7% (Waters Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 25 times the retention time of salbutamol.

MOBILE PHASE

22 volumes of *acetonitrile* and 78 volumes of a solution containing 0.287% w/v of *sodium heptanesulfonate* and 0.25% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.65 with 2M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention of impurity D with reference to salbutamol (retention time about 2 minutes) is about 2.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (1%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

The total impurity content is not greater than 2%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dilute the injection to produce a solution containing the equivalent of 0.0025% w/v of salbutamol.

(2) 0.003% w/v of *salbutamol sulfate BPCRS*.

(3) 0.003% w/v of *salbutamol sulfate BPCRS* and 0.0025% w/v of *2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* (impurity C).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 5 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *propan-2-ol*, 300 volumes of 0.05M *ammonium acetate* and 685 volumes of *water*, the pH of the mixture being adjusted to 4.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{21}NO_3$ using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of salbutamol.

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Salbutamol Nebuliser Solution

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Nebuliser Solution is a solution of Salbutamol Sulfate in a suitable vehicle, intended to be converted into aerosols by nebulisers.

The nebuliser solution complies with the requirements stated under Preparations for Inhalation and with the following requirements.

Content of salbutamol, $C_{13}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute the solution being examined with sufficient 0.1M *hydrochloric acid* to produce a solution containing the equivalent of 0.008% w/v of salbutamol. The *light absorption* of the resulting solution, Appendix II B, in the range 230 nm to 350 nm exhibits a maximum only at 276 nm.

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (2) corresponds to the salbutamol peak in the chromatogram obtained with solution (3).

C. Dilute the solution being examined with sufficient *water* to produce a solution containing the equivalent of 0.025% w/v of salbutamol. The resulting solution yields reaction A characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

pH, 3.0 to 5.0, Appendix V L.

Salbutamol ketone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the nebuliser solution, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.050% w/v of salbutamol.

(2) 0.00025% w/v of *salbutamol ketone impurity BPCRS* (impurity J) in *water*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1.5 volumes of *propan-2-ol* and 98.5 volumes of 0.1M *ammonium acetate* adjusted to pH 4.5 with *glacial acetic acid*.

Mobile phase B *propan-2-ol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-20	100→86	0→14	linear gradient
20-30	86	14	isocratic
30-31	86→100	14→0	linear gradient
31-45	100	0	re-equilibration

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salbutamol ketone (impurity J) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dilute a quantity of the nebuliser solution with sufficient of the mobile phase to produce a solution containing the equivalent of 0.05% w/v of salbutamol.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.0004% w/v of *salbutamol impurity B BPCRS* and 0.0005% w/v of *salbutamol sulfate BPCRS*.

(4) 0.00025% w/v of *salbutamol impurity D EPCRS*.

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with spherical *end-capped octylsilyl silica gel for chromatography* (5 µm) with a specific surface area of 335 m^2 per g, a pore size of 10 nm and a carbon loading of 11.7% (Waters Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

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(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 25 times the retention time of salbutamol.

MOBILE PHASE

22 volumes of *acetonitrile* and 78 volumes of a solution containing 0.287% w/v of *sodium heptanesulfonate* and 0.25% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.65 with 2M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention of impurity D with reference to salbutamol (retention time, about 2 minutes) is about 2.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salbutamol impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

The total impurity content is not greater than 1%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Dilute a volume of the nebuliser solution containing the equivalent of 4 mg of salbutamol to 50 mL with *0.1M hydrochloric acid*. Measure the *absorbance* of the resulting solution at the maximum at 276 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell. Calculate the content of $C_{13}H_{21}NO_3$ in the solution from the absorbance obtained from a solution prepared by diluting 1 volume of a 0.1% w/v solution of *salbutamol sulfate BPCRS* to 10 volumes with *0.1M hydrochloric acid* and from the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

STORAGE

Salbutamol Nebuliser Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of salbutamol.

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Salbutamol Oral Solution

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Oral Solution is a solution of Salbutamol Sulfate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of salbutamol, $C_{13}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.3 to 4.0, Appendix V L.

2-*tert*-Butylamino-1-(4-hydroxy-3-methylphenyl)ethanol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add to a volume of the oral solution containing the equivalent of 5 mg of salbutamol sufficient mobile phase A to produce 50 mL, mix, filter through a glass microfibre filter (Whatman GF/C is suitable) and use the filtrate.

(2) 0.00005% w/v of *2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* (impurity C) in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C8 is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

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(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1.5 volumes of *propan-2-ol* and 98.5 volumes of 0.1M *ammonium acetate* adjusted to pH 4.5 with *glacial acetic acid*.

Mobile phase B *propan-2-ol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-20	100→86	0→14	linear gradient
20-30	86	14	isocratic
30-31	86→100	14→0	linear gradient
31-45	100	0	re-equilibration

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to 2-*tert*-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the oral solution containing the equivalent of 2 mg of salbutamol with sufficient of mobile phase A to produce 50 mL and filter through a glass microfibre filter (Whatman GF/C is suitable).

(2) 0.004% w/v of *salbutamol sulfate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under 2-*tert*-Butylamino-1-(4-hydroxy-3-methylphenyl)ethanol may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{21}NO_3$ in the oral solution using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

STORAGE

Salbutamol Oral Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of salbutamol.

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IMPURITIES

The impurities limited by the requirements of this monograph include impurity C listed under Salbutamol Sulfate.

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Salbutamol Pressurised Inhalation, Suspension

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Pressurised Inhalation, Suspension is a suspension of either Salbutamol or Salbutamol Sulfate in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation, suspension complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. *Preparations for inhalation: Aerodynamic Assessment of Fine Particles*. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of salbutamol, $C_{13}H_{21}NO_3$

85.0 to 115.0% of the stated delivered dose (ex-acutator).

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, in the range 1650 to 400 cm^{-1} is concordant with the *reference spectrum* of either salbutamol (*RS 314*) or salbutamol sulfate (*RS 315*), as appropriate. Examine the substance as a dispersion in *potassium bromide* prepared in the following manner. Discharge the inhaler a sufficient number of times into a mortar to obtain 2 mg of Salbutamol, grind the residue thoroughly with 0.1 g of *potassium bromide*, add a further 0.2 g of *potassium bromide* and mix thoroughly.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

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(1) Shake a quantity of the pressurised inhalation containing 20 mg of Salbutamol with sufficient *water* to produce a solution containing 0.08% w/v of salbutamol.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.08% w/v of *salbutamol sulfate for system suitability EPCRS* and 0.00075% w/v of *salbutamol ketone impurity BPCRS* (impurity J).

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Hypersil 100 C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 273 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1M *ammonium acetate*, adjusted to pH 4.5 with *acetic acid*.

Mobile phase B *propan-2-ol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	96	4	isocratic
5-20	96→86	4→14	linear gradient
20-30	86	14	isocratic
30-31	86→96	14→4	linear gradient
31-45	96	4	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to salbutamol (retention time of about 6 minutes) are: impurity J, about 0.9; impurity C, about 2.1; impurity D, about 2.3, impurity N, about 2.5 and impurity F, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.1, where *Hp* is the height above the baseline of the peak due to impurity J and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to salbutamol.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity N and impurity F is at least 1.2.

LIMITS

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Use the chromatogram obtained with solution (3) to identify the peaks due to impurities C, D, F, J and N in the chromatogram obtained from solution (1). Multiply the area of any peak corresponding to impurity C, F, J and N by a correction factor of 1.7, 0.6, 0.2 and 1.4 respectively.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of delivered dose

Complies with the requirements stated under *Pressurised Metered-dose Preparations for Inhalation* using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under *Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose* and dissolve the collected dose in sufficient *methanol* to produce a solution containing the equivalent of 0.000075% w/v of Salbutamol.
(2) 0.000092% w/v of *salbutamol sulfate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 3 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.85 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 276 nm.
(f) Inject 150 µL of each solution.

MOBILE PHASE

238 volumes of 0.1% w/v of *ammonium acetate solution* and 762 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid, unless in the chromatogram obtained with solution (2), the *symmetry factor* for the peak due to salbutamol is less than 2.5.

DETERMINATION OF CONTENT

Calculate the content of salbutamol, $C_{13}H_{21}NO_3$ per delivered dose using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

ASSAY

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Use the average of the individual results determined in the test for Uniformity of delivered dose.

LABELLING

The label states the content of active ingredient in terms of the equivalent amount of salbutamol.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Salbutamol.

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Salbutamol Prolonged-release Capsules

General Notices

Prolonged-release Salbutamol Capsules

Salbutamol Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Prolonged-release Capsules contain Salbutamol Sulfate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Salbutamol Sulfate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of salbutamol, $C_{13}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing the equivalent of 4 mg of salbutamol with 10 mL of *water* and filter. The filtrate yields the reactions characteristic of *sulfates*, Appendix VI.

B. Shake a quantity of the contents of the capsules containing the equivalent of 2.5 mg of salbutamol with 50 mL of a 2% w/v solution of *sodium tetraborate*, add 1 mL of a 3% w/v solution of *4-aminoantipyrine*, 10 mL of a 2% w/v solution of *potassium hexacyanoferrate(III)* and 10 mL of *chloroform*, shake and allow to separate. An orange-red colour is produced in the chloroform layer.

C. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake with the aid of ultrasound, a quantity of the contents of the capsules containing the equivalent of 20 mg of salbutamol with 5 mL of the mobile phase, add sufficient mobile phase to produce 10 mL and filter the resulting solution through a 0.45-µm filter (Whatman GF/C is suitable), discarding the first 1 mL of filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Dilute 3 volumes of solution (2) to 10 volumes with the mobile phase.

(4) 0.0004% w/v of *salbutamol impurity B BPCRS* and 0.0005% w/v of *salbutamol sulfate BPCRS* in the mobile phase.

(5) 0.001% w/v of *salbutamol impurity D EPCRS* in the mobile phase.

(6) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with spherical *end-capped octylsilyl silica gel for chromatography* (5 µm) with a specific surface area of 335 m^2 per g, a pore size of 10 nm and a carbon loading of 11.7% (Waters Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 25 times the retention time of salbutamol.

MOBILE PHASE

22 volumes of *acetonitrile* and 78 volumes of a solution containing 0.287% w/v of *sodium heptanesulfonate* and 0.25% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.65 with 2M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention of impurity D with reference to salbutamol (retention time about 2 minutes) is about 2.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to salbutamol and salbutamol impurity B is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salbutamol impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

The total impurity content is not greater than 1%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1 %).

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ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake with the aid of ultrasound a quantity of the capsule contents containing the equivalent of 20 mg of salbutamol with 5 mL of the mobile phase, add sufficient mobile phase to produce 100 mL and filter the resulting solution through a 0.45-µm filter (Whatman GF/C is suitable), discarding the first 10 mL of filtrate.

(2) 0.024% w/v of *salbutamol sulfate BPCRS* in the mobile phase.

(3) 0.0004% w/v of *salbutamol impurity B BPCRS* and 0.0005% w/v of *salbutamol sulfate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to salbutamol and salbutamol impurity B is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{21}NO_3$ in the capsules using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of salbutamol.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Salbutamol Sulfate.

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Salbutamol Sulfate

General Notices

Salbutamol Sulphate

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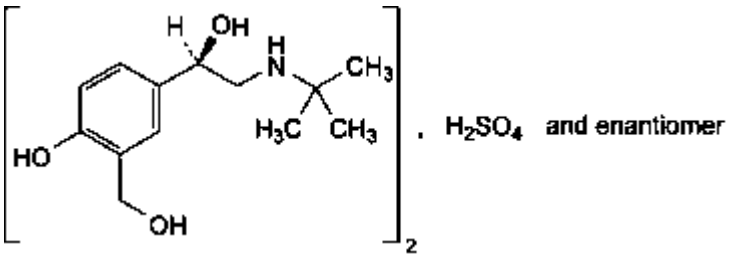

$C_{26}H_{44}N_2O_{10}S$ 576.7 *51022-70-9*

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

Preparations

Salbutamol Inhalation Powder

Salbutamol Inhalation Powder, pre-metered

Salbutamol Injection

Salbutamol Nebuliser Solution

Salbutamol Oral Solution

Salbutamol Pressurised Inhalation

Salbutamol Tablets

Salbutamol Prolonged-release Capsules

Ph Eur

DEFINITION

Bis[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol] sulfate.

Content

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98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, practically insoluble or very slightly soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 80.0 mg in a 10 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of the solution to 100.0 mL with a 10 g/L solution of *hydrochloric acid R*.

Spectral range 230-350 nm.

Absorption maximum At 276 nm.

Specific absorbance at the absorption maximum 55 to 64.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *salbutamol sulfate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*. Dry the residues and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 12 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 12 mg of *salbutamol sulfate CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *water R*, *ethyl acetate R*, *2-propanol R*, *methyl isobutyl ketone R* (3:18:35:45:50 *V/V/V/V/V*).

Application 1 µL.

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Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 1 g/L solution of *methylbenzothiazolone hydrazone hydrochloride R* in a 90 per cent *V/V* solution of *methanol R*, followed by a 20 g/L solution of *potassium ferricyanide R* in a mixture of 1 volume of *concentrated ammonia R1* and 3 volumes of *water R*, followed by a further spraying with a 1 g/L solution of *methylbenzothiazolone hydrazone hydrochloride R* in a 90 per cent *V/V* solution of *methanol R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in 50 mL of a 20 g/L solution of *disodium tetraborate R*. Add 1 mL of a 30 g/L solution of *4-aminoantipyrine R*, 10 mL of *methylene chloride R* and 10 mL of a 20 g/L solution of *potassium ferricyanide R*. Shake and allow to separate. An orange-red colour develops in the methylene chloride layer.

E. It gives reaction (a) of sulfates (*2.3.1*).

TESTS

Solution S

Dissolve 0.250 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Acidity or alkalinity

To 10 mL of solution S add 0.15 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 3.0 mg of *salbutamol impurity D CRS* and 3.0 mg of *salbutamol impurity F CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A. Dilute 2.0 mL of the solution to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

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Reference solution (c) With the aid of ultrasound, dissolve the contents of a vial of *salbutamol impurity J CRS* in 1.0 mL of the test solution.

Reference solution (d) Dissolve 1 mg of *salbutamol impurity D CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (e) Dilute 0.4 mL of reference solution (d) to 10 mL with mobile phase A. Dissolve the contents of a vial of *salbutamol sulfate for system suitability CRS* (containing impurities C, F, N and O) in 1 mL of this solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.45 g of *sodium dihydrogen phosphate monohydrate R* in 900 mL of a 0.05 per cent *V/V* solution of *triethylamine R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with a 0.05 per cent *V/V* solution of *triethylamine R*;

— *mobile phase B*: *methanol R*, *acetonitrile R* (35:65 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 30	95 → 10	5 → 90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 20 µL of the test solution and reference solutions (a), (b), (c) and (e).

Relative retention With reference to salbutamol (retention time = about 7 min): impurity J = about 0.9; impurity C = about 1.6; impurity N = about 1.67; impurity D = about 1.68; impurity F = about 1.77; impurity O = about 1.82.

Identification of impurities Use the chromatogram supplied with *salbutamol sulfate for system suitability CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities C, D, F, N and O; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity J.

System suitability:

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity N and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity D in the chromatogram obtained with

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reference solution (e); minimum 2.0, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to salbutamol in the chromatogram obtained with reference solution (c).

Limits:

— *impurities D, F*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities C, N, O*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: maximum 0.9 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Boron

Maximum 50 ppm.

Test solution To 50 mg of the substance to be examined add 5 mL of a solution containing 13 g/L of *anhydrous sodium carbonate R* and 17 g/L of *potassium carbonate R*. Evaporate to dryness on a water-bath and dry at 120 °C. Ignite the residue rapidly until the organic matter has been destroyed, allow to cool and add 0.5 mL of *water R* and 3.0 mL of a freshly prepared 1.25 g/L solution of *curcumin R* in *glacial acetic acid R*. Warm gently to effect solution, allow to cool and add 3.0 mL of a mixture prepared by adding 5 mL of *sulfuric acid R*, slowly and with stirring, to 5 mL of *glacial acetic acid R*. Mix and allow to stand for 30 min. Dilute to 100.0 mL with *ethanol (96 per cent) R*, filter and use the filtrate.

Reference solution Dissolve 0.572 g of *boric acid R* in 1000.0 mL of *water R*. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. To 2.5 mL of this solution add 5 mL of a solution containing 13 g/L of *anhydrous sodium carbonate R* and 17 g/L of *potassium carbonate R*, and treat this mixture in the same manner as the test solution.

Measure the absorbance (*2.2.25*) of the test solution and of the reference solution at the absorption maximum at about 555 nm. The absorbance of the test solution is not greater than that of the reference solution.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.400 g in 5 mL of *formic acid R* and add 35 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 57.67 mg of $C_{26}H_{44}N_2O_{10}S$.

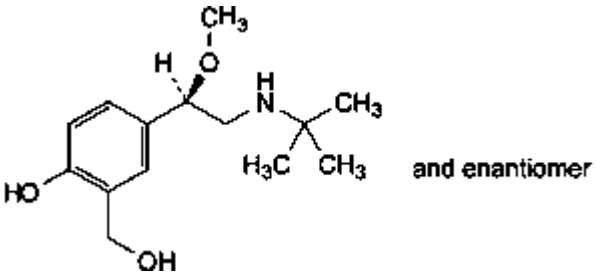
STORAGE

Protected from light.

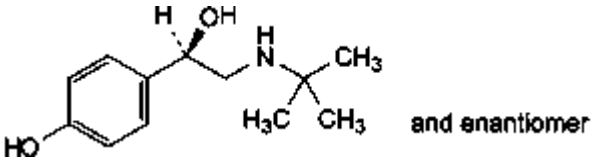
IMPURITIES

Specified impurities *C, D, F, N, O.*

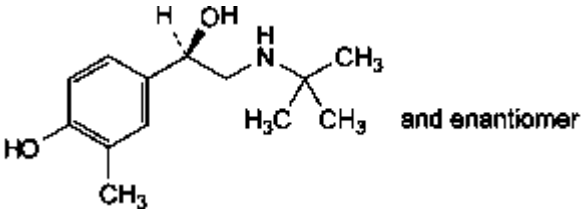
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, E, G, I, J, K, L, M.*



A. [5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-methoxyethyl]-2-hydroxyphenyl]methanol,



B. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxyphenyl)ethanol,



C. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxy-3-methylphenyl)ethanol,

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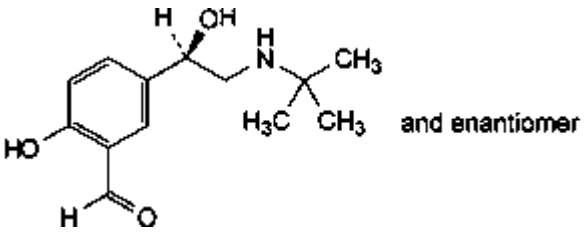
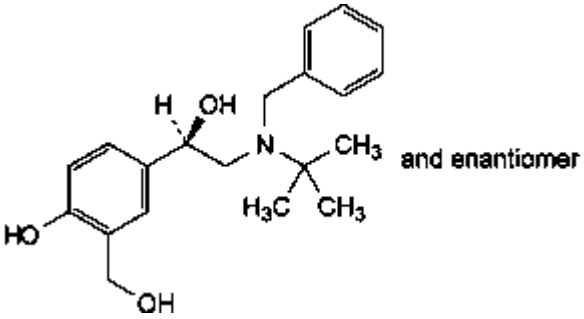


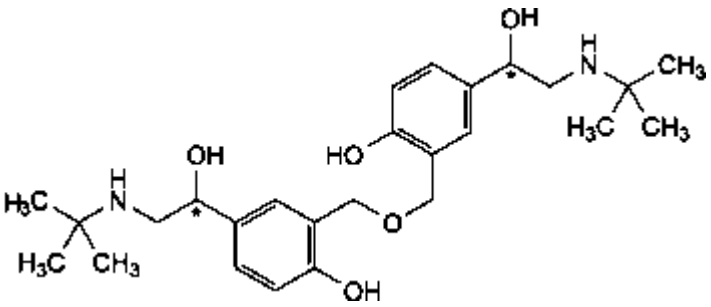
and enantiomer

D. 5-[(1*RS*)-2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxybenzaldehyde,

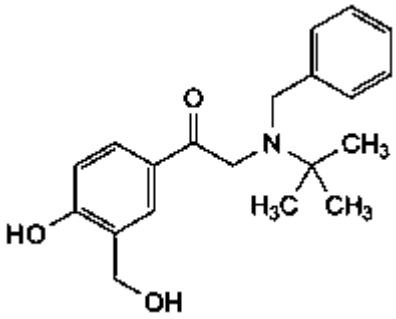


and enantiomer

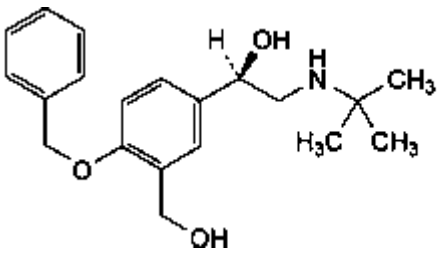
E. (1*RS*)-2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol,



F. 1,1′-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol],



G. 2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone,



and enantiomer

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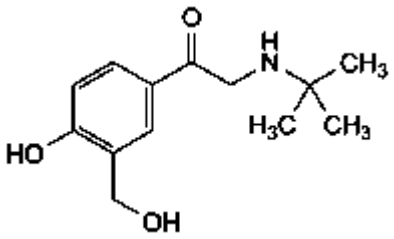
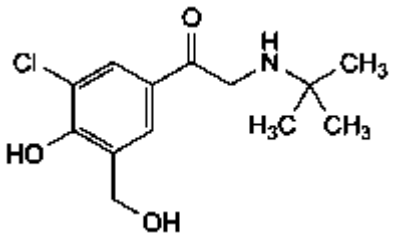
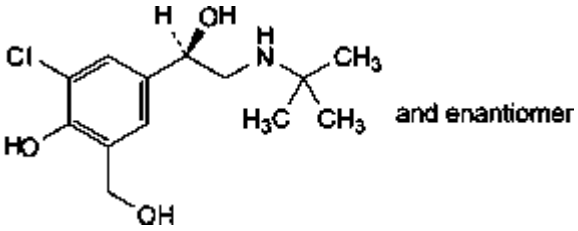
I. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]ethanol,



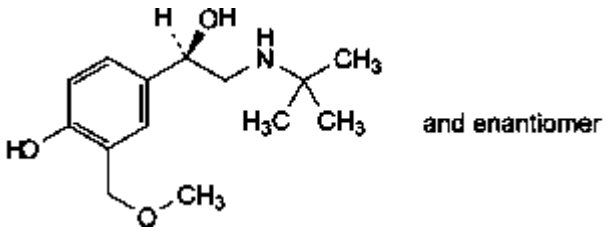
J. 2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (salbutamone),



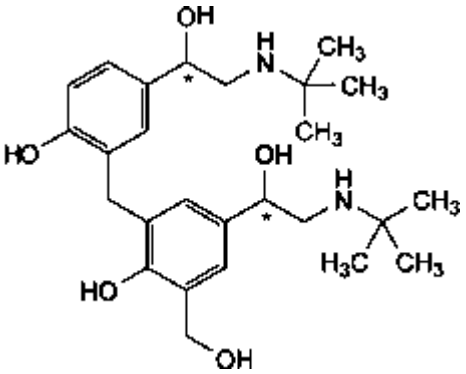
K. 2-[(1,1-dimethylethyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanone,



L. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,



M. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(methoxymethyl)phenyl]ethanol,



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N. 2-[(1,1-dimethylethyl)amino]-1-[3-[[5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]methyl]-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,

O. unknown structure.

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Salbutamol Tablets

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Tablets contain Salbutamol Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of salbutamol, $C_{13}H_{21}NO_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 10 mg of salbutamol with 10 mL of *methanol* (*80%*) and filter.

(2) 0.12% w/v of *salbutamol sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 18 cm.

(e) After removal of the plate, dry in air, spray with a 0.1% w/v solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride* in *methanol* (*90%*) followed by a 2% w/v solution of *potassium hexacyanoferrate(III)* in a mixture of 1 volume of 18M *ammonia* and 3 volumes of *water* and spray again with the solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride*.

MOBILE PHASE

3 volumes of 13.5M *ammonia*, 18 volumes of *water*, 35 volumes of *ethyl acetate*, 45 volumes of *propan-2-ol* and 50 volumes of *4-methylpentan-2-one*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

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B. Shake a quantity of the powdered tablets containing the equivalent of 2.5 mg of salbutamol with 50 mL of a 2% w/v solution of *sodium tetraborate*, add 1 mL of a 3% w/v solution of *4-aminoantipyrine*, 10 mL of a 2% w/v solution of *potassium hexacyanoferrate(III)* and 10 mL of *chloroform*, shake and allow to separate. An orange-red colour is produced in the chloroform layer.

C. Shake a quantity of the powdered tablets containing the equivalent of 4 mg of salbutamol with 10 mL of *water* and filter. The filtrate yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the tablets containing the equivalent of 48 mg of salbutamol with 60 mL of *ethanol* (*50%*) for 30 minutes, filter, evaporate to dryness using a rotary evaporator and gentle heat and dissolve the residue in 2 mL of *water*; if the residue is coloured, pass the final solution through a column (3 cm × 6 mm) packed with *activated acid aluminium oxide* (Brockmann Grade I is suitable).

(2) 0.058% w/v of *salbutamol sulfate BPCRS* in *water*.

(3) 0.022% w/v of *salbutamol sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 18 cm.

(e) After removal of the plate, dry in air, spray with a 0.1% w/v solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride* in *methanol* (*90%*) followed by a 2% w/v solution of *potassium hexacyanoferrate(III)* in a mixture of 1 volume of 18M *ammonia* and 3 volumes of *water* and spray again with the solution of *3-methylbenzothiazolin-2-one hydrazone hydrochloride*.

MOBILE PHASE

3 volumes of 13.5M *ammonia*, 18 volumes of *water*, 35 volumes of *ethyl acetate*, 45 volumes of *propan-2-ol* and 50 volumes of *4-methylpentan-2-one*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (2%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.75%).

Uniformity of content

Tablets containing less than the equivalent of 2 mg and/or less than 2% w/w of salbutamol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of *water* to one tablet, shake for 1 hour, add sufficient *water* to produce 100 mL, mix, centrifuge and use the supernatant liquid.

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(2) 0.05% w/v of *2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* (impurity C) and 0.06% w/v of *salbutamol sulfate BPCRS* in the mobile phase.

(3) 0.0024% w/v of *salbutamol sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 5 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *propan-2-ol*, 30 volumes of 0.05M *ammonium acetate* and 65 volumes of *water*, adjust the pH of the mixture to 4.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{21}NO_3$ in each tablet using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of salbutamol

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of salbutamol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 tablets with 100 mL of *water* for 1 hour, add sufficient *water* to produce a solution containing the equivalent of 0.040% w/v of salbutamol, mix, centrifuge and use the supernatant liquid.

(2) 0.040% w/v of *2-tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* (impurity C) and 0.048% w/v of *salbutamol sulfate BPCRS* in *methanol* (*10%*).

(3) 0.048% w/v of *salbutamol sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 1.5.

DETERMINATION OF CONTENT

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Calculate the content of $C_{13}H_{21}NO_3$ in the tablets using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of salbutamol.

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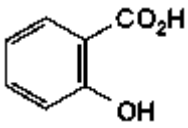
Salicylic Acid

General Notices

(Ph. Eur. monograph 0366)



$C_7H_6O_3$ 138.1 *69-72-7*

Action and use

Keratolytic.

Preparations

Coal Tar and Salicylic Acid Ointment

Dithranol and Salicylic Acid Ointment

Salicylic Acid Collodion

Salicylic Acid Cream

Salicylic Acid Ointment

Zinc and Salicylic Acid Paste

Ph Eur

DEFINITION

2-Hydroxybenzenecarboxylic acid.

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or white or colourless, acicular crystals.

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Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Melting point (2.2.14): 158 °C to 161 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *salicylic acid CRS*.

C. Dissolve about 30 mg in 5 mL of *0.05 M sodium hydroxide*, neutralise if necessary and dilute to 20 mL with *water R*. 1 mL of the solution gives reaction (a) of salicylates (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in 50 mL of boiling *distilled water R*, cool and filter.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1 g in 10 mL of *ethanol (96 per cent) R*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.50 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *phenol R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *salicylic acid impurity B CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 50 mg of *4-hydroxybenzoic acid R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (e) Dilute a mixture of 1.0 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Reference solution (f) Dilute a mixture of 0.1 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Column:

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— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R*, *methanol R*, *water R* (1:40:60 *V/V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 10 µL of the test solution and reference solutions (d), (e) and (f).

Identification of impurities Use the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, B and C.

Relative retention With reference to impurity C (retention time = about 9.5 min): impurity A = about 0.6; impurity B = about 0.8.

System suitability Reference solution (e):

— the 3rd peak in the chromatogram corresponds to the peak due to impurity C in the chromatogram obtained with reference solution (d);

— *resolution*: minimum 1.0 between the peaks due to impurities B and C; if necessary, adjust the quantity of acetic acid in the mobile phase.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.1 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.05 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.02 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (f) (0.05 per cent);

— *total*: not more than twice the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.2 per cent);

— *disregard limit*: 0.3 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.03 per cent). Do not disregard the peak due to impurity C.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

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Sulfates

Maximum 200 ppm.

Dissolve 1.0 g in 5 mL of *dimethylformamide R* and add 4 mL of *water R*. Mix thoroughly. Add 0.2 mL of *dilute hydrochloric acid R* and 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*. After 15 min any opalescence in the solution is not more intense than that in a standard prepared as follows: to 2 mL of *sulfate standard solution (100 ppm SO_4) R* add 0.2 mL of *dilute hydrochloric acid R*, 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*, 3 mL of *water R* and 5 mL of *dimethylformamide R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Dissolve 0.120 g in 30 mL of *ethanol (96 per cent) R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, using 0.1 mL of *phenol red solution R* as indicator.

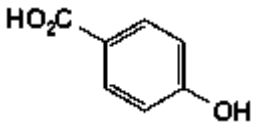
1 mL of *0.1 M sodium hydroxide* is equivalent to 13.81 mg of $C_7H_6O_3$.

STORAGE

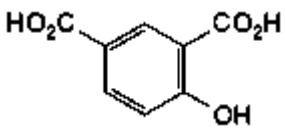
Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. 4-hydroxybenzoic acid,



B. 4-hydroxyisophthalic acid,

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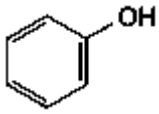

C. phenol.

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Salicylic Acid Collodion

General Notices

DEFINITION

Salicylic Acid	120 g
Flexible Collodion	Sufficient to produce 1000 mL

The collodion complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of salicylic acid, $C_7H_6O_3$

13.0 to 15.8% w/w.

ASSAY

Dilute 2 g to 200 mL with *acetone* and to 2 mL of this solution add 35 mL of *acetate buffer pH 2.45* and 4 mL of a freshly prepared 0.5% w/v solution of *iron(III) chloride hexahydrate*. Dilute to 50 mL with *acetate buffer pH 2.45*, filter, discarding the first 10 mL of the filtrate, and measure the *absorbance* of the resulting solution at the maximum at 525 nm, Appendix II B. Calculate the content of $C_7H_6O_3$ from the *absorbance* obtained by repeating the operation using 2 mL of a 0.12% w/v solution of *salicylic acid* in *ethanol* (*96%*) and beginning at the words ‘add 35 mL of *acetate buffer pH 2.45* ...’.

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Salicylic Acid Cream

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Keratolytic.

DEFINITION

Salicylic Acid Cream contains Salicylic Acid in Aqueous Cream.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the cream also complies with the requirements stated under Unlicensed Medicines.

Content of salicylic acid, $C_7H_6O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake 1 g with 10 mL of *water*, filter and add to the filtrate *iron(III) chloride solution R1*; an intense reddish violet colour is produced which persists on the addition of 6M *acetic acid*. Add 2M *hydrochloric acid*; the colour disappears and a white, crystalline precipitate is produced.

ASSAY

Dissolve a quantity of the cream containing 0.25 g of Salicylic Acid in a mixture of 20 mL of *ethanol* (*96%*), previously neutralised to *phenol red solution*, and 20 mL of *ether* and titrate with *0.1M sodium hydroxide VS* using *phenol red solution* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 13.81 mg of $C_7H_6O_3$.

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Salicylic Acid Ointment

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Keratolytic.

DEFINITION

Salicylic Acid Ointment contains Salicylic Acid in a suitable water-emulsifying basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the ointment also complies with the requirements stated under Unlicensed Medicines.

Content of salicylic acid, $C_7H_6O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake 1 g with 10 mL of *water*, filter and add to the filtrate *iron(III) chloride solution R1*; an intense reddish violet colour is produced which persists on the addition of 6M *acetic acid*. Add 2M *hydrochloric acid*; the colour disappears and a white, crystalline precipitate is produced.

ASSAY

Dissolve a quantity of the ointment containing 0.25 g of Salicylic Acid in a mixture of 20 mL of *ethanol* (*96%*), previously neutralised to *phenol red solution*, and 20 mL of *ether* and titrate with *0.1M sodium hydroxide VS* using *phenol red solution* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 13.81 mg of $C_7H_6O_3$.

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Salmeterol Inhalation Powder, pre-metered

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salmeterol Inhalation Powder, pre-metered consists of Salmeterol Xinafoate in microfine powder or equivalent either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. *Preparations for inhalation: Aerodynamic Assessment of Fine Particles*. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of salmeterol, $C_{25}H_{37}NO_4$

92.5 to 107.5% of the stated amount of the pre-metered unit.

IDENTIFICATION

A. Dissolve the contents of a pre-metered unit in 30 volumes of *water* and 70 volumes of *methanol*. The *light absorption* of this solution, Appendix II B, is in the range 210 to 350 nm and is concordant with that of a 0.0004% w/v solution of *salmeterol xinafoate EPCRS* in the same solvent.

B. In the test for Uniformity of delivered dose, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to salmeterol in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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Solution A 30 volumes of *water* and 70 volumes of *methanol*.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient solution A to produce a solution containing the equivalent of 0.00025% w/v of salmeterol.

(2) 0.0004% w/v of *salmeterol xinafoate EPCRS* in solution A.

(3) 0.0005% w/v of *salmeterol xinafoate for system suitability EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5µm) (Hypersil ODS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 276 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

0.5 volumes of *formic acid*, 35 volumes of 0.15M *ammonium acetate* and 65 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.1, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to salmeterol.

DETERMINATION OF CONTENT

Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{36}H_{45}NO_7$ in *salmeterol xinafoate EPCRS*. Each mg of $C_{36}H_{45}NO_7$ is equivalent to 0.6880 mg of $C_{25}H_{37}NO_4$. Repeat the procedure as described for pre-metered systems under Powders for Inhalation, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 30 volumes of *water* and 70 volumes of *methanol*.

(1) Dissolve a quantity of the powder for inhalation containing the equivalent of 0.6 mg of salmeterol in solution A, mix with the aid of ultrasound and dilute to 100 mL with solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.00011% w/v of *salmeterol xinafoate impurity 1 BPCRS* in solution A.

(4) 0.0005% w/v of *salmeterol xinafoate for system suitability EPCRS* in solution A.

(5) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 276 nm. At twice the retention time of salmeterol, change the wavelength to 254 nm to enable detection of salmeterol xinafoate impurity 1.

(f) Inject 200 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of salmeterol.

MOBILE PHASE

0.5 volumes of *formic acid*, 35 volumes of 0.15M *ammonium acetate* and 65 volumes of *methanol*

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to salmeterol (retention time about 5 minutes) are: impurity A, about 0.4; xinafoic acid, about 0.6; impurity C, about 0.7; impurity E, about 0.95; impurity F, about 1.4 and impurity 1, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *peak-to-valley ratio* is at least 1.1, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to salmeterol.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3.0%);

the area of any other secondary peaks is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of any other secondary peaks is not greater than twice the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solution A 30 volumes of *water* and 70 volumes of *methanol*.

(1) Dissolve a quantity of the mixed contents of 20 pre-metered units equivalent to 0.6 mg of salmeterol with solution A, mix with the aid of ultrasound, add sufficient solution A to produce 100 mL and filter.

(2) 0.0009% w/v of *salmeterol xinafoate EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Uniformity of delivered dose may be used.

DETERMINATION OF CONTENT

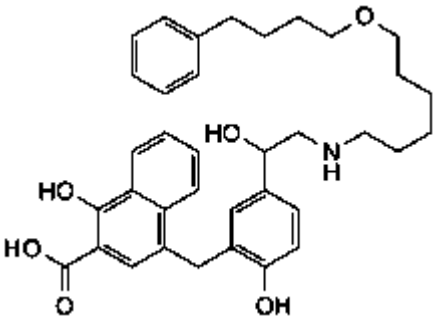
Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{36}H_{45}NO_7$ in *salmeterol xinafoate EPCRS*. Each mg of $C_{36}H_{45}NO_7$ is equivalent to 0.6880 mg of $C_{25}H_{37}NO_4$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent metered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include A, C, E and F listed under Salmeterol Xinafoate and:



1. *rac*-1-hydroxy-4-{[2-hydroxy-5-(1-hydroxy-2-{6-(4-phenylbutoxy)hexyl]amino}ethyl)phenyl]methyl}naphthalene-2-carboxylic acid.

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Salmeterol Pressurised Inhalation, Suspension

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salmeterol Pressurised Inhalation, Suspension is a suspension of Salmeterol Xinafoate in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. *Preparations for inhalation: Aerodynamic Assessment of Fine Particles*. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of salmeterol, $C_{25}H_{37}NO_4$

85.0 to 115.0% of the stated delivered dose (ex-actuator).

IDENTIFICATION

A. Cool the contents of the pressurised container, remove the valve assembly and allow the propellant to evaporate. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Salmeterol Xinafoate *(RS 499)*.
B. In the Uniformity of delivered dose, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

Complies with the requirements stated under *Pressurised Metered-dose Preparations for Inhalation* using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol* to produce a solution containing the

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equivalent of 0.000021% w/v of salmeterol.

(2) 0.0000375% w/v of *salmeterol xinafoate EPCRS* in *methanol*.

(3) 0.0000375% w/v of *salmeterol xinafoate for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (3.0 mm × 5.0 cm) packed with *octadecylsilyl silica gel for chromatography* (5µm) (Hypersil ODS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a fluorimetric detector with an excitation wavelength of 225 nm and an emission wavelength of 305 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

1 volume of 0.0025M *sodium dodecyl sulfate* containing 1% v/v *glacial acetic acid* and 10 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the relative retention of impurity F with reference to salmeterol (retention time about 2.6 minutes) is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to salmeterol.

DETERMINATION OF CONTENT

Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{36}H_{45}NO_7$ in *salmeterol xinafoate EPCRS*. Each mg of $C_{36}H_{45}NO_7$ is equivalent to 0.6880 mg of $C_{25}H_{37}NO_4$. Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A A mixture of equal volumes of *acetonitrile* and *water*.

(1) Prepare the sample in an appropriate manner and dissolve the sample in sufficient solution A to produce a solution containing the equivalent of 0.02% w/v of salmeterol.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.054% w/v of *salmeterol xinafoate for system suitability EPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5µm) (X Terra MS-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Solution B Dilute 1 volume of 1M *potassium dihydrogen phosphate*, previously adjusted to pH 2.5 with *orthophosphoric acid*, to 100 volumes with *water*.

Mobile phase A 0.005M *sodium dodecyl sulfate* in a mixture of equal volumes of solution B and *acetonitrile*.

Mobile phase B 0.005M *sodium dodecyl sulfate* in a mixture of 2 volumes of solution B and 8 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-20	100→0	0→100	linear gradient
20-25	0	100	isocratic
25-26	0→100	100→0	linear gradient
26-31	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to salmeterol (retention time about 12 minutes) are: xinafoic acid, about 0.1; impurity A, about 0.4; impurity B, about 0.7; impurity C, about 0.85; impurity D, about 0.93; impurity E, about 0.96; impurity F, about 1.2 and impurity G, about 2.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between salmeterol and impurity E is at least 1.5.

LIMITS

Identify any peak corresponding to impurity D in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salmeterol impurity G is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

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the sum of the areas of all impurities is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

LABELLING

The label states the content of active ingredient in terms of the equivalent delivered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, D, E, F and G listed under Salmeterol Xinafoate.

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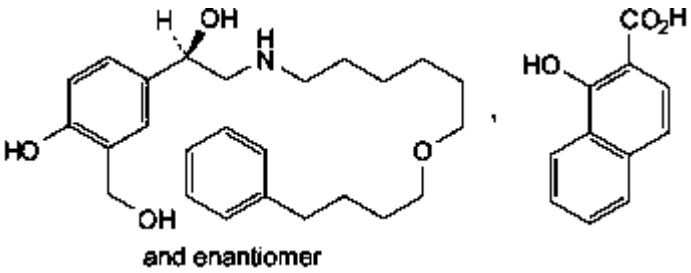
Salmeterol Xinafoate

General Notices

(Ph. Eur. monograph 1765)



$C_{36}H_{45}NO_7$ 604 *94749-08-3*

Action and use

$Beta_2$-adrenoceptor agonist; bronchodilator.

Preparations

Fluticasone and Salmeterol Inhalation Powder, pre-metered

Fluticasone and Salmeterol Inhalation Powder

Fluticasone and Salmeterol Pressurised Inhalation, Suspension

Salmeterol Inhalation Powder, pre-metered

Salmeterol Pressurised Inhalation, Suspension

Ph Eur

DEFINITION

(1*RS*)-1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol 1-hydroxynaphthalene-2-carboxylate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

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Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison salmeterol xinafoate CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light*.

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dissolve the contents of a vial of salmeterol xinafoate for system suitability CRS (containing impurities E and G) in 1 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of salmeterol xinafoate for peak identification CRS (containing impurity D) in the solvent mixture and dilute to 1.0 mL with the solvent mixture.

Reference solution (d) Dissolve 25.0 mg of salmeterol xinafoate CRS in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (e) Dilute 1.0 mL of reference solution (a) to 20.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: mix 24 volumes of a 7.71 g/L solution of ammonium acetate R and 24 volumes of a 28.84 g/L solution of sodium dodecyl sulfate R and adjust to pH 2.7 with glacial acetic acid R; mix with 52 volumes of acetonitrile R;

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— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 16	100	0
16 - 36	100 → 30	0 → 70
36 - 45	30	70

Flow rate 2 mL/min.

Detection Spectrophotometer at 278 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *salmeterol xinafoate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities E and G; use the chromatogram supplied with *salmeterol xinafoate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to salmeterol (retention time = about 13 min): xinafoic acid = about 0.2; impurity D = about 0.8; impurity E = about 0.9; impurity G = about 2.7.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 10, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to salmeterol.

Calculation of percentage contents:

— for each impurity, use the concentration of salmeterol xinafoate in reference solution (b).

Limits:

— *impurities D, G*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to xinafoic acid.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase A.

Injection 20 µL of test solution (b) and reference solutions (d) and (e).

Run time Until complete elution of the peak due to salmeterol (about 16 min).

System suitability Reference solution (e):

— *peak-to-valley ratio*: minimum 10, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to salmeterol.

Calculate the percentage content of $C_{36}H_{45}NO_7$ using the chromatogram obtained with reference solution (d) and taking into account the assigned content of *salmeterol xinafoate CRS*.

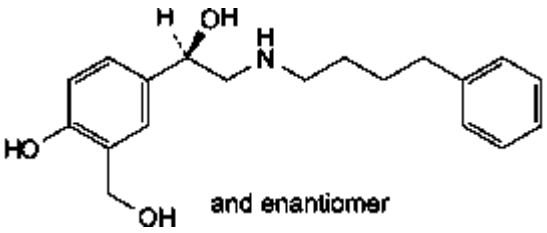
STORAGE

Protected from light.

IMPURITIES

Specified impurities *D, G*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, F*.



A. (1*RS*)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[(4-phenylbutyl)amino]ethanol,

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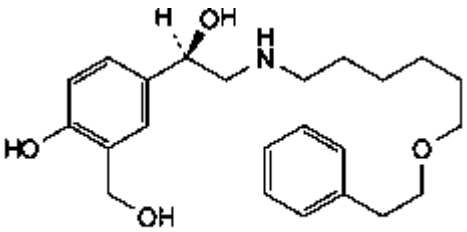
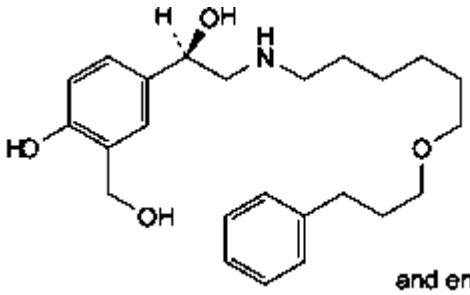


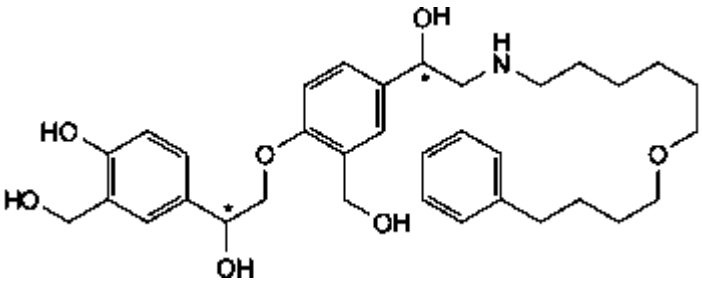
and enantiomer

B. (1*RS*)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(2-phenylethoxy)hexyl]amino]ethanol,

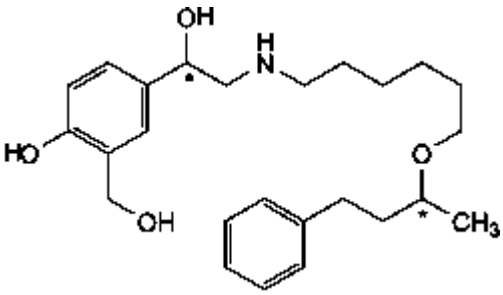


and enantiomer

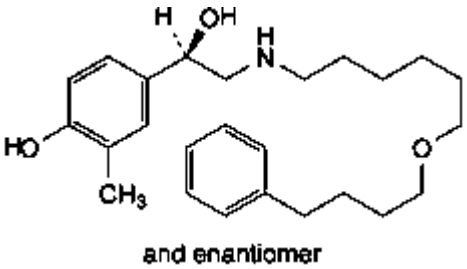
C. (1*RS*)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(3-phenylpropoxy)hexyl]amino]ethanol,



D. 1-[4-[2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethoxy]-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol,



E. 1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(1-methyl-3-phenylpropoxy)hexyl]amino]ethanol,



and enantiomer

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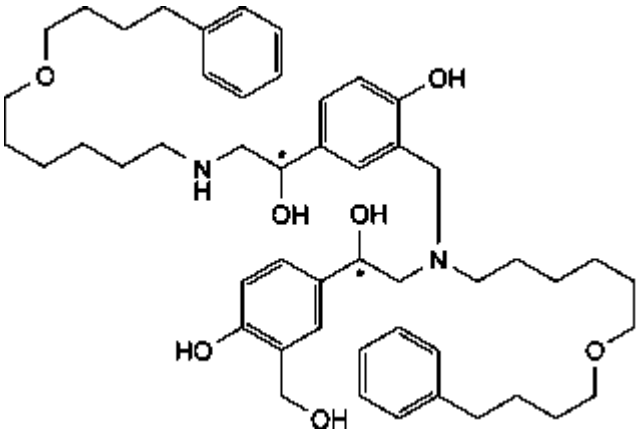
F. (1*RS*)-1-(4-hydroxy-3-methylphenyl)-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol,



G. 1-[4-hydroxy-3-[[[2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl][6-(4-phenylbutoxy)hexyl]amino]methyl]phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol.

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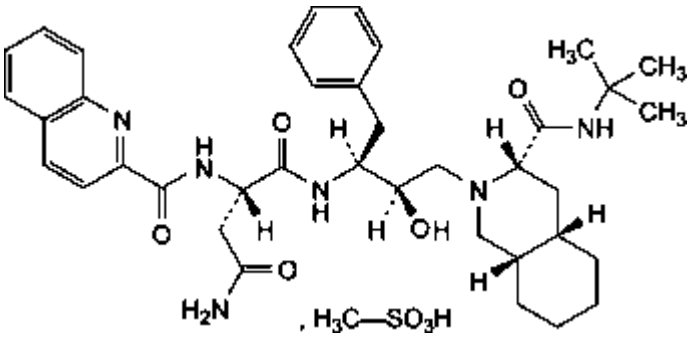
Saquinavir Mesilate

General Notices

(Ph. Eur. monograph 2267)



$C_{39}H_{54}N_6O_8S$ 767 *149845-06-7*

Action and use

Protease inhibitor; antiviral (HIV).

Ph Eur

DEFINITION

(2*S*)-N^1-[(1*S*,2*R*)-1-Benzyl-3-[(3*S*,4a*S*,8a*S*)-3-[(1,1-dimethylethyl)carbamoyl]octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl]-2-[(quinolin-2-ylcarbonyl)amino]butanediamide methanesulfonate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in saquinavir mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

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White or almost white, slightly hygroscopic powder.

Solubility

Practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *saquinavir mesilate CRS*.

TESTS

Specific optical rotation (2.2.7)

-42.0 to -35.0 (anhydrous substance).

Dissolve 0.25 g in *anhydrous methanol R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *water for chromatography R*, *acetonitrile R1* (47:53 *V/V*).

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture, using sonication, and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *saquinavir for system suitability CRS* (containing impurities A, B, C and D) in 1.0 mL of the solvent mixture and sonicate for 2 min.

Reference solution (c) Dissolve 30.0 mg of *saquinavir mesilate CRS* in the solvent mixture, using sonication, and dilute to 100.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: to 2.5 mL of *strong sodium hydroxide solution R* add 900 mL of *water for chromatography R*, adjust to pH 1.8 with *perchloric acid R* and dilute to 1000 mL with *water for chromatography R*;

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— *mobile phase B*: mobile phase A, *acetonitrile R1* (38:62 *V/V*);

Time (min)	Mobile phase A (per cent)	Mobile phase B (per cent)
0 - 1	50	50
1 - 31	50 → 0	50 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *saquinavir for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to saquinavir (retention time = about 17 min): impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.5; impurity D = about 0.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to saquinavir.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.5; impurity B = 0.5; impurity C = 2.5;

— *impurities A, B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 10 µL of the test solution and reference solution (c).

Calculate the percentage content of saquinavir mesilate from the assigned content of *saquinavir mesilate CRS*.

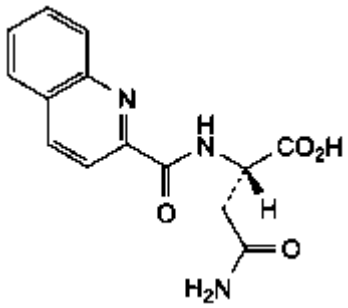
STORAGE

In an airtight container, protected from light.

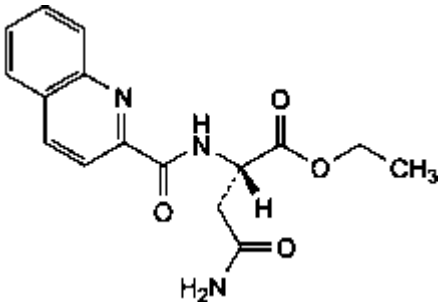
IMPURITIES

Specified impurities *A, B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, F, G, H.*



A. (2*S*)-4-amino-4-oxo-2-[(quinolin-2-ylcarbonyl)amino]butanoic acid,



B. ethyl (2*S*)-4-amino-4-oxo-2-[(quinolin-2-ylcarbonyl)amino]butanoate,

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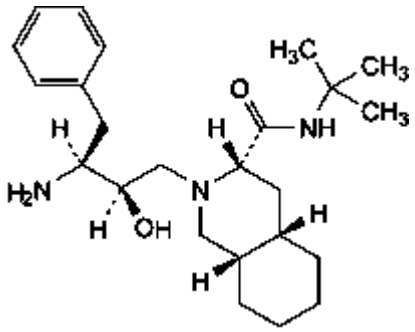
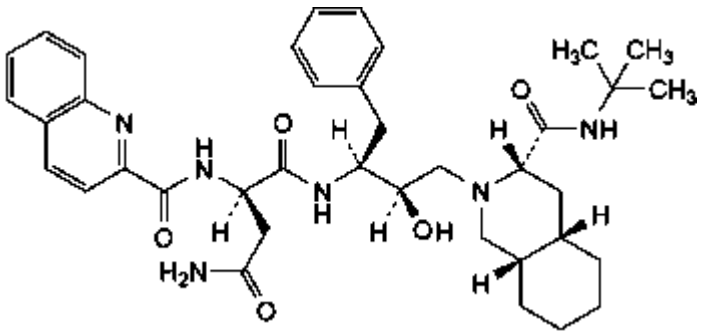
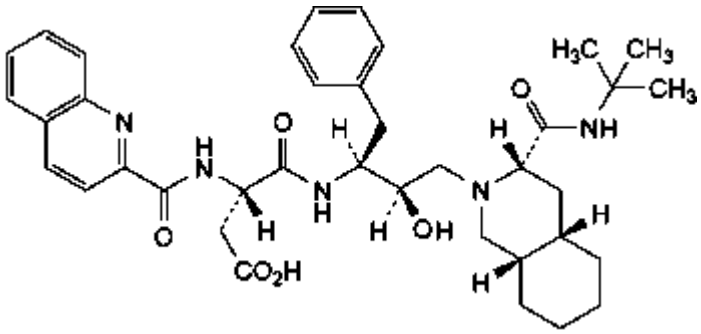


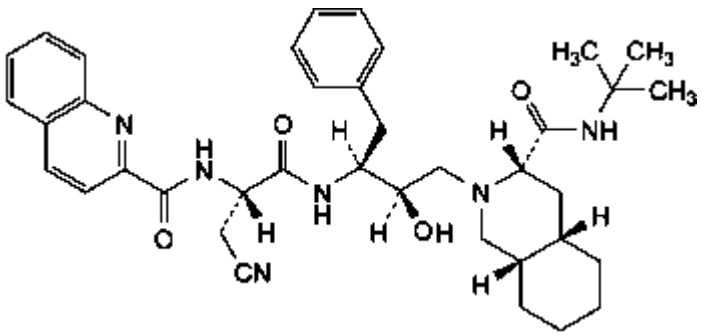
C. (3*S*,4a*S*,8a*S*)-2-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*-(1,1-dimethylethyl)decahydroisoquinoline-3-carboxamide,



D. (2*R*)-N^1-[(1*S*,2*R*)-1-benzyl-3-[(3*S*,4a*S*,8a*S*)-3-[(1,1-dimethylethyl)carbamoyl]octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl]-2-[(quinolin-2-ylcarbonyl)amino]butanediamide (2-*epi*-saquinavir),



E. (3*S*)-4-[[(1*S*,2*R*)-1-benzyl-3-[(3*S*,4a*S*,8a*S*)-3-[(1,1-dimethylethyl)carbamoyl]octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl]amino]-4-oxo-3-[(quinolin-2-ylcarbonyl)amino]butanoic acid,



F. *N*-[(1*S*)-2-[[(1*S*,2*R*)-1-benzyl-3-[(3*S*,4a*S*,8a*S*)-3-[(1,1-dimethylethyl)carbamoyl]octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl]amino]-1-(cyanomethyl)-2-oxoethyl]quinoline-2-carboxamide,

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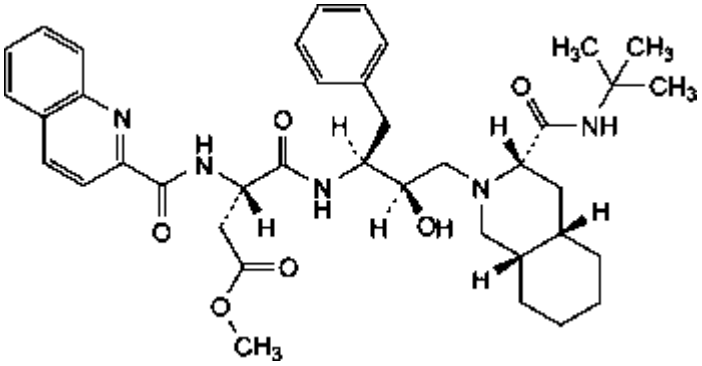
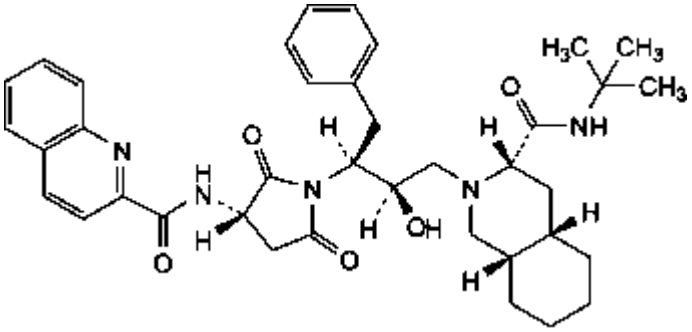


G. methyl (3*S*)-4-[[(1*S*,2*R*)-1-benzyl-3-[(3*S*,4a*S*,8a*S*)-3-[(1,1-dimethylethyl)carbamoyl]octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl]amino]-4-oxo-3-[(quinolin-2-ylcarbonyl)amino]butanoate,



H. *N*-[(3*S*)-1-[(1*S*,2*R*)-1-benzyl-3-[(3*S*,4a*S*,8a*S*)-3-[(1,1-dimethylethyl)carbamoyl]octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl]-2,5-dioxopyrrolidin-3-yl]quinoline-2-carboxamide.

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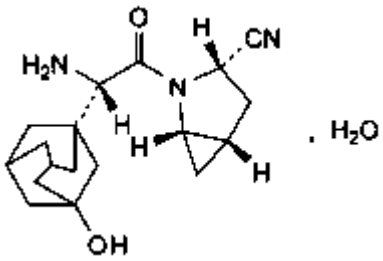
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Saxagliptin Monohydrate

General Notices

(Ph. Eur. monograph 3136)



$C_{18}H_{25}N_3O_2,H_2O$ 333.4 *945667-22-1*

Action and use

Dipeptidylpeptidase-4 inhibitor; treatment of type 2 diabetes mellitus.

Ph Eur

DEFINITION

(1*S*,3*S*,5*S*)-2-[(*S*)-Amino(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is produced by highly stereoselective methods of manufacture; consideration must be given to the formation of potential stereoisomeric impurities during the manufacturing process, and procedures must be implemented for the appropriate control of these impurities.

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Sparingly soluble in water, soluble in anhydrous ethanol, very slightly soluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison saxagliptin monohydrate CRS.

TESTS

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 54.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 54.0 mg of saxagliptin monohydrate CRS in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 20.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of saxagliptin impurity mixture CRS (containing impurities A and B) in 1.0 mL of mobile phase A.

Reference solution (d) Dissolve the contents of a vial of saxagliptin for system suitability CRS (containing impurity C) in 1.0 mL of mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: trifluoroacetic acid R, methanol R2, water for chromatography R (1:100:900 *V/V/V*);

— *mobile phase B*: trifluoroacetic acid R, water for chromatography R, methanol R2 (1:100:900 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 22	100 → 80	0 → 20
22 - 42	80 → 0	20 → 100

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Flow rate 0.6 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 15 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B; use the chromatogram supplied with *saxagliptin for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to saxagliptin (retention time = about 21 min): impurity A = about 0.73; impurity B = about 0.75; impurity C = about 1.1.

System suitability:

— *peak-to-valley ratio*: minimum 1.4, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to saxagliptin in the chromatogram obtained with reference solution (d); minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A in the chromatogram obtained with reference solution (c).

Calculation of percentage content:

— *correction factor*: multiply the peak area of impurity A by 0.7.

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.50 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Water (2.5.12)

5.2 per cent to 6.1 per cent, determined on 0.100 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances, with the following modifications.

Injection Test solution and reference solution (a).

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System suitability Reference solution (a):

— *symmetry factor*: maximum 6.0.

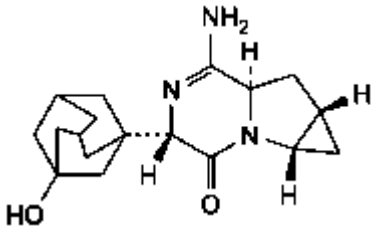
Calculate the percentage content of $C_{18}H_{25}N_3O_2$ taking into account the assigned content of *saxagliptin monohydrate CRS*.

STORAGE

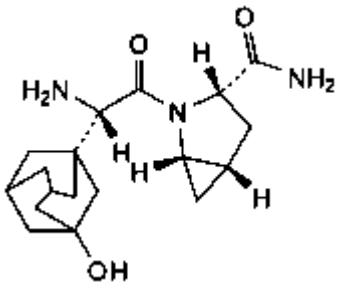
At a temperature of 2 °C to 8 °C.

IMPURITIES

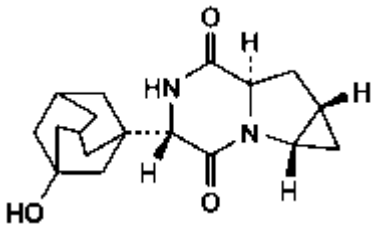
Specified impurities *A, B, C.*



A. (1a*S*,4*S*,6a*R*,7a*S*)-6-amino-4-(3-hydroxyadamantan-1-yl)-1,1a,4,6a,7,7a-hexahydro-3*H*-cyclopropa[4,5]pyrrolo[1,2-*a*]pyrazin-3-one,



B. (1*S*,3*S*,5*S*)-2-[(*S*)-amino(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide,



C. (1a*S*,4*S*,6a*R*,7a*S*)-4-(3-hydroxyadamantan-1-yl)hexahydro-1*H*-cyclopropa[4,5]pyrrolo[1,2-*a*]pyrazine-3,6-dione.

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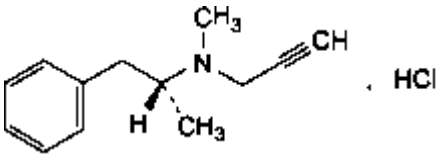
Selegiline Hydrochloride

General Notices

(Ph. Eur. monograph 1260)



$C_{13}H_{18}ClN$ 223.7 *14611-52-0*

Action and use

Monoamine oxidase type B inhibitor; treatment of Parkinson’s disease.

Preparations

Selegiline Oral Solution

Selegiline Tablets

Ph Eur

DEFINITION

N-Methyl-*N*-[(1*R*)-1-methyl-2-phenylethyl]prop-2-yn-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, slightly soluble in acetone and in ethyl acetate.

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About 143 °C.

IDENTIFICATION

Carry out either tests A, B, D or tests B, C, D.

A. Specific optical rotation (2.2.7): -12.0 to -10.0 (dried substance).

Dissolve 2.00 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *selegiline hydrochloride CRS*.

C. Enantiomeric purity (see Tests).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

3.5 to 4.5.

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in a mixture of 10 µL of *butylamine R* and 1 mL of *2-propanol R* and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 8.0 mg of *(RS)-selegiline hydrochloride CRS* in a mixture of 10 µL of *butylamine R* and 1 mL of *2-propanol R* and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 0.5 mL of reference solution (a) to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R*.

Mobile phase *2-propanol R*, *cyclohexane R* (0.2:99.8 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

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Relative retention With reference to (*R*)-selegiline (retention time = about 6 min): impurity E = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity E and (*R*)-selegiline; if necessary, adjust the concentration of 2-propanol in the mobile phase.

Limit:

— *impurity E*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent).

Related substances

Liquid chromatography (2.2.29).

Butylammonium acetate buffer solution Dilute 4 mL of *butylamine R* in 900 mL of *water R*, adjust to pH 6.5 with *acetic acid R* and dilute to 1000.0 mL with *water R*.

Test solution Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 50 mg of the substance to be examined and 10 mg of *butyl parahydroxybenzoate R* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R1*, butylammonium acetate buffer solution (50:50 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 1.7 times the retention time of selegiline.

Relative retention With reference to selegiline (retention time = about 14 min): butyl parahydroxybenzoate = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to butyl parahydroxybenzoate and selegiline.

Limits:

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— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.5 kPa for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 22.37 mg of $C_{13}H_{18}ClN$.

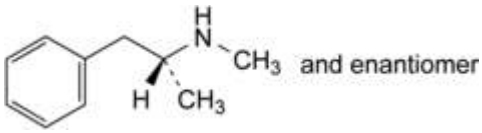
STORAGE

Protected from light.

IMPURITIES

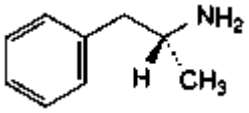
Specified impurities E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, G.



and enantiomer

A. (2*RS*)-*N*-methyl-1-phenylpropan-2-amine ((*RS*)-metamfetamine),



B. (2*R*)-1-phenylpropan-2-amine (amfetamine),

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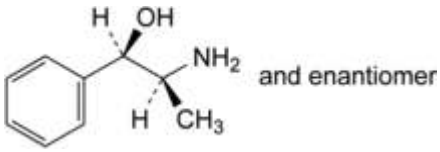
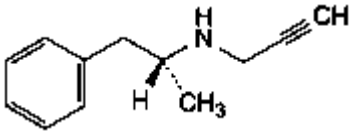
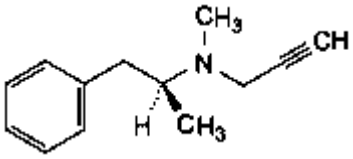


and enantiomer

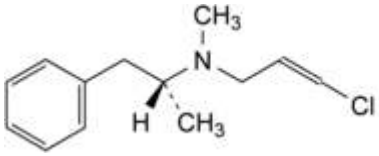
C. (1*RS*,2*SR*)-2-amino-1-phenylpropan-1-ol (phenylpropanolamine),



D. *N*-[(1*R*)-1-methyl-2-phenylethyl]prop-2-yn-1-amine (desmethylselegiline),



E. *N*-methyl-*N*-[(1*S*)-1-methyl-2-phenylethyl]prop-2-yn-1-amine,



and enantiomer

G. (2*EZ*)-3-chloro-*N*-methyl-*N*-[(1*RS*)-1-methyl-2-phenylethyl]prop-2-en-1-amine.

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Selegiline Oral Solution

General Notices

Action and use

Monoamine oxidase type B inhibitor; treatment of Parkinson's disease.

DEFINITION

Selegiline Oral Solution is a solution of Selegiline Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of selegiline hydrochloride, $C_{13}H_{18}ClN$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

(*S*)-Selegiline

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add to a weighed quantity of the oral solution containing 20 mg of Selegiline Hydrochloride 1 mL of *propan-2-ol* and 10 µL of *butylamine*, dilute to 20 mL with the mobile phase, shake thoroughly, filter and use the filtrate.

(2) Dissolve 8 mg of (RS)-*selegiline hydrochloride EPCRS* in a mixture of 10 µL of *butylamine* and 1 mL of *propan-2-ol* and dilute to 20 mL with the mobile phase.

(3) Dilute 0.5 mL of solution (2) to 20 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel OD for chiral separation* (Chiralcel OD is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

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(f) Inject 20 µL of each solution.

MOBILE PHASE

0.2 volume of *propan-2-ol* and 99.8 volumes of *cyclohexane*

SYSTEM SUITABILITY

When the chromatograms are recorded in the prescribed conditions, the retention time of (*S*)-selegiline is about 10 minutes. Adjust the sensitivity of the system so that the height of the peaks in the chromatogram obtained with solution (3) is about 10% of the full scale of the recorder. The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks corresponding to (*S*)-selegiline and (*R*)-selegiline is at least 1.5. If necessary, adjust the concentration of propan-2-ol in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

The area of any peak corresponding to (*S*)-selegiline is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.5%).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Adjust the pH of a quantity of the oral solution containing 10 mg of Selegiline Hydrochloride to 12 with 1M *sodium hydroxide*, add 2 mL of *chloroform*, shake for 30 minutes, allow to separate and use the chloroform layer.
(2) Prepare solution (2) in the same manner as solution (1) but using 4 mL of a 0.25% w/v solution of *selegiline hydrochloride BPCRS* in 0.1M *hydrochloric acid* in place of the oral solution.
(3) Adjust the pH of 1 mL of a 0.025% w/v solution of *selegiline hydrochloride BPCRS* in 0.1M *hydrochloric acid* to 12 with 1M *sodium hydroxide*, add 10 mL of *chloroform*, shake for 30 minutes, allow to separate and use the chloroform layer.
(4) Dilute 2 volumes of solution (3) to 5 volumes with *chloroform*.
(5) Adjust the pH of 2 mL of a 0.025% w/v solution of *methylamphetamine hydrochloride* in 0.1M *hydrochloric acid* to 12 with 1M *sodium hydroxide*, add 10 mL of *chloroform*, shake for 30 minutes, allow to separate and use the chloroform layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC silica gel* F_{254} *plate.*
(b) Use the mobile phase as described below.
(c) Apply 50 µL of each solution.
(d) Develop the plate to 155 cm.
(e) After removal of the plate, dry in air, spray with a solution prepared by mixing 2 volumes of a solution in *acetone* containing 10% w/v of *iron*(III) *chloride* and 4% w/v of *iodine* and 1 volume of a 40% w/v solution of (+)-*tartaric acid* in *water* and allowing to stand for 15 minutes before use. Examine the plate in daylight immediately after spraying.

MOBILE PHASE

0.5 volume of 13.5M *ammonia*, 10 volumes of *1,4-dioxan*, 10 volumes of *propan-2-ol*, 10 volumes of *toluene* and 30 volumes of *xylene*. Use an unlined tank and add the mobile phase immediately before placing the plate in the tank.

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LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to methylamphetamine is not more intense than the spot in the chromatogram obtained with solution (5) (1%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%) and not more than two such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.2%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 10 mL of a mixture of equal volumes of *acetonitrile* and *methanol* to a weighed quantity of the oral solution containing 10 mg of Selegiline Hydrochloride, mix with the aid of ultrasound for 5 minutes, add 40 mL of a mixture of equal volumes of *acetonitrile* and *methanol* and shake mechanically for 15 minutes. Add sufficient *water* to produce 100 mL and dilute 5 volumes of the resulting solution to 10 volumes with the mobile phase.

(2) 0.005% w/v of *selegiline hydrochloride BPCRS* in the mobile phase.

(3) 0.005% w/v of *selegiline hydrochloride BPCRS* and 0.001% w/v of *nortriptyline hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dilute 250 mL of *methanol* and 250 mL of *acetonitrile* to 1000 mL with a solution prepared by dissolving 4 mL of *butylamine* in 900 mL of *water*, adjusting the pH to 6.5 with *acetic acid*, and adding sufficient *water* to produce 1000 mL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{13}H_{18}ClN$, weight in volume, using the declared content of $C_{13}H_{18}ClN$ in *selegiline hydrochloride BPCRS*.

STORAGE

Selegiline Oral Solution should not be refrigerated.

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Selegiline Tablets

General Notices

Action and use

Monoamine oxidase type B inhibitor; treatment of Parkinson's disease.

DEFINITION

Selegiline Tablets contain Selegiline Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of selegiline hydrochloride, $C_{13}H_{18}ClN$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Selegiline Hydrochloride with 2 mL of *water* and 1 mL of 1M *sodium hydroxide*. Extract with 10 mL of *dichloromethane*, filter the extract through *anhydrous sodium sulfate* and evaporate the filtrate to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of selegiline (*RS 400*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

(*S*)-Selegiline

Carry out the method for *liquid chromatography*, Appendix III A, using the following solutions. For solution (1) add to a quantity of the powdered tablets containing 20 mg of Selegiline Hydrochloride 1 mL of *propan-2-ol* and 10 µL of *butylamine*, dilute to 10 mL with the mobile phase, shake thoroughly, filter and use the filtrate. For solution (2) dissolve 8 mg of *(RS)-selegiline hydrochloride EPCRS* in a mixture of 10 µL of *butylamine* and 1 mL of *propan-2-ol* and dilute to 10 mL with the mobile phase. For solution (3) dilute 0.5 mL of solution (2) to 20 mL with the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *silica gel OD for chiral separation* (Chiralcel OD is suitable), (b) as the mobile phase with a flow rate of 0.5 mL per minute a mixture of 0.2 volumes of *propan-2-ol* and 99.8 volumes of *cyclohexane* and (c) a detection wavelength of 220 nm.

Inject 20 µL of each solution. When the chromatograms are recorded in the prescribed conditions, the retention time of (*S*)-selegiline is about 10 minutes. Adjust the sensitivity of the system so that the height of the peaks in the chromatogram obtained with solution (3) is

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about 10% of the full scale of the recorder. The test is not valid unless the *resolution factor* between the peaks corresponding to (*S*)-selegiline and (*R*)-selegiline in the chromatogram obtained with solution (2) is at least 1.5. If necessary, adjust the concentration of propan-2-ol in the mobile phase.

In the chromatogram obtained with solution (1), any peak corresponding to (*S*)-selegiline is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the powdered tablets containing 20 mg of Selegiline Hydrochloride with 10 mL of a mixture of equal volumes of *methanol* and *acetonitrile*, filter and dilute 5 mL of the filtrate to 10 mL with *water*. For solution (2) dilute 1 volume of solution (1) to 10 volumes with the mobile phase and dilute 1 volume of this solution to 50 volumes with the mobile phase. Solution (3) contains 0.001% w/v of *methylamphetamine hydrochloride* in the mobile phase. Solution (4) contains 0.005% w/v of *selegiline hydrochloride BPCRS* and 0.001% w/v of *nortriptyline hydrochloride BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture prepared in the following manner: dilute 250 mL of *methanol* and 250 mL of *acetonitrile* to 1000 mL with a solution prepared by dissolving 4 mL of *butylamine* in 900 mL of *water*, adjusting the pH to 6.5 with *acetic acid*, and adding sufficient *water* to produce 1000 mL and (c) a detection wavelength of 215 nm.

Inject 20 µL of each solution. The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the two principal peaks is at least 3.0.

For solution (1) allow the chromatography to proceed for at least 2.5 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than 2.5 times the area of the peak in the chromatogram obtained with solution (2) (0.5%), the area of not more than two such peaks is greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%) and the sum of the areas of any such peaks is not greater than six times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

If, in the chromatogram obtained with solution (1), the area of any peak corresponding to methylamphetamine is greater than half the area of the peak in the chromatogram obtained with solution (3), the following limits apply. The area of any peak corresponding to methylamphetamine is not greater than the area of the peak in the chromatogram obtained with solution (3) (1%), the area of any other *secondary peak* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%) and the sum of the areas of any such peaks is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (1%). In each case, disregard any peak with an area less than 0.1 times that of the area of the principal peak in the chromatogram obtained with solution (2) (0.02%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the powdered tablets containing 10 mg of Selegiline Hydrochloride with 100 mL of a mixture of equal volumes of *methanol* and *acetonitrile*, filter and dilute 50 mL of the filtrate to 100 mL with *water*. Solution (2) contains 0.005% w/v of *selegiline*

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hydrochloride BPCRS in the mobile phase. Solution (3) contains 0.005% w/v of *selegiline hydrochloride BPCRS* and 0.001% w/v of *nortriptyline hydrochloride BPCRS* in the mobile phase.

The chromatographic conditions described under Related substances may be used.

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.0.

Calculate the content of $C_{13}H_{18}ClN$ in the tablets from the chromatograms obtained and using the declared content of $C_{13}H_{18}ClN$ in *selegiline hydrochloride BPCRS*.

STORAGE

Selegiline Tablets should be protected from light and moisture.

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Selenium Sulfide

General Notices

Selenium Disulphide

(Selenium Disulfide, Ph. Eur. monograph 1147)

SeS_2 143.1 *7488-56-4*

Action and use

Used in treatment of dandruff and seborrhoeic dermatitis of the scalp.

Preparation

Selenium Sulfide Scalp Application

Ph Eur

DEFINITION

Content

52.0 per cent to 55.5 per cent of Se.

CHARACTERS

Appearance

Bright orange or reddish-brown powder.

Solubility

Practically insoluble in water.

IDENTIFICATION

A. Gently boil about 50 mg with 5 mL of *nitric acid R* for 30 min. Dilute to 50 mL with *water R* and filter. To 5 mL of the filtrate add 10 mL of *water R* and 5 g of *urea R*. Heat to boiling, cool and add 1.5 mL of *potassium iodide solution R*. A yellow or orange colour is produced which darkens rapidly on standing. This solution is used in identification test B.

B. Allow the coloured solution obtained under identification A to stand for 10 min and filter through *kieselguhr for chromatography R*. 5 mL of the filtrate gives reaction (a) of sulfates (*2.3.1*).

TESTS

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Soluble selenium compounds

Maximum 5 ppm, calculated as Se.

To 10 g add 100 mL of *water R*, mix well, allow to stand for 1 h with frequent shaking and filter. To 10 mL of the filtrate add 2 mL of a 115 g/L solution of *anhydrous formic acid R*, dilute to 50 mL with *water R* and adjust to pH 2.0-3.0 with an 115 g/L solution of *anhydrous formic acid R*. Add 2 mL of a 5 g/L solution of *3,3'-diaminobenzidine tetrahydrochloride R*. Allow to stand for 45 min and then adjust to pH 6.0-7.0 with *dilute ammonia R1*. Shake the solution for 1 min with 10 mL of *toluene R* and allow the phases to separate. The absorbance (*2.2.25*) of the upper layer measured at 420 nm is not greater than that of a standard prepared at the same time and in the same manner beginning at the words “add 2 mL of an 115 g/L solution of *anhydrous formic acid R*” and using 5 mL of *selenium standard solution (1 ppm Se) R* instead of 10 mL of the filtrate.

ASSAY

To 0.100 g add 25 mL of *fuming nitric acid R* and heat on a water-bath for 1 h; a small insoluble residue may remain. Cool and dilute to 100.0 mL with *water R*. To 25.0 mL of this solution add 50 mL of *water R* and 5 g of *urea R* and heat to boiling. Cool, add 7 mL of *potassium iodide solution R* and 3 mL of *starch solution R*. Titrate immediately with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 1.974 mg of Se.

Ph Eur

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Selenium Sulfide Scalp Application

General Notices

Selenium Sulphide Scalp Application

Selenium Sulfide Application

Selenium Sulfide Cutaneous Suspension

DEFINITION

Selenium Sulfide Scalp Application is a *cutaneous suspension* of Selenium Sulfide in a suitable liquid basis.

The scalp application complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of selenium sulfide, SeS_2

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Gently boil a quantity containing 50 mg of Selenium Sulfide with 5 mL of *nitric acid* for 1 hour, dilute to 50 mL with *water* and filter. To 5 mL of the filtrate add 10 mL of *water* and 5 g of *urea*, boil, cool and add 2 mL of *dilute potassium iodide solution*. A yellow to orange colour is produced, which darkens rapidly on standing.

B. Allow the coloured solution obtained in test A to stand for 10 minutes and filter through *kieselguhr*. The filtrate yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

pH, 4.0 to 5.5, Appendix V L.

ASSAY

To a quantity containing 0.15 g of Selenium Sulfide add 25 mL of *fuming nitric acid*, heat on a water bath for 2 hours, cool and dilute to 250 mL with *water*. To 25 mL of the solution add 10 g of *urea* and 25 mL of *water*, boil, cool, add 10 mL of *dilute potassium iodide solution* and 10 mL of *chloroform* and titrate immediately with 0.05M *sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Shake vigorously as the end point is approached. Each mL of 0.05M *sodium thiosulfate VS* is equivalent to 1.789 mg of SeS_2.

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Self-emulsifying Glyceryl Monostearate

General Notices

Self-emulsifying Monostearin; Self-emulsifying Mono-and Diglycerides of Food Fatty Acids

Action and use

Excipient.

DEFINITION

Self-emulsifying Glyceryl Monostearate is a mixture consisting principally of mono-, di- and triglycerides of stearic and palmitic acids and of minor proportions of glycerides of other fatty acids; it may also contain free glycerol, free fatty acids and soap. It contains not less than 30.0% of monoglycerides, calculated as $C_{21}H_{42}O_4$, not more than 7.0% of free glycerol, calculated as $C_3H_8O_3$, and not more than 6.0% of soap, calculated as sodium oleate, $C_{18}H_{33}NaO_2$, all calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white to cream coloured, hard, waxy solid.

Dispersible in hot *water*; soluble in hot *absolute ethanol*, in hot *liquid paraffin* and, subject to turbidity at concentrations below 20%, in hot vegetable oils.

TESTS

Acid value

Not more than 6, Appendix X B.

Iodine value

Not more than 3 *(iodine monochloride method)*, Appendix X E.

Alkalinity

Shake 1 g with 20 mL of hot *carbon dioxide-free water* and allow to cool with continuous shaking. The pH of the aqueous layer is 8.0 to 10.0, Appendix V L.

Water

Not more than 2.0% w/w, Appendix IX C. Use 0.5 g and a mixture of 10 mL of *anhydrous methanol* and 10 mL of anhydrous *chloroform* as the solvent.

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ASSAY

For free glycerol

Dissolve 0.4 g in 50 mL of *dichloromethane* in a ground-glass-stoppered separating funnel, cool if necessary, add 25 mL of *water* and shake vigorously for 1 minute; add 0.2 mL of *glacial acetic acid*, if necessary, to break the emulsion. Repeat the extraction a further three times using 25-, 20- and 20- mL quantities of *water* and reserve the dichloromethane solution for the Assay for monoglycerides. Filter the combined aqueous extracts through a filter paper moistened with *water*, wash the filter with two 5 mL quantities of *water* and dilute the combined filtrate and washings to 100 mL with *water*. To 50 mL of this solution add 25 mL of *periodic acetic acid solution*, shaking cautiously, allow to stand at 25° to 30° for 30 minutes and add 100 mL of *water* and 12 mL of *potassium iodide solution*. Titrate with 0.1M *sodium thiosulfate VS* using 1 mL of *starch solution* as indicator. Repeat the determination using 50 mL of *water* in place of the 50 mL of the solution being examined. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 2.3 mg of glycerol.

For monoglycerides

Filter the reserved dichloromethane solution obtained in the Assay for free glycerol through absorbent cotton and wash the separating funnel and the filter with three 5 mL quantities of *dichloromethane*. Dilute the combined filtrate and washings to 100 mL with *dichloromethane* and to 50 mL of the solution add 25 mL of *periodic acetic acid solution*, shaking cautiously. Allow to stand at 25° to 30° for 30 minutes and add 100 mL of *water* and 12 mL of *potassium iodide solution*. Titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using 1 mL of *starch solution* as indicator. Repeat the determination using 50 mL of *dichloromethane* in place of the 50 mL of the solution of the substance being examined. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 17.9 mg of 1-monoacylglycerols, calculated as $C_{21}H_{42}O_4$. The quantity of 0.1M *sodium thiosulfate VS* used in the assay is not less than 85% of the quantity of sodium thiosulfate used in the blank assay.

For soap

Add 10 g to a mixture of 60 mL of *acetone* and 0.15 mL of a 0.5% w/v solution of *bromophenol blue* in a mixture of 20 mL of *ethanol (20%)* and 80 mL of *water*, the solvent having been previously neutralised with *0.1M hydrochloric acid VS* or *0.1M sodium hydroxide VS*. Warm gently on a water bath until solution is complete and titrate with *0.1M hydrochloric acid VS* until the blue colour is discharged. Allow to stand for 20 minutes, warm until any solidified matter has redissolved and, if the blue colour reappears, continue the titration. Each mL of *0.1M hydrochloric acid VS* is equivalent to 30.45 mg of $C_{18}H_{33}NaO_2$.

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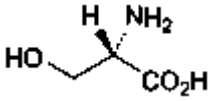
Serine

General Notices

(Ph. Eur. monograph 0788)



$C_3H_7NO_3$ 105.1 *56-45-1*

Action and use

Amino acid.

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DEFINITION

(2*S*)-2-Amino-3-hydroxypropanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

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B. Infrared absorption spectrophotometry (2.2.24).

Comparison serine CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 1 per cent *V/V* solution of hydrochloric acid R and dilute to 50 mL with the same solution.

Reference solution Dissolve 10 mg of serine CRS in a 1 per cent *V/V* solution of hydrochloric acid R and dilute to 50 mL with the same solution.

Plate TLC silica gel plate R.

Mobile phase glacial acetic acid R, water R, butanol R (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with ninhydrin solution R and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 1 mL of a 10 g/L solution of the substance to be examined in a test tube, add 5 mL of a 20 g/L solution of sodium periodate R. Heat on a water-bath and collect the vapour on glass wool moistened with water R and inserted in the opening of the test tube. After heating for 5 min, transfer the glass wool to a test tube containing 1 mL of a 15 g/L solution of chromotropic acid, sodium salt R and 3 mL of sulfuric acid R. Heat on a water-bath for 10 min. A violet-red colour is produced.

TESTS

Solution S

Dissolve 2.5 g in distilled water R and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

+ 14.0 to + 16.0 (dried substance).

Dissolve 2.50 g in dilute hydrochloric acid R and dilute to 25.0 mL with the same acid.

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Ninhydrin-positive substances

Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A dilute hydrochloric acid R1 or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of proline R in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of ammonium standard solution (100 ppm NH_4) R to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of isoleucine R and 30 mg of leucine R in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— resolution: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of serine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

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The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 10.51 mg of $C_3H_7NO_3$.

STORAGE

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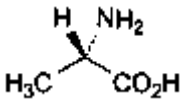
Protected from light.

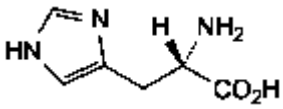
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.



A. (2*S*)-2-aminopropanoic acid (alanine),

B. 2-aminoacetic acid (glycine),



C. (2*S*)-2-amino-3-(imidazol-4-yl)propanoic acid (histidine).

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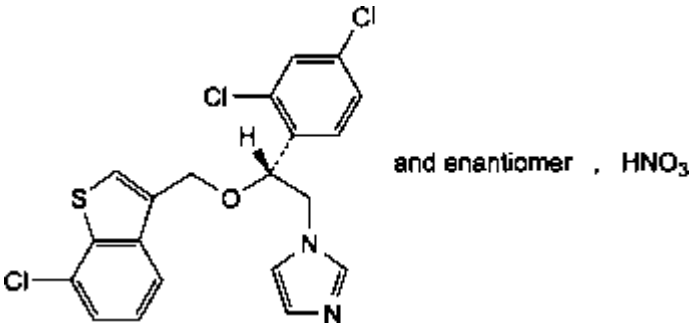
Sertaconazole Nitrate

General Notices

(Ph. Eur. monograph 1148)



$C_{20}H_{16}Cl_3N_3O_4S$ 500.8 *99592-39-9*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[(2*RS*)-2-[(7-Chloro-1-benzothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole nitrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Melting point (*2.2.14*): 156 °C to 161 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *sertaconazole nitrate CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 0.1 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *enilconazole impurity E CRS* (sertaconazole nitrate impurity A) in the mobile phase and dilute to 200 mL with the mobile phase. Dilute 1 mL of the solution to 10 mL with the mobile phase (solution A). Dissolve 5 mg of the substance to be examined in solution A and dilute to 5 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (10 µm).

Mobile phase *acetonitrile for chromatography R*, 1.5 g/L solution of *sodium dihydrogen phosphate R* (37:63 *V/V*).

Flow rate 1.6 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 1.3 times the retention time of sertaconazole.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to sertaconazole (retention time = about 19 min): nitrate ion = about 0.05; impurity A = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and sertaconazole.

Calculation of percentage contents:

— for each impurity, use the concentration of sertaconazole nitrate in reference solution (a).

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Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to the nitrate ion.

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of a mixture of equal volumes of *anhydrous acetic acid R* and *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

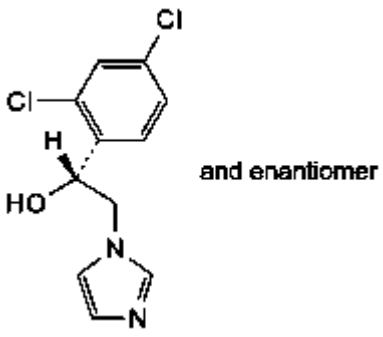
1 mL of *0.1 M perchloric acid* is equivalent to 50.08 mg of $C_{20}H_{16}Cl_3N_3O_4S$.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethan-1-ol,

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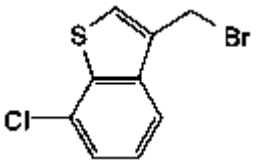
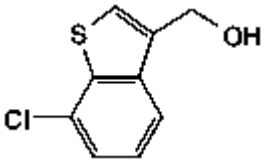


B. 3-(bromomethyl)-7-chloro-1-benzothiophene,



C. (7-chloro-1-benzothiophen-3-yl)methanol.

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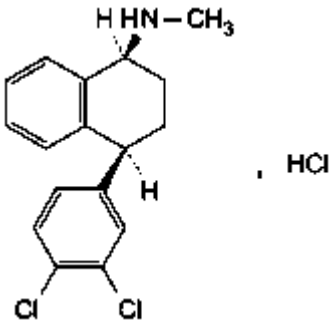
Sertraline Hydrochloride

General Notices

(Ph. Eur. monograph 1705)



$C_{17}H_{18}Cl_3N$ 342.7 *79559-97-0*

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

Preparation

Sertraline Tablets

Ph Eur

DEFINITION

(1*S*,4*S*)-4-(3,4-Dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, slightly soluble in acetone and in 2-propanol.

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It shows polymorphism (5.9).

IDENTIFICATION

Carry out either tests A, B, C or tests B, C, D.

A. Specific optical rotation (2.2.7): + 38.8 to + 43.0 (anhydrous substance), measured at 25 °C.

Solvent mixture Dilute 1 volume of a 103 g/L solution of *hydrochloric acid R* to 20 volumes with *methanol R*.

Dissolve 0.250 g in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *sertraline hydrochloride CRS*.

If the spectra obtained in the solid state show differences, record new spectra using 10 g/L solutions in *methylene chloride R*.

C. Dissolve 10 mg in 5 mL of *anhydrous ethanol R* and add 5 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

D. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29). *Prepare the test solution immediately before use*.

Solvent mixture *diethylamine R*, *hexane R*, *2-propanol R* (1:40:60 *V/V/V*).

Test solution Dissolve 60.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *sertraline for system suitability CRS* (containing impurity G) in 1 mL of the solvent mixture.

Reference solution (b) Dilute 0.5 mL of the test solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm).

Mobile phase Mix 30 volumes of *hexane R* and 70 volumes of a mixture of 1 volume of *diethylamine R*, 25 volumes of *2-propanol R* and 975 volumes of *hexane R*.

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 20 µL.

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Run time Twice the retention time of sertraline.

Identification of impurities Use the chromatogram supplied with *sertraline for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity G.

Relative retention With reference to sertraline (retention time = about 15 min): impurity G = about 1.3.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to sertraline and impurity G in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 10 for the peak due to sertraline in the chromatogram obtained with reference solution (b).

Limit:

— *impurity G*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent).

Impurity E

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase A, mobile phase B (50:50 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5.0 mg of *sertraline impurity E CRS* (mandelic acid) in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *benzoic acid R* and 20 mg of *mandelic acid R* (impurity E) in the solvent mixture and dilute to 50 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (3 µm).

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *sodium laurilsulfate R* in 800 mL of *water for chromatography R* and add 200 mL of *acetonitrile for chromatography R*; add 1.0 mL of *phosphoric acid R* and mix;

— *mobile phase B*: dissolve 1.0 g of *sodium laurilsulfate R* in 100 mL of *water for chromatography R* and add 900 mL of *acetonitrile for chromatography R*; add 1.0 mL of *phosphoric acid R* and mix;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	60	40
8 - 9	60 → 10	40 → 90
9 - 16	10	90

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (b) to identify the peak due to benzoic acid.

Relative retention With reference to sertraline (retention time = about 18 min): impurity E = about 0.2; benzoic acid = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity E and benzoic acid.

Limit:

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Introduce 0.250 g of the substance to be examined into a 15 mL stoppered centrifuge tube, add 2.0 mL of *methanol R* and 0.20 mL of a 25 per cent solution of *potassium carbonate R* and mix in a vortex mixer for 30 s. Add 8.0 mL of *methylene chloride R*, stopper the tube and mix in a vortex mixer for 60 s. Add 1 g of *anhydrous sodium sulfate R*, mix well and then centrifuge for about 5 min.

Reference solution (a) Dissolve the contents of a vial of *sertraline for peak identification CRS* (containing impurities A, B, C and F) in 0.2 mL of *methylene chloride R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 20.0 mL with *methylene chloride R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 1.0 µm).

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Carrier gas *helium for chromatography R*.

Flow rate 9 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	200
	1 - 31	200 → 260
	31 - 39	260
Injection port		250
Detector		280

Detection Flame ionisation.

Injection 1 µL.

Identification of impurities Use the chromatogram supplied with *sertraline for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and F.

Relative retention With reference to sertraline (retention time = about 24 min): impurity B = about 0.5; impurities C and D = about 0.7; impurity A = about 1.05; impurity F = about 1.1.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to sertraline.

Limits:

— *sum of impurities C and D*: maximum 0.8 per cent;

— *impurities A, B, F*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Water (*2.5.12*)

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Maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*).

Buffer solution To 28.6 mL of *glacial acetic acid R* slowly add, while stirring and cooling, 34.8 mL of *triethylamine R*, and dilute to 100 mL with *water for chromatography R*. Dilute 10 mL of this solution to 1000 mL with *water for chromatography R*.

Test solution Dissolve 55.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution Dissolve 55.0 mg of *sertraline hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R*, buffer solution, *acetonitrile R* (15:40:45 *V/V/V*).

Flow rate 1.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time Twice the retention time of sertraline.

Retention time Sertraline = about 1.9 min.

Calculate the percentage content of $C_{17}H_{18}Cl_3N$ taking into account the assigned content of *sertraline hydrochloride CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

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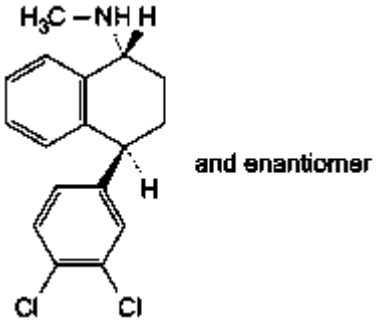
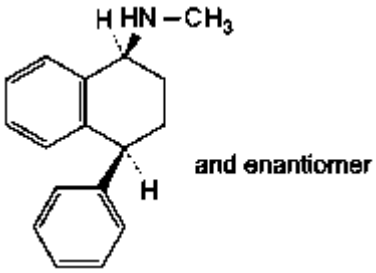
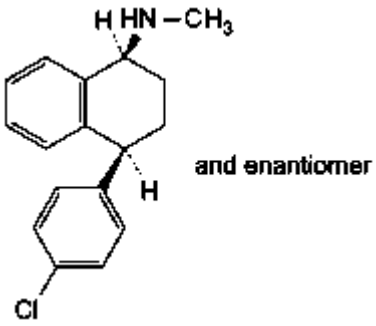


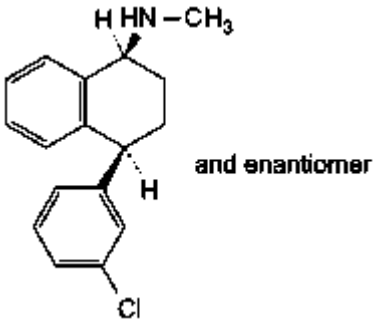
A. (1*RS*,4*SR*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine,



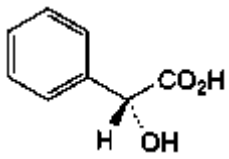
B. (1*RS*,4*RS*)-*N*-methyl-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-amine,



C. (1*RS*,4*RS*)-4-(4-chlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine,



D. (1*RS*,4*RS*)-4-(3-chlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine,



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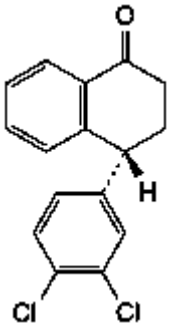
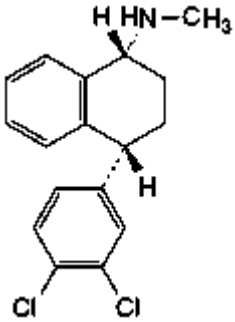
E. (2*R*)-hydroxyphenylacetic acid ((*R*)-mandelic acid),



F. (4*R*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one,



G. (1*R*,4*R*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (sertraline enantiomer).

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Sertraline Tablets

General Notices

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

DEFINITION

Sertraline Tablets contain Sertraline Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sertraline, $C_{17}H_{17}Cl_2N$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 0.22 g of sertraline with 10 mL of *absolute ethanol* for 10 minutes and filter. Evaporate the filtrate to dryness and dry the residue at 60° under vacuum for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with *reference spectrum A* of sertraline hydrochloride *(RS 460)*. If the spectrum thus obtained is not concordant, record a solution spectrum using a 1.0% w/v solution of the residue obtained above in *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with *reference spectrum B* of sertraline hydrochloride *(RS 443)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of *sodium acetate buffer solution pH 4.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a 10-mL sample of the medium and filter (Whatman GF/C is suitable), discard the first 5 mL of filtrate.

(2) 0.0056% w/v of *sertraline hydrochloride BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.8 mL per minute.

(d) Use a column temperature 30°.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *methanol*, 40 volumes of a solution containing 0.286% v/v *glacial acetic acid* and 0.348% v/v *triethylamine* and 45 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions the retention time of sertraline is about 2 minutes.

DETERMINATION OF CONTENT

Calculate the content of sertraline, $C_{17}H_{17}Cl_2N$, in the medium using the declared content of $C_{17}H_{17}Cl_2N$,HCl in *sertraline hydrochloride BPCRS*. Each mg of $C_{17}H_{17}Cl_2N$,HCl is equivalent to 0.8936 mg of $C_{17}H_{17}Cl_2N$.

LIMITS

The amount of sertraline released after 30 minutes is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 30 volumes of *acetonitrile* and 70 volumes of *water*.

(1) Shake a quantity of whole tablets containing the equivalent of 0.45 g of sertraline with 150 mL of solution A until fully dispersed. Mix for 5 minutes with the aid of ultrasound and add sufficient solvent A to produce 200 mL, mix and filter (Whatman PVDF is suitable), discarding the first 5 mL of filtrate.

(2) Dilute 1 volume of solution (1) to 500 volumes with solution A.

(3) 0.001% w/v of *(R)-mandelic acid* in solution A.

(4) 0.25% w/v of *sertraline hydrochloride impurity standard BPCRS* in solution A.

(5) Dilute 1 volume of solution (2) to 2 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

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MOBILE PHASE

Mobile phase A 0.272% w/v of *potassium dihydrogen orthophosphate* in *water*, adjusted to pH 3.0 with *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	70	30	isocratic
30-40	70→60	30→40	linear gradient
40-41	60→70	40→30	linear gradient
41-50	70	30	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *sertraline hydrochloride impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

the area of any peak corresponding to (*R*)-mandelic acid is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

The total impurity content, excluding impurity C, is not greater than 1.5%.

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix for 45 minutes with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 0.19 g of sertraline with 150 mL of mobile phase, shake for 30 minutes, cool, add sufficient *water* to produce 200 mL, mix and filter (Whatman GF/C is suitable), discarding the first 5 mL of filtrate. Dilute 1 volume of the filtrate to 20 volumes with mobile phase.
(2) 0.005% w/v of *sertraline hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

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Calculate the content of $C_{17}H_{17}Cl_2N$ in the tablets using the declared content of $C_{17}H_{17}Cl_2N$,HCl in *sertraline hydrochloride BPCRS*.

Each mg of $C_{17}H_{17}Cl_2N$,HCl is equivalent to 0.8936 mg of $C_{17}H_{17}Cl_2N$.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of sertraline.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and E listed under Sertraline Hydrochloride.

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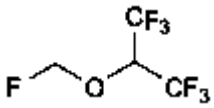
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Sevoflurane

General Notices

(Ph. Eur. monograph 2269)



$C_4H_3F_7O$ 200.1 *28523-86-6*

Action and use

General anaesthetic.

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DEFINITION

1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane.

CHARACTERS

Appearance

Clear, colourless, volatile liquid.

Solubility

Slightly soluble in water, miscible with ethanol (96 per cent).

Relative density

About 1.52.

bp

About 59 °C.

It is non-flammable.

It decomposes in the presence of Lewis acids; this decomposition is inhibited by water in sufficient quantity.

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IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation Examine the substance in the gaseous state or in the liquid state.

Comparison *sevoflurane CRS*.

TESTS

Acidity or alkalinity

Introduce 20.0 mL of the substance to be examined and 20 mL of *carbon dioxide-free water R* into a separating funnel, shake for 3 min and allow to stand. Collect the aqueous upper layer and add 0.2 mL of *bromocresol purple solution R*. Not more than 0.10 mL of *0.01 M sodium hydroxide* or 0.60 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Refractive index (*2.2.6*)

1.2745 to 1.2760.

Related substances

Gas chromatography (*2.2.28*).

Internal standard *methylal R*.

Test solution Introduce 20.0 mL of the substance to be examined into a vial and seal with a cap fitted with a septum. Using a microsyringe, add 5 µL of the internal standard and mix thoroughly.

Reference solution (a) Introduce 2.0 mL of *heptane R* into a screw-cap vial and immediately seal with a cap fitted with a septum. Using a microsyringe, add about 20 µL of the substance to be examined. Record the quantity added, in milligrams, of the substance to be examined (M_2). Then, using a microsyringe, add about 20 µL of the internal standard. Record the quantity added, in milligrams, of the internal standard (M_1).

Reference solution (b) *sevoflurane for system suitability CRS* (containing impurities A and B).

Reference solution (c) Introduce 20.0 mL of *heptane R* into a vial and seal with a cap fitted with a septum. Using a microsyringe, add 20 µL of the substance to be examined and mix thoroughly. Dilute 0.5 mL of this solution to 100.0 mL with *heptane R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 3 µm).

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Carrier gas helium for chromatography R.

Flow rate 1.0 mL/min.

Split ratio 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	40
	10 - 26	40 → 200
	26 - 40	200
Injection port		200
Detector		225

Detection Flame ionisation.

Injection 2 µL; rinse the syringe with a solution containing heptane R before injection of the reference solutions; rinse the syringe with the substance to be examined before injection of the test solution.

Identification of impurities Use the chromatogram supplied with sevoflurane for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to sevoflurane (retention time = about 6.6 min): impurity A = about 0.78; impurity B = about 0.83; internal standard = about 1.35.

System suitability Reference solution (b):

— resolution: minimum 2.0 between the peaks due to impurities A and B.

Calculate the relative response factor (F_1) for reference solution (a), using the following expression:

$$\frac{M_1 \times R}{M_2}$$

M_1 = mass of the internal standard in reference solution (a), in milligrams;

M_2 = mass of the substance to be examined in reference solution (a), in milligrams;

R = ratio of the area of the peak due to sevoflurane to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (a).

Calculate the content of each impurity in the substance to be examined, in parts per million, using the following expression:

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$$\frac{0.859 \times R_1 \times 250}{1.52 \times F_1}$$

0.859	=	relative density of the internal standard;
1.52	=	relative density of sevoflurane;
R_1	=	ratio of the area of the peak due to the impurity to the area of the peak due to the internal standard from the chromatogram obtained with the test solution;
F_1	=	relative response factor for reference solution (a).

Limits:

— *impurity A*: maximum 25 ppm;

— *impurity B*: maximum 100 ppm;

— *unspecified impurities*: for each impurity, maximum 100 ppm;

— *total*: maximum 300 ppm;

— *disregard limit*: the area of the peak due to sevoflurane in the chromatogram obtained with reference solution (c) (5 ppm).

Fluorides

Maximum 2 µg/mL.

Potentiometry (*2.2.36, Method I*). *Use plastic utensils throughout this test*.

Buffer solution Dissolve 0.5 g of *sodium citrate R* and 55 g of *sodium chloride R* in 350 mL of *water R*. Carefully add 75 g of *sodium hydroxide R* and shake to dissolve. Cool to room temperature and carefully add 225 mL of *glacial acetic acid R* while stirring. Cool and add 300 mL of *2-propanol R*. Dilute with *water R* to 1000.0 mL. The apparent pH of this solution is between 5.0 and 5.5.

Test solution Introduce 50.0 mL of the substance to be examined and 50.0 mL of *water R* into a separating funnel, shake vigorously for 3 min and allow the layers to separate completely. Dilute 25.0 mL of the upper aqueous layer to 50.0 mL with the buffer solution.

Fluoride standard solution (1000 ppm F) Dissolve 221.0 mg of *sodium fluoride R*, previously dried at 150 °C for 4 h, in *water R*. Add 1.0 mL of *0.01 M sodium hydroxide* and dilute to 100.0 mL with *water R*.

Reference stock solutions Dilute the fluoride standard solution (1000 ppm F) with *water R* to obtain solutions having known concentrations of about 5 µg, 2 µg, 0.5 µg, and 0.2 µg of fluoride per millilitre.

Reference solutions Dilute 25.0 mL of each reference stock solution to 50.0 mL with the buffer solution.

Indicator electrode Fluoride-selective.

Reference electrode Silver-silver chloride.

Apparatus Voltmeter capable of a minimum reproducibility of ± 0.2 mV.

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Carry out the measurements on the reference solutions and test solution. To take measurements, transfer the solution under test to a 100 mL beaker containing a polytetrafluoroethylene-coated magnetic stirring bar, and immerse the electrodes. Allow to stir on a magnetic stirrer with an insulated top until equilibrium is attained (about 2-3 min), and record the potential. Rinse the electrodes with the buffer solution and dry, taking care to avoid damaging the crystal of the specific-ion electrode.

Calculate the concentration of fluorides using the calibration curve.

Non-volatile residue

Maximum 100 mg/L.

Transfer 10.0 mL to a tared evaporating dish, evaporate to dryness on a water-bath and dry the residue at 105 °C for 2 h. The residue weighs a maximum of 1.0 mg.

Water (2.5.12)

Maximum 0.050 per cent *m/m*, determined on 10.0 mL.

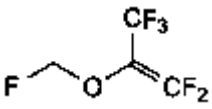
STORAGE

In an airtight, stainless-steel container, protected from light.

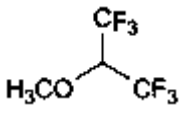
IMPURITIES

Specified impurities *A, B.*

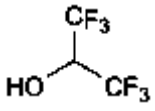
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



A. 1,1,3,3,3-pentafluoro-2-(fluoromethoxy)prop-1-ene,



B. 1,1,1,3,3,3-hexafluoro-2-methoxypropane,



C. 1,1,1,3,3,3-hexafluoropropan-2-ol.

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General Notices

(Ph. Eur. monograph 1149)

Action and use

Excipient.

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DEFINITION

Purified material obtained from the resinous secretion of the female insect *Kerria lacca* (Kerr) Lindinger (*Laccifer lacca* Kerr). There are 4 types of shellac depending on the nature of the treatment of crude secretion (seedlac): wax-containing shellac, bleached shellac, dewaxed shellac and bleached, dewaxed shellac.

Wax-containing shellac is obtained from seedlac: it is purified by filtration of the molten substance and/or by hot extraction using a suitable solvent.

Bleached shellac is obtained from seedlac by treatment with sodium hypochlorite after dissolution in a suitable alkaline solution, precipitation by dilute acid and drying.

Dewaxed shellac is obtained from wax-containing shellac or seedlac by treatment with a suitable solvent and removal of the insoluble wax by filtering.

Bleached, dewaxed shellac is obtained from wax-containing shellac or seedlac by treatment with sodium hypochlorite after dissolution in a suitable alkaline solution; the insoluble wax is removed by filtration. It is precipitated by dilute acid and dried.

CHARACTERS

Appearance

Brownish-orange or yellow, shining, translucent, hard or brittle, more or less thin flakes (wax-containing shellac and dewaxed shellac), or a creamy white or brownish-yellow powder (bleached shellac and bleached, dewaxed shellac).

Solubility

Practically insoluble in water, gives a more or less opalescent solution (wax containing shellac and bleached shellac) or a clear solution (dewaxed shellac and bleached, dewaxed shellac) in anhydrous ethanol. When warmed it is sparingly soluble or soluble in alkaline solutions.

IDENTIFICATION

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A. Thin-layer chromatography (2.2.27).

Test solution Heat 0.25 g of the powdered substance (500) (2.9.12) on a water-bath with 2 mL of *dilute sodium hydroxide solution R* for 5 min. Cool, add 5 mL of *ethyl acetate R* and slowly, with stirring, 2 mL of *dilute acetic acid R*. Shake and filter the upper layer through *anhydrous sodium sulfate R*.

Reference solution Dissolve 6.0 mg of *aleuritic acid R* in 1.0 mL of *methanol R*, heating slightly if necessary.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetic acid R*, *methanol R*, *methylene chloride R*, *ethyl acetate R* (1:8:32:60 *V/V/V/V*).

Application 10 µL, as bands.

Development Twice over a path of 15 cm.

Drying In air.

Detection Spray with *anisaldehyde solution R*, heat at 100-105 °C for 5-10 min and examine in daylight.

Results The chromatogram obtained with the test solution shows several coloured zones, one of which is similar in position and colour to the zone in the chromatogram obtained with the reference solution. Above this zone the chromatogram obtained with the test solution shows a pink zone and below it several violet zones. Below the zone due to aleuritic acid, there is a light blue zone (shellolic acid) accompanied by zones of the same colour but of lower intensity. Other faint grey and violet zones may be visible.

B. Examine the chromatograms obtained in the test for colophony.

Results For wax-containing shellac, in the chromatogram obtained with the test solution, a more or less strong bluish-grey zone is visible, just above the zone due to thymolphthalein in the chromatogram obtained with the reference solution; for dewaxed shellac, no such zone is visible just above the zone due to thymolphthalein in the chromatogram obtained with the reference solution.

TESTS

Acid value (2.5.1)

65 to 95 (dried substance).

Examine 1.00 g of the coarsely ground substance. Determine the end-point potentiometrically (2.2.20).

Colophony

Thin-layer chromatography (2.2.27) as described under identification test A with the following modifications.

Test solution Dissolve 50 mg of the powdered substance (500) (2.9.12), with heating, in a mixture of 0.5 mL of *methylene chloride R* and 0.5 mL of *methanol R*.

Reference solution Dissolve 2.0 mg of *thymolphthalein R* in 1.0 mL of *methanol R*.

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Detection Examine in ultraviolet light at 254 nm; mark the quenching zones in the chromatogram obtained with the test solution that have similar R_F values to that of the quenching zone due to thymolphthalein in the chromatogram obtained with the reference solution; spray with *anisaldehyde solution R*, heat at 100-105 °C for 5-10 min and examine in daylight.

Results The chromatogram obtained with the reference solution shows a principal zone with a reddish-violet colour (thymolphthalein). None of the quenching zones in the chromatogram obtained with the test solution that have an R_F value similar to the zone due to thymolphthalein in the reference solution show a more or less strong violet or brownish colour (colophony). Disregard any faint violet zone at this level that does not show quenching before spraying and heating.

Arsenic (*2.4.2, Method A*)

Maximum 3 ppm.

Introduce 0.33 g of the substance to be examined and 5 mL of *sulfuric acid R* into a combustion flask. Carefully add a few millilitres of *strong hydrogen peroxide solution R* and heat to boiling until a clear, colourless solution is obtained. Continue heating to eliminate the water and as much sulfuric acid as possible and dilute to 25 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent for unbleached shellac and maximum 6.0 per cent for bleached shellac, determined on 1.000 g of the powdered substance (500) (*2.9.12*) by drying in an oven at 40-45 °C for 24 h.

STORAGE

Protected from light. Store bleached shellac and bleached, dewaxed shellac at a temperature not exceeding 15 °C.

LABELLING

The label indicates the type of shellac.

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Sildenafil Chewable Tablets

General Notices

Chewable Sildenafil Tablets

Action and use

Selective inhibitor of cyclic GMP specific phosphodiesterase (Type V) with vasodilator action; treatment of male erectile dysfunction.

DEFINITION

Sildenafil Chewable Tablets contain Sildenafil Citrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sildenafil, $C_{22}H_{30}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 25 mg of sildenafil with 10 mL of *methanol* and filter.

(2) 0.35% w/v of *sildenafil citrate EPCRS* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *methanol* and 8 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single spot with the same retention and colour as solution (2).

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *0.01M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution containing the equivalent of 0.0027% w/v of sildenafil, at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell, Appendix II B.

(2) Measure the *absorbance* of a 0.0038% w/v solution of *sildenafil citrate EPCRS* in *0.01M hydrochloric acid* at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the medium using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

LIMITS

The amount of sildenafil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse 10 tablets in the minimum volume of *water* possible (not exceeding 10% of the overall solvent mixture) and add sufficient *acetonitrile* to produce a solution expected to contain the equivalent of 0.1% w/v of sildenafil and filter. Dilute 1 volume of this solution to 2 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, dilute 1 volume of this solution to 5 volumes with the same solvent.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute 1 volume of this solution to 250 volumes with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).

(4) 0.000075% w/v of *sildenafil impurity A EPCRS* in the mobile phase.

(5) Dilute 2.5 volumes of solution (2) to 10 volumes with the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phases described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of sildenafil.

MOBILE PHASE

17 volumes of *acetonitrile*, 25 volumes of *methanol* and 58 volumes of a 0.7% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention relative to sildenafil (retention time about 7 minutes) of impurity B is about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *peak* due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse 10 tablets in the minimum volume of *water* possible (not exceeding 10% of the overall solvent mixture) and add sufficient *acetonitrile* to produce a solution expected to contain the equivalent of 0.1% w/v of sildenafil and filter. Dilute 1 volume of this solution to 50 volumes with mobile phase.

(2) 0.0028% w/v of *sildenafil citrate EPCRS* in the mobile phase.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute the resulting solution to 250 mL with the mobile phase (*in-situ*

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degradation of sildenafil to produce impurity B).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the tablets using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sildenafil Citrate.

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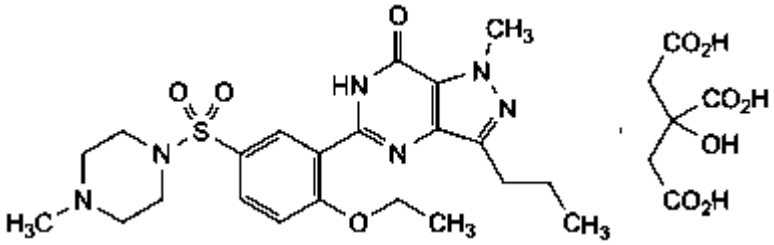
Sildenafil Citrate

General Notices

(Ph. Eur. monograph 2270)



$C_{28}H_{38}N_6O_{11}S$ 667 *171599-83-0*

Action and use

Selective inhibitor of cyclic GMP-specific phosphodiesterase (Type V) with vasodilator action; treatment of erectile dysfunction.

Preparations

Sildenafil Tablets

Sildenafil Chewable Tablets

Sildenafil Orodispersible Tablets

Sildenafil Orodispersible Films

Sildenafil Powder for Oral Suspension

Sildenafil Injection

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DEFINITION

5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

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Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Slightly soluble in water and in methanol, practically insoluble in hexane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *sildenafil citrate CRS*.

TESTS

Impurity E

Thin-layer chromatography (2.2.27).

Solvent mixture *concentrated ammonia R*, *water R*, *methanol R* (5:25:75 *V/V/V*).

Test solution Dissolve 35.0 mg of the substance to be examined in 2.0 mL of the solvent mixture, with the aid of ultrasound if necessary.

Reference solution (a) Dissolve 7.0 mg of *imidazole CRS* (impurity E) in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Mix 1 mL of the test solution and 1 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R* (2-10 µm).

Mobile phase *concentrated ammonia R*, *ethanol (96 per cent) R*, *ethyl acetate R*, *methylene chloride R* (1:20:30:50 *V/V/V/V*).

Application 10 µL of the test solution and reference solutions (b) and (c) as bands of 6 mm.

Development Over 2/3 of the plate.

Drying At 100 °C for about 15 min.

Detection Expose to iodine vapour until the plate is light brown and examine under ultraviolet light at 254 nm.

Retardation factors Citrate = about 0; impurity E = about 0.25; sildenafil = about 0.4.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated zones.

Limit:

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— *impurity E*: any zone due to impurity E is not more intense than the principal zone in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 2.72 g of potassium dihydrogen phosphate R in 900 mL of water for chromatography R and adjust to pH 6.5 with a 120 g/L solution of potassium hydroxide R in water for chromatography R. Dilute to 1.0 L with water for chromatography R.

Solvent mixture acetonitrile for chromatography R, mobile phase A (10:90 *V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 2.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of sildenafil impurity A CRS in test solution (a) and dilute to 10.0 mL with test solution (a). Dilute 1.0 mL of the solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of sildenafil for peak identification CRS (containing impurity D) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 25.0 mg of sildenafil citrate CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: acetonitrile for chromatography R, buffer solution (20:80 *V/V*);

— *mobile phase B*: buffer solution, methanol R1, acetonitrile for chromatography R (20:20:60 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	75	25
3 - 26	75 → 30	25 → 70
26 - 38	30	70

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Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *sildenafil for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to sildenafil (retention time = about 16 min): impurity D = about 0.15; impurity A = about 1.25.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to sildenafil and impurity A.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 0.7;

— for each impurity, use the concentration of sildenafil citrate in reference solution (c).

Limits:

— *impurities A, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to citrate.

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.00 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{28}H_{38}N_6O_{11}S$ taking into account the assigned content of *sildenafil citrate CRS*.

STORAGE

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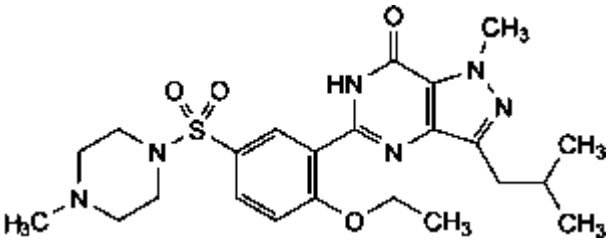
In airtight container.

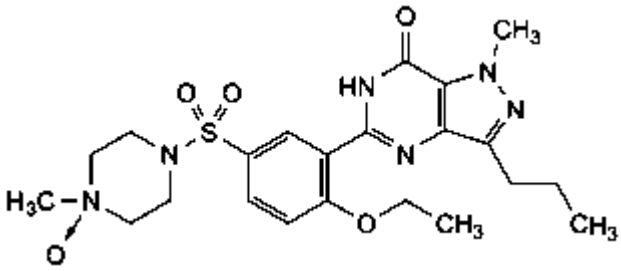
IMPURITIES

Specified impurities *A, D, E.*

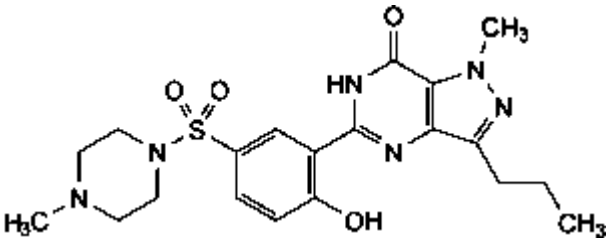
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, F, G.*



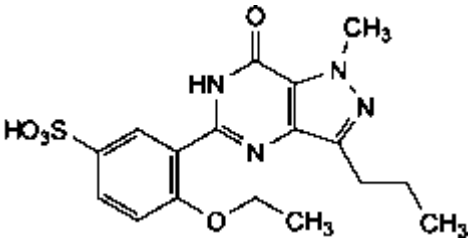
A. 5-[2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-(2-methylpropyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,



B. 1-methyl-4-[[4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)phenyl]sulfonyl]piperazine 1-oxide,



C. 5-[2-hydroxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,



D. 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzenesulfonic acid,

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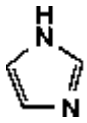
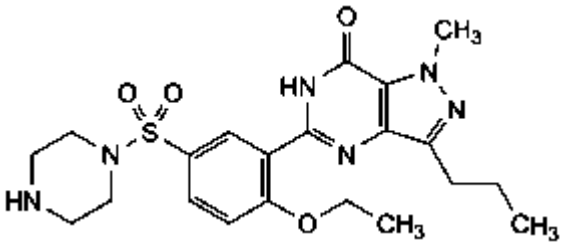
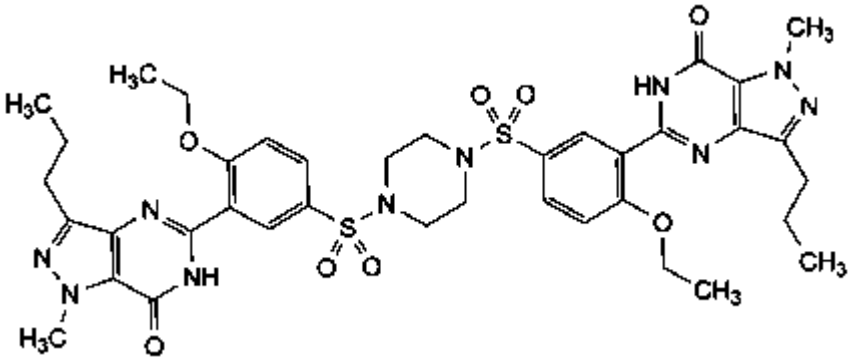


E. 1*H*-imidazole,



F. 5-[2-ethoxy-5-(piperazin-1-ylsulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,



G. 5,5′-[piperazin-1,4-diylbis[dioxo-λ^6-sulfanediyl(2-ethoxy-5,1-phenylene)]]bis(1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one).

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Sildenafil Injection

General Notices

Action and use

Selective inhibitor of cyclic GMP specific phosphodiesterase (Type V) with vasodilator action; treatment of pulmonary arterial hypertension.

DEFINITION

Sildenafil Injection is a sterile solution containing Sildenafil Citrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sildenafil, $C_{22}H_{30}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the injection diluted with *methanol*, if necessary, to contain the equivalent of 0.08% w/v of sildenafil.

(2) 0.11% w/v of *sildenafil citrate EPCRS* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 30 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *methanol* and 8 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single spot with the same retention and colour as solution (2).

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the injection diluted with mobile phase, if necessary, to contain the equivalent of 0.08% w/v of sildenafil.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, further dilute 1 volume of this solution to 5 volumes with the same solvent.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute 1 volume of this solution to 250 volumes with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).

(4) 0.00012% w/v of *sildenafil impurity A EPCRS* in the mobile phase.

(5) Dilute 2.5 volumes of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel* (5 µm) (Waters C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of sildenafil.

MOBILE PHASE

17 volumes of *acetonitrile*, 25 volumes of *methanol* and 58 volumes of a 0.7% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to sildenafil (retention time about 7 minutes) of impurity B is about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.15%);

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the area of any other *secondary peak* is not greater than the area of the peak due to sildenafil in the chromatogram obtained with solution (2) (0.2%);

the sum of the impurities is not greater than 0.50%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the injection diluted with mobile phase, if necessary, to contain the equivalent of 0.0008% w/v of sildenafil.

(2) 0.0011% w/v of *sildenafil citrate EPCRS* in the mobile phase.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute the resulting solution to 250 mL with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}N_6O_4S$ in the injection using the declared content of $C_{28}H_{38}N_6O_{11}S$ in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sildenafil Citrate.

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Sildenafil Orodispersible Films

General Notices

Orodispersible Sildenafil Films

Action and use

Selective inhibitor of cyclic GMP specific phosphodiesterase (Type V) with vasodilator action; treatment of male erectile dysfunction.

DEFINITION

Sildenafil Orodispersible Films contain Sildenafil Citrate.

The films comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of sildenafil, $C_{22}H_{30}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of orodispersible films containing the equivalent of 25 mg of sildenafil with 10 mL of *methanol* and filter.

(2) 0.35% w/v of *sildenafil citrate EPCRS* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *methanol* and 8 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single spot with the same retention and colour to solution (2).

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *0.01M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 15 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution containing the equivalent of 0.0027% w/v of sildenafil, at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell, Appendix II B.

(2) Measure the *absorbance* of a 0.0038% w/v solution of *sildenafil citrate EPCRS* in *0.01M hydrochloric acid* at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the medium using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

LIMITS

The amount of sildenafil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of orodispersible films containing the equivalent of 100 mg of sildenafil in 10 mL of *water*. Dilute to 100 mL with *acetonitrile* and filter. Dilute 1 volume of this solution to 2 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, further dilute 1 volume of this solution to 5 volumes with the same solvent.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute 1 volume of this solution to 250 volumes with the mobile phase (in-situ degradation of sildenafil to produce impurity B).

(4) 0.000075% w/v of *sildenafil impurity A EPCRS* in the mobile phase.

(5) Dilute 2.5 volumes of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phases described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of sildenafil.

MOBILE PHASE

17 volumes of *acetonitrile*, 25 volumes of *methanol* and 58 volumes of a 0.7% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to sildenafil (retention time about 7 minutes) of impurity B is about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of impurities is not greater than 0.50%;

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse ten films in the minimum volume of *water* possible (not exceeding 10% of the overall solvent mixture) and add sufficient *acetonitrile* to produce a solution expected to contain the equivalent of 0.1% w/v of sildenafil and filter. Dilute 1 volume of this solution to 50 volumes with mobile phase.

(2) 0.0028% w/v of *sildenafil citrate EPCRS* in the mobile phase.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute the resulting solution to 250 mL with the mobile phase (in-situ degradation of sildenafil to produce impurity B).

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the orodispersible films using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sildenafil Citrate.

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Sildenafil Orodispersible Tablets

General Notices

Orodispersible Sildenafil Tablets

Action and use

Selective inhibitor of cyclic GMP specific phosphodiesterase (Type V) with vasodilator action; treatment of male erectile dysfunction.

DEFINITION

Sildenafil Orodispersible Tablets contain Sildenafil Citrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sildenafil, $C_{22}H_{30}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 25 mg of sildenafil with 10 mL of *methanol* and filter.

(2) 0.35% w/v of *sildenafil citrate EPCRS* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *methanol* and 8 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single spot with the same retention and colour to solution (2).

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 900 mL of *0.01M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 15 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution containing the equivalent of 0.0027% w/v of sildenafil, at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell, Appendix II B.
(2) Measure the *absorbance* of a 0.0038% w/v solution of *sildenafil citrate EPCRS* in *0.01M hydrochloric acid* at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the medium using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

LIMITS

The amount of sildenafil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse ten tablets in the minimum volume of *water* possible (not exceeding 10% of the overall solvent mixture) and add sufficient *acetonitrile* to produce a solution expected to contain the equivalent of 0.1% w/v of sildenafil and filter. Dilute 1 volume of this solution to 2 volumes with the mobile phase.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, further dilute 1 volume of this solution to 5 volumes with the same solvent.
(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute 1 volume of this solution to 250 volumes with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).
(4) 0.000075% w/v of *sildenafil impurity A EPCRS* in the mobile phase.
(5) Dilute 2.5 volumes of solution (2) to 10 volumes with the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of sildenafil.

MOBILE PHASE

17 volumes of *acetonitrile*, 25 volumes of *methanol* and 58 volumes of a 0.7% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to sildenafil (retention time about 7 minutes) of impurity B is about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.15%);

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of impurities is not greater than 0.50%;

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse ten tablets in the minimum volume of *water* possible (not exceeding 10% of the overall solvent mixture) and add sufficient *acetonitrile* to produce a solution expected to contain the equivalent of 0.1% w/v of sildenafil and filter. Dilute 1 volume of this solution to 50 volumes with mobile phase.

(2) 0.0028% w/v of *sildenafil citrate EPCRS* in the mobile phase.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute the resulting solution to 250 mL with the mobile phase (in-situ degradation of sildenafil to produce impurity B).

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the tablets using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sildenafil Citrate.

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Sildenafil Powder for Oral Suspension

General Notices

Action and use

Selective inhibitor of cyclic GMP specific phosphodiesterase (Type V) with vasodilator action; treatment of pulmonary arterial hypertension.

DEFINITION

Sildenafil Powder for Oral Suspension contains Sildenafil Citrate.

The powder complies with the requirements stated under Powders and Granules for Oral Solutions and Suspensions stated under Oral Liquids and with the following requirements.

Content of sildenafil, $C_{22}H_{30}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powder containing the equivalent of 25 mg of sildenafil with 10 mL of *methanol* and filter.

(2) 0.35% w/v of *sildenafil citrate EPCRS* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *methanol* and 8 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single spot with the same retention and colour as solution (2).

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powder containing the equivalent of 0.1 g of sildenafil in 10 mL of *water*. Add 90 mL of *acetonitrile* and filter. Dilute 1 volume of this solution to 2 volumes with the mobile phase.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of this solution to 5 volumes with the same solvent.
(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute 1 volume of this solution to 250 volumes with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).
(4) 0.000075% w/v of *sildenafil impurity A EPCRS* in the mobile phase.
(5) Dilute 2.5 volumes of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel* (5 µm) (Waters C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 290 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of sildenafil.

MOBILE PHASE

17 volumes of *acetonitrile*, 25 volumes of *methanol* and 58 volumes of a 0.7% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to sildenafil (retention time about 7 minutes) of impurity B is about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak due to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the impurities is not greater than 0.50%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powder containing the equivalent of 0.1 g of sildenafil in 10 mL of water. Dilute to 100 mL with *acetonitrile* and filter. Dilute 1 volume of this solution to 50 volumes with the mobile phase.
(2) 0.0028% w/v of *sildenafil citrate EPCRS* in the mobile phase.
(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute the solution to 250 mL with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}N_6O_4S$ in the powder using the declared content of $C_{28}H_{38}N_6O_{11}S$ in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sildenafil Citrate.

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Sildenafil Tablets

General Notices

Action and use

Selective inhibitor of cyclic GMP specific phosphodiesterase (Type V) with vasodilator action; treatment of male erectile dysfunction.

DEFINITION

Sildenafil Tablets contain Sildenafil Citrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sildenafil, $C_{22}H_{30}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 25 mg of sildenafil with 10 mL of *methanol* and filter.

(2) 0.35% w/v of *sildenafil citrate EPCRS* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *methanol* and 8 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single spot with the same retention and colour as solution (2).

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *0.01M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution containing the equivalent of 0.0027% w/v of sildenafil, at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell, Appendix II B.

(2) Measure the *absorbance* of a 0.0038% w/v solution of *sildenafil citrate EPCRS* in *0.01M hydrochloric acid* at the maximum at 290 nm using *0.01M hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the medium using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

LIMITS

The amount of sildenafil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse ten tablets in the minimum volume of *water* possible (not exceeding 10% of the overall solvent mixture) and add sufficient *acetonitrile* to produce a solution expected to contain the equivalent of 0.1% w/v of sildenafil and filter. Dilute 1 volume of this solution to 2 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, further dilute 1 volume of this solution to 5 volumes with the same solvent.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute 1 volume of this solution to 250 volumes with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).

(4) 0.000075% w/v of *sildenafil impurity A EPCRS* in the mobile phase.

(5) Dilute 2.5 volumes of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel* (5 µm) (Waters C18 is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of sildenafil.

MOBILE PHASE

17 volumes of *acetonitrile*, 25 volumes of *methanol* and 58 volumes of a 0.7% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to sildenafil (retention time about 7 minutes) of impurity B is about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the impurities is not greater than 0.50%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse 10 tablets in the minimum volume of *water* possible (not exceeding 10% of the overall solvent mixture) and add sufficient *acetonitrile* to produce a solution expected to contain the equivalent of 0.1% w/v of sildenafil and filter. Dilute 1 volume of this solution to 50 volumes with mobile phase.

(2) 0.0028% w/v of *sildenafil citrate EPCRS* in the mobile phase.

(3) Dissolve 70 mg of *sildenafil citrate EPCRS* in 1 mL of a mixture containing 1 volume of *formic acid* and 2 volumes of *hydrogen peroxide solution (100 vol)* and allow to stand for 10 minutes. Dilute the resulting solution to 250 mL with the mobile phase (*in-situ* degradation of sildenafil to produce impurity B).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sildenafil and impurity B is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}N_6O_4S$ in the tablets using the declared content of $C_{28}H_{38}N_6O_{11}S$ in *sildenafil citrate EPCRS*. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118 mg of $C_{22}H_{30}N_6O_4S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sildenafil Citrate.

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Silver Nitrate

General Notices

(Ph. Eur. monograph 0009)

$AgNO_3$ 169.9 *7761-88-8*

Action and use

Antiseptic.

Preparations

Silver Nitrate Eye Drops

Silver Nitrate Solution

Silver Nitrate Sterile Solution

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or transparent, colourless crystals.

Solubility

Very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. 10 mg gives the reaction of nitrates (*2.3.1*).

B. 10 mg gives the reaction of silver (*2.3.1*).

TESTS

Solution S

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Dissolve 2.0 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 2 mL of solution S add 0.1 mL of *bromocresol green solution R*. The solution is blue. To 2 mL of solution S add 0.1 mL of *phenol red solution R*. The solution is yellow.

Foreign salts

Maximum 0.3 per cent.

To 30 mL of solution S, add 7.5 mL of *dilute hydrochloric acid R*, shake vigorously, heat for 5 min on a water-bath and filter. Evaporate 20 mL of the filtrate to dryness on a water-bath and dry at 100-105 °C. The residue weighs a maximum of 2 mg.

Aluminium, lead, copper and bismuth

Dissolve 1.0 g in a mixture of 4 mL of *concentrated ammonia R* and 6 mL of *water R*. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

ASSAY

Dissolve 0.300 g in 50 mL of *water R*, add 2 mL of *dilute nitric acid R* and 2 mL of *ferric ammonium sulfate solution R2*. Titrate with *0.1 M ammonium thiocyanate* until a reddish-yellow colour is obtained.

1 mL of *0.1 M ammonium thiocyanate* is equivalent to 16.99 mg of $AgNO_3$.

STORAGE

In a non-metallic container, protected from light.

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Silver Nitrate Eye Drops

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

DEFINITION

Silver Nitrate Eye Drops are a sterile solution of Silver Nitrate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of silver nitrate, $AgNO_3$,

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields the reactions characteristic of *silver salts* and of *nitrates*, Appendix VI.

TESTS

Acidity

pH, 4.5 to 6.0, Appendix V L.

Clarity and colour of solution

The solution is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

ASSAY

Dilute a volume containing 50 mg of Silver Nitrate with 20 mL of *water* and add 2 mL of *dilute nitric acid* and 2 mL of *ammonium iron(III) sulfate solution R2*. Titrate with 0.02M *ammonium thiocyanate VS* until a reddish-yellow colour is obtained. Each mL of 0.02M *ammonium thiocyanate VS* is equivalent to 3.397 mg of $AgNO_3$.

STORAGE

Silver Nitrate Eye Drops should be protected from light.

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Silver Nitrate Solution

General Notices

Silver Nitrate Cutaneous Solution

NOTE: This monograph has been developed to cover unlicensed formulations.

DEFINITION

Silver Nitrate Solution is a *cutaneous solution*. It contains Silver Nitrate in Purified Water.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements. Where appropriate, the solution also complies with the requirements stated under Unlicensed Medicines.

Content of silver nitrate, $AgNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields the reactions characteristic of *silver salts* and of *nitrates*, Appendix VI.

TESTS

Acidity

pH, 4.5 to 6.0, Appendix V L.

Clarity and colour of solution

The solution is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

ASSAY

Dilute a volume containing 50 mg of Silver Nitrate with 20 mL of *water* and add 2 mL of *dilute nitric acid* and 2 mL of *ammonium iron(III) sulfate solution R2*. Titrate with *0.02M ammonium thiocyanate VS* until a reddish-yellow colour is obtained. Each mL of *0.02M ammonium thiocyanate VS* is equivalent to 3.397 mg of $AgNO_3$.

STORAGE

Silver Nitrate Solution should be protected from light.

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Silver Nitrate Sterile Solution

General Notices

Sterile Silver Nitrate Solution

NOTE: This monograph has been developed to cover unlicensed formulations.

DEFINITION

Silver Nitrate Sterile Solution is a sterile *cutaneous solution*. It contains Silver Nitrate in Purified Water.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements. Where appropriate, the solution also complies with the requirements stated under Unlicensed Medicines.

Content of silver nitrate, $AgNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields the reactions characteristic of *silver salts* and of *nitrates*, Appendix VI.

TESTS

Acidity

pH, 4.5 to 6.0, Appendix V L.

Clarity and colour of solution

The solution is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

Sterility

Complies with the *test for sterility*, Appendix XVI A.

ASSAY

Dilute a volume containing 50 mg of Silver Nitrate with 20 mL of *water* and add 2 mL of *dilute nitric acid* and 2 mL of *ammonium iron(III) sulfate solution R2*. Titrate with *0.02M ammonium thiocyanate VS* until a reddish-yellow colour is obtained. Each mL of *0.02M ammonium thiocyanate VS* is equivalent to 3.397 mg of $AgNO_3$.

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Silver Nitrate Sterile Solution should be protected from light.

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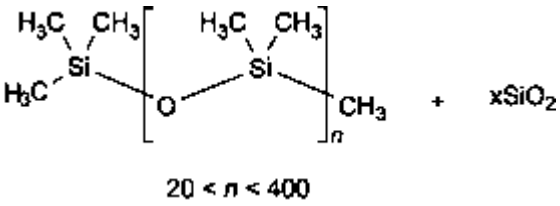
Simeticone

General Notices

(Ph. Eur. monograph 1470)



8050-81-5

Action and use

Silicon dioxide analogue; defoaming agent.

Ph Eur

DEFINITION

Mixture of α-trimethylsilyl-ω-methylpoly[oxy(dimethylsilanediyl)] and silicon dioxide.

Simeticone is prepared by incorporation of 4 per cent to 7 per cent silica into poly(dimethylsiloxane) with a degree of polymerisation between 20 and 400.

Content

90.5 per cent to 99.0 per cent of poly(dimethylsiloxane).

PRODUCTION

Poly(dimethylsiloxane) is obtained by hydrolysis and polycondensation of dichlorodimethylsilane and chlorotrimethylsilane and the silica is modified at the surface by incorporation of methylsilyl groups.

CHARACTERS

Appearance

Viscous, greyish-white, opalescent liquid.

Solubility

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Practically insoluble in water, very slightly soluble or practically insoluble in anhydrous ethanol, practically insoluble in methanol, partly miscible with ethyl acetate, with methylene chloride, with methyl ethyl ketone and with toluene.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Thin films between plates of *sodium chloride R*.

Absorption maxima At 2964 cm^{-1}, 2905 cm^{-1}, 1412 cm^{-1}, 1260 cm^{-1} and 1020 cm^{-1}.

B. Heat 0.5 g in a test-tube over a small flame until white fumes begin to appear. Invert the tube over a 2nd tube containing 1 mL of a 1 g/L solution of *chromotropic acid, sodium salt R* in *sulfuric acid R* so that the fumes reach the solution. Shake the 2nd tube for about 10 s and heat on a water-bath for 5 min. The solution is violet.

C. The residue obtained in the test for silica under Assay gives the reaction of silicates (2.3.1).

TESTS

Acidity

To 2.0 g add 25 mL of a mixture of equal volumes of *anhydrous ethanol R* and *ether R*, previously neutralised to 0.2 mL of *bromothymol blue solution R1*, and shake. Not more than 3.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the solution to blue.

Defoaming activity

Foaming solution Dissolve 5.0 g of *docusate sodium R* in 1 L of *water R*, warm to 50 °C if necessary.

Defoaming solution To 50 mL of *methyl ethyl ketone R* add 0.250 g of the substance to be examined, warm to not more than 50 °C with shaking.

Into a 250 mL cylindrical tube about 5 cm in diameter introduce 100 mL of foaming solution and 1 mL of defoaming solution. Close tightly and fix the tube on a suitable oscillating shaker that complies with the following conditions:

— 250-300 oscillations per minute;

— angle of oscillation of about 10°;

— oscillation radius of about 10 cm.

Shake for 10 s and record the time between the end of the shaking and the instant the 1st portion of foam-free liquid surface appears.

This duration is not longer than 15 s.

Mineral oils

Place 2.0 g in a test-tube and examine in ultraviolet light at 365 nm. The fluorescence is not more intense than that of a solution containing 0.1 ppm of *quinine sulfate R* in *0.005 M sulfuric acid* examined in the same conditions.

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Phenylated compounds

The corrected absorbance (2.2.25) is not greater than 0.2.

Test solution Dissolve 5.0 g with shaking in 10.0 mL of *cyclohexane R*.

Spectral range 200-350 nm.

Calculate the corrected absorbance using the following expression:

$$B - C$$

B	=	absorbance at the absorption maximum between 250 nm and 270 nm;
C	=	absorbance at 300 nm.

Volatile matter

Maximum 1.0 per cent, determined on 1.00 g by heating in an oven at 150 °C for 2 h. Carry out the test using a dish 60 mm in diameter and 10 mm deep.

ASSAY

Silica

Heat not less than 20.0 mg to 800 °C increasing the temperature by 20 °C/min under a current of *nitrogen R* at a flow rate of 200 mL/min and weigh the residue (silica).

Poly(dimethylsiloxane)

Infrared absorption spectrophotometry (2.2.24).

Test solution Place about 50 mg (*E*) in a screw-capped 125 mL cylindrical tube, add 25.0 mL of *toluene R*, swirl manually to disperse and add 50 mL of *dilute hydrochloric acid R*, close the tube and place on a vortex mixer; shake for 5 min. Transfer the contents of the tube to a separating funnel, allow to settle and transfer 5 mL of the upper layer to a screw-capped test-tube containing 0.5 g of *anhydrous sodium sulfate R*. Cap and shake vigorously manually. Centrifuge to obtain a clear solution.

Reference solution Introduce about 0.20 g of *dimeticone CRS* (poly(dimethylsiloxane)) into 100.0 mL of *toluene R*. Prepare the reference solution in the same way as for the test solution, using 25.0 mL of the dimeticone solution obtained above.

Blank solution Shake 10 mL of *toluene R* with 1 g of *anhydrous sodium sulfate R*. Centrifuge the resulting suspension.

Record the infrared absorption spectra for the test solution and the reference solution in 0.5 mm cells, from 1330 cm^{-1} to 1180 cm^{-1}. Determine the absorbance of the band at 1260 cm^{-1}.

Calculate the percentage content of poly(dimethylsiloxane) using the following expression:

$$\frac{25 \times C \times A_M \times 100}{A_E \times E}$$

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A_M	=	absorbance of the test solution;
A_E	=	absorbance of the reference solution;
C	=	concentration of the reference solution, in milligrams per millilitre;
E	=	mass of the substance to be examined, in milligrams.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for simeticone used as defoaming agent.

Defoaming activity

(see Tests).

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Simeticone for Oral Use

General Notices

Action and use

Silicon dioxide analogue; defoaming agent.

Preparations

Simeticone Suspension for Infants

When activated dimethicone is prescribed or demanded, Simeticone for Oral Use shall be dispensed or supplied.

DEFINITION

Simeticone for Oral Use contains not less than 4.5% and not more than 8.0% w/w of silica, SiO_2, and not less than 91.0% and not more than 97.0% w/w of Dimeticone 1000. It is prepared by the addition of finely powdered silica to Dimeticone 1000.

CHARACTERISTICS

A viscous, grey, translucent liquid.

Immiscible with *water* and with *ethanol (96%)*; almost completely soluble in *toluene*, leaving a residue of silica.

IDENTIFICATION

A. The *infrared absorption spectrum* of the supernatant liquid obtained by centrifugation, Appendix II A, is concordant with the *reference spectrum* of dimeticone *(RS 381)*.

B. Ignite; dense white fumes are evolved leaving a white residue which is insoluble in *hydrochloric acid*.

TESTS

Acidity

Dissolve 15.0 g in a mixture of 15 mL of *toluene* and 15 mL of *butan-1-ol*, previously neutralised to a 0.5% w/v solution of *bromophenol blue* in *ethanol (96%)*, and titrate with *0.1M ethanolic potassium hydroxide VS* using the bromophenol blue solution as indicator. Not more than 0.15 mL is required to change the colour of the solution.

Refractive index

Of the supernatant liquid obtained in Identification test A, 1.4050 to 1.4080, Appendix V E.

Viscosity

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Of the supernatant liquid obtained in Identification test A, 950 to 1050 $mm^2 s^{-1}$, Appendix V H, Method I, using a U-tube viscometer (size G).

Weight per mL

Of the supernatant liquid obtained in Identification test A, 0.965 to 0.980 g, Appendix V G.

ASSAY

For silica

To 1 g add 50 mL of *toluene*, mix well and filter through an ignited silica crucible. Wash the residue thoroughly with *toluene*, dry at 105° and ignite to constant weight at 500°.

For dimeticone

Place 40 mg in a stoppered centrifuge tube, add 20 mL of *toluene* and shake for 20 minutes. Filter and record the *infrared absorption spectrum*, Appendix II A, of a 0.5-mm layer of the filtrate over the range 1330 to 1180 cm^{-1} (7.52 to 8.47 µm). Measure the absorbance of the CH_3Si stretching band at the maximum at 1261 cm^{-1} (7.93 µm). Repeat the operation using *dimeticone EPCRS* in place of the preparation being examined.

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Simeticone Suspension for Infants

General Notices

Action and use

Silicon dioxide analogue; defoaming agent.

DEFINITION

Simeticone Suspension for Infants is a suspension of Simeticone for Oral Use in a suitable flavoured aqueous vehicle.

The suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of dimeticone

90.0 to 110.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, of the sample solution prepared in the Assay is concordant with that obtained for the solution of *dimeticone EPCRS*. Disregard the region of the spectrum from 850 cm^{-1} to 750 cm^{-1}.

TESTS

Acidity

pH, 3.0 to 5.0, Appendix V L.

Defoaming activity

Dissolve 1.0 g of *octoxinol 10* in sufficient *water* to produce 100 mL (foaming solution). To a weighed quantity of the suspension containing 0.3 g of dimeticone add sufficient *water* to produce 30 g and mix thoroughly (test solution). Into a suitable container introduce 100 mL of the foaming solution and 0.5 mL of the test solution. Close tightly and shake the mixture for 10 seconds at 300 oscillations per minute, at an angle of oscillation of about ±10° and an oscillation radius of about 13 cm. The time between the end of the shaking and the instant the first portion of foam-free liquid surface appears is not greater than 45 seconds.

ASSAY

Add 25 mL of *toluene*, pre-washed with 1M *sodium hydroxide*, and 50 mL of 1M *sodium hydroxide* to a quantity of the suspension containing 50 mg of dimeticone and shake mechanically for 5 minutes. Allow the mixture to stand for 5 minutes, centrifuge the upper layer and dry with *anhydrous sodium sulfate*. Record the *infrared absorption spectrum*, Appendix II A, of a 0.5 mm layer of the clear solution over the range

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1375 to 1125 cm^{-1} (7.27 to 8.89 µm). Measure the absorbance of the CH_3Si stretching band at the maximum at 1261 cm^{-1} (7.93 µm).

Repeat the operation using a 0.2% w/v solution of *dimeticone EPCRS* in *toluene*. Determine the *weight per mL* of the suspension, Appendix V G, and calculate the content of dimeticone weight in volume.

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Simple Eye Ointment

General Notices

Eye Ointment Basis

DEFINITION

Wool Fat	100 g
Yellow Soft Paraffin	800 g
Liquid Paraffin	Sufficient to produce 1000 g

Extemporaneous preparation

The following directions apply.

Melt together the Wool Fat and the Yellow Soft Paraffin, add the Liquid Paraffin, filter the hot mixture through coarse filter paper placed in a heated funnel, sterilise the filtrate by *dry heat* at a minimum of 150° for not less than 1 hour and allow to cool.

The eye ointment complies with the requirements stated under Eye Preparations.

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Simple Linctus

General Notices

Simple Oral Solution

DEFINITION

Simple Linctus is an *oral solution* containing 2.5% w/v of Citric Acid Monohydrate in a suitable vehicle with an anise flavour.

The linctus complies with the requirements stated under Oral Liquids and with the following requirements.

Content of free acid, calculated as citric acid monohydrate, $C_6H_8O_7,H_2O$

2.00 to 2.65% w/v.

IDENTIFICATION

Dilute 5 mL to 50 mL with *water*, add 2 g of *activated charcoal*, mix and filter. To 1 mL of the filtrate add 1 mL of *pyridine*, swirl to mix, add 5 mL of *acetic anhydride* and mix using, for example, a rotary vortex mixer. Immediately place in a water bath at about 30° for 5 minutes. A yellow colour is produced.

ASSAY

Dilute 15 g with 50 mL of *water* and titrate with *0.5M sodium hydroxide VS* using 2 mL of *thymol blue solution* as indicator. Each mL of *0.5M sodium hydroxide VS* is equivalent to 35.02 mg of $C_6H_8O_7,H_2O$. Determine the *weight per mL* of the linctus, Appendix V G, and calculate the content of $C_6H_8O_7,H_2O$, weight in volume.

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Simple Ointment

General Notices

DEFINITION

Wool Fat	50 g
Hard Paraffin	50 g
Cetostearyl Alcohol	50 g
White Soft Paraffin or Yellow Soft Paraffin	850 g

Unless otherwise directed in the monograph, when Simple Ointment is used in a white ointment, it should be prepared with White Soft Paraffin; when used in a coloured ointment it should be prepared with Yellow Soft Paraffin.

Extemporaneous preparation

The following directions apply.

Mix the ingredients, heat gently with stirring until homogeneous and stir until cold.

The ointment complies with the requirements stated under Topical Semi-solid Preparations.

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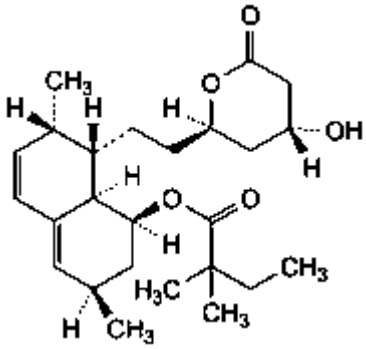
Simvastatin

General Notices

(Ph. Eur. monograph 1563)



$C_{25}H_{38}O_5$ 418.6 *79902-63-9*

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

Preparations

Simvastatin Tablets

Simvastatin Oral Suspension

Ph Eur

DEFINITION

(1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-Hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate.

Content

97.0 per cent to 102.0 per cent (dried substance).

A suitable antioxidant may be added.

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *simvastatin CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 0.2 g in *methanol R* and dilute to 20 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 285 to + 300 (dried substance).

Dissolve 0.125 g in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*) *Prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *simvastatin CRS* in the solvent mixture and dilute to 5.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *simvastatin for system suitability CRS* (containing impurities A, B, C, D, E, F, G, I and J) in 1 mL of the solvent mixture.

Reference solution (d) Dissolve 4.0 mg of *simvastatin impurity K CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 5.0 mL with the solvent mixture.

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Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, 0.1 per cent *V/V* solution of *phosphoric acid R* (40:60 *V/V*);

— *mobile phase B*: 0.1 per cent *V/V* solution of *phosphoric acid R*, *acetonitrile R1* (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 5	100 → 80	0 → 20
5 - 33	80 → 60	20 → 40
33 - 34	60 → 0	40 → 100
34 - 45	0	100

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 238 nm and, for impurity K, at 200 nm.

Autosampler Set at 8 °C.

Injection 5 µL of test solution (a) and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram supplied with *simvastatin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D, E, F, G, I and J; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity K.

Relative retention With reference to simvastatin (retention time = about 19 min): impurity I = about 0.67; impurity A = about 0.69; impurity E = about 0.81; impurity F = about 0.83; impurity G = about 0.9; impurity K = about 1.2; impurity B = about 1.69; impurity J = about 1.74; impurity C = about 1.76; impurity D = about 2.3.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity E; minimum 1.5, where H_p = height above

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the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity J.

Calculation of percentage contents:

— for impurity K, use the concentration of impurity K in reference solution (d) and the peak areas recorded at 200 nm;

— for impurities other than K, use the concentration of simvastatin in reference solution (a) and the peak areas recorded at 238 nm.

Limits:

— *impurities E, F*: for each impurity, maximum 0.5 per cent;

— *sum of impurities A and I*: maximum 0.4 per cent;

— *impurity D*: maximum 0.4 per cent;

— *impurity K at 200 nm*: maximum 0.4 per cent;

— *impurities B, C*: for each impurity, maximum 0.3 per cent;

— *impurities G, J*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 3.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator under high vacuum at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	70	30
14 - 15	70 → 0	30 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
15 - 20	0	100

Injection Test solution (b) and reference solution (b).

Calculate the percentage content of $C_{25}H_{38}O_5$ taking into account the assigned content of *simvastatin CRS*.

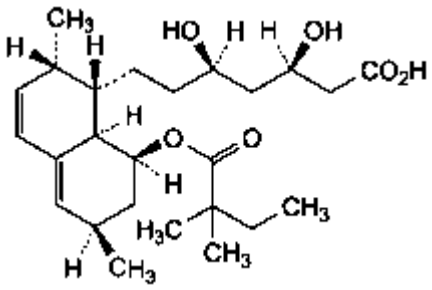
STORAGE

Protected from light. If no antioxidant is present, store under nitrogen, in an airtight container.

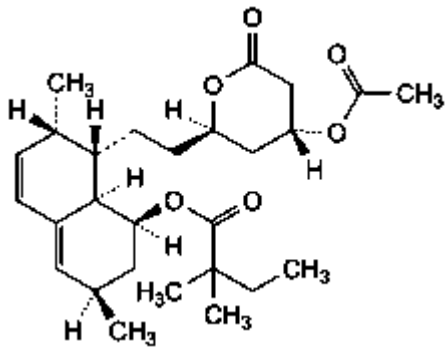
IMPURITIES

Specified impurities *A, B, C, D, E, F, G, I, J, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, M, N.*



A. (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid (tenivastatin),



B. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-(acetyloxy)-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate,

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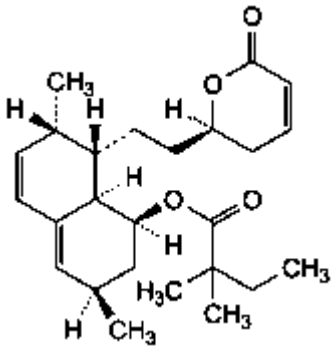
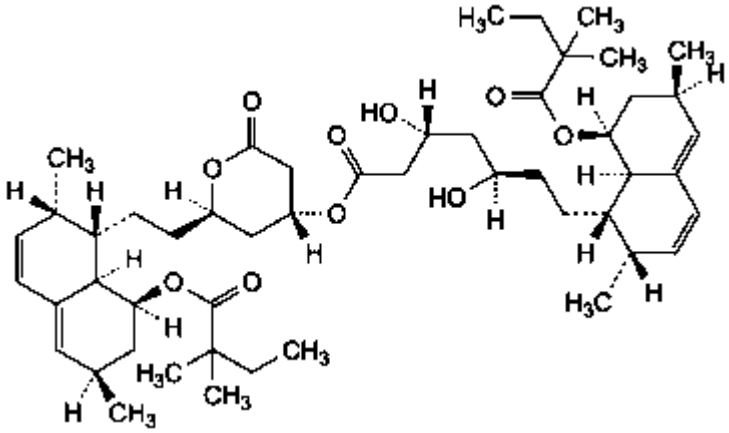
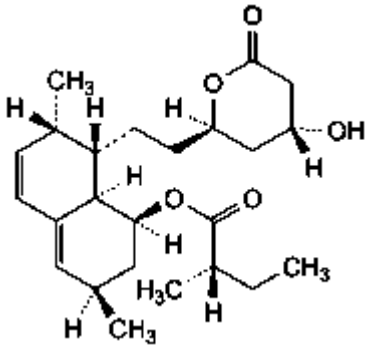


C. (1*S*,3*R*,7*S*,8*S*,8a*R*)-3,7-dimethyl-8-[2-[(2*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate,



D. (2*R*,4*R*)-2-[2-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]ethyl]-6-oxooxan-4-yl (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoate,



E. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate (lovastatin),

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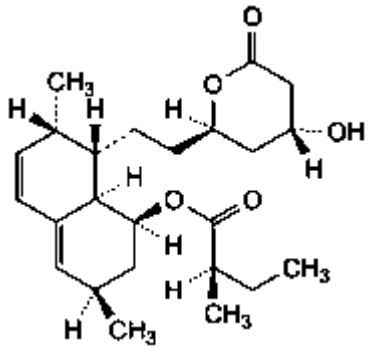
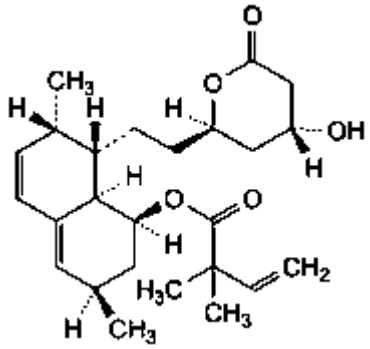
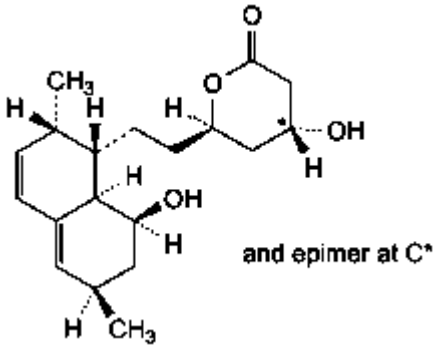


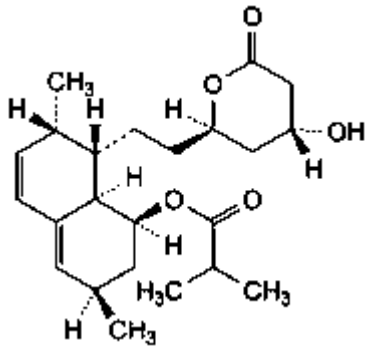
F. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*R*)-2-methylbutanoate (epilovastatin),



G. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbut-3-enoate,



H. (4*RS*,6*R*)-4-hydroxy-6-[2-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-hydroxy-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]ethyl]oxan-2-one,



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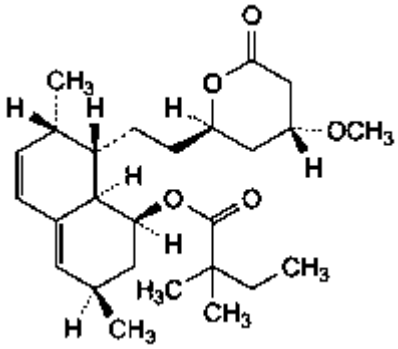
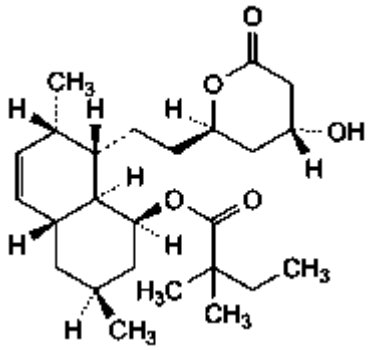
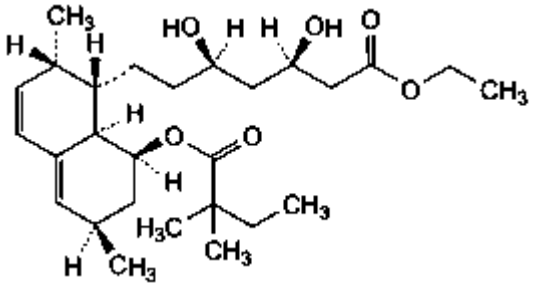
I. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2-methylpropanoate,



J. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-methoxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate,



K. (1*S*,3*S*,4a*R*,7*S*,8*S*,8a*S*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl 2,2-dimethylbutanoate,



M. ethyl (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoate,

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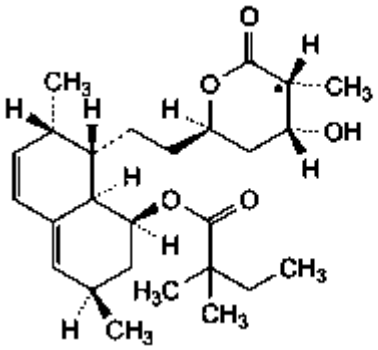

and epimer at C*

N. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*,5*RS*)-4-hydroxy-5-methyl-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate.

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Simvastatin Oral Suspension

General Notices

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

DEFINITION

Simvastatin Oral Suspension is a suspension of Simvastatin in a suitable flavoured vehicle.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Simvastatin. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of simvastatin, $C_{25}H_{38}O_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *dichloromethane*.

(1) Shake a quantity of the oral suspension containing 25 mg of Simvastatin with 10 mL of *dichloromethane* for 10 minutes. Allow to separate and use the lower layer.

(2) 0.25% w/v of *simvastatin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

12 volumes of *propan-2-ol*, 23 volumes of *dichloromethane* and 65 volumes of *cyclohexane*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in solution A.

45 volumes of a 0.14% w/v solution of *potassium dihydrogen phosphate*, adjusted to pH 4.0 with *orthophosphoric acid*, and 55 volumes of *acetonitrile* (solution A).

(1) Mix with the aid of ultrasound a quantity of the oral suspension containing 16 mg of Simvastatin with 30 mL of solution A. Add a sufficient volume of solution A to produce 50 mL and mix. Centrifuge and filter (0.45-µm PVDF syringe filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.2% w/v of *simvastatin for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Zorbax Eclipse XDB-C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.4 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 238 nm.
(f) Use an autosampler temperature of 8°
(g) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A 40 volumes of *acetonitrile* and 60 volumes of a 0.1% v/v solution of *orthophosphoric acid*.

Mobile phase B 5 volumes of a 0.1% v/v solution of *orthophosphoric acid* and 95 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	100	0	isocratic
4-5	100→80	0→20	linear gradient
5-33	80→60	20→40	linear gradient
33-34	60→0	40→100	linear gradient
34-37	0	100	isocratic

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
37-38	0→100	100→0	linear gradient
38-45	100	0	re-equilibration

Use the chromatogram supplied with *simvastatin for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B C, D, E, F, G, I and J.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to simvastatin (retention time about 19 minutes) are: impurity I, about 0.67; impurity A, about 0.69; impurity E, about 0.81; impurity F, about 0.83; impurity G, about 0.9; impurity B, about 1.69; impurity J, about 1.74; impurity C, about 1.8 and impurity D, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3):

the peak-to-valley ratio is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity E;

the peak-to-valley ratio is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity J.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurities A and I is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (6%);

the area of any peak corresponding to impurity B, C, E or F is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity D or G is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks*, other than any peaks corresponding to impurities A + I, B, C, D, E, F and G, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

45 volumes of a 0.14% w/v solution of *potassium dihydrogen phosphate*, adjusted to pH 4.0 with *orthophosphoric acid*, and 55 volumes of *acetonitrile*. Mix and filter (solvent B).

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Carry out the method for *liquid chromatography*, Appendix III D protected from light, using the following solutions prepared immediately before use, in solution B.

(1) Mix with the aid of ultrasound a weighed quantity of the oral suspension containing 16 mg of Simvastatin with 30 mL of solution B. Add a sufficient volume of solution B to produce 50 mL and mix. Centrifuge and filter (0.45-µm PVDF syringe filter is suitable). Dilute 5 volumes to 200 volumes.

(2) 0.0008% w/v of *simvastatin BPCRS*.

(3) 0.002% w/v of each of *simvastatin BPCRS* and *lovastatin EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used. Inject 50 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to simvastatin and lovastatin (impurity E) is at least 3.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{25}H_{38}O_5$, weight in volume, using the declared content of $C_{25}H_{38}O_5$ in *simvastatin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Simvastatin.

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Simvastatin Tablets

General Notices

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

DEFINITION

Simvastatin Tablets contain Simvastatin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of simvastatin, $C_{25}H_{38}O_5$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Simvastatin with 20 mL of *dichloromethane*, filter through a glass fibre filter (Whatman GF/C is suitable) and evaporate the filtrate to dryness under a stream of *nitrogen*. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of simvastatin *(RS 423)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *sodium dihydrogen orthophosphate* containing 0.5% w/v of *sodium dodecyl sulfate* and adjusted to pH 7.0 with 1 M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a 20 -mL sample of the medium, filter and transfer 10 mL of the filtrate into a centrifuge tube containing 0.1 g of *manganese(IV) oxide, pre-washed*. Shake the tube for 30 minutes, or until the manganese(IV) oxide is completely dispersed and centrifuge. Measure the *absorbance* of the clear supernatant liquid, suitably diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.001% w/v of Simvastatin, at the maximum at 247 nm and at the minimum at 257 nm, Appendix II B using dissolution medium that has been similarly treated with *manganese(IV) oxide , pre-washed* in the reference cell.

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(2) Measure the *absorbance* of a 0.001% w/v solution of *simvastatin BPCRS* prepared by dissolving *simvastatin BPCRS* in the dissolution medium and treating with *manganese(IV) oxide , pre-washed* as described for solution (1), at 247 nm and at 257 nm, using dissolution medium that has been similarly treated with *manganese(IV) oxide , pre-washed* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of simvastatin, $C_{25}H_{38}O_5$, in the medium using the differences in *absorbance* at 247 nm and at 257 nm and using the declared content of $C_{25}H_{38}O_5$ in *simvastatin BPCRS*.

LIMITS

The amount of simvastatin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in solution A.

Mix 40 volumes of a 0.14% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 4.0 with *orthophosphoric acid*, and 60 volumes of *acetonitrile* (solution A).

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Simvastatin with 20 mL of solution A. Add sufficient solution A to produce 50 mL, mix and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.2% w/v of *simvastatin for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Zorbax Eclipse XDB-C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.4 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 238 nm.
(f) Use an autosampler temperature of 8°
(g) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A 40 volumes of *acetonitrile* and 60 volumes of a 0.1% v/v solution of *orthophosphoric acid*.

Mobile phase B 5 volumes of a 0.1% v/v solution of *orthophosphoric acid* and 95 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	100	0	isocratic
4-5	100→80	0→20	linear gradient

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
5-33	80→60	20→40	linear gradient
33-34	60→0	40→100	linear gradient
34-48	0	100	isocratic
48-49	0→100	100→0	linear gradient
50-55	100	0	re-equilibration

Use the chromatogram supplied with *simvastatin for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B C, D, E, F, G, I and J.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to simvastatin (retention time about 19 minutes) are: impurity I, about 0.67; impurity A, about 0.69; impurity E, about 0.81; impurity F, about 0.83; impurity G, about 0.9; impurity B, about 1.69; impurity J, about 1.74; impurity C, about 1.8 and impurity D, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3):

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity E;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity J.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to impurities A and I is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity B, C, E or F is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity D or G is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks*, other than any peaks corresponding to impurities A + I, B, C, D, E, F and G, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

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ASSAY

Add 3 mL of *glacial acetic acid* to 900 mL of *water*, adjust the pH to 4.0 with 1M *sodium hydroxide* and add sufficient *water* to produce 1000 mL. Mix 1 volume of this solution with 4 volumes of *acetonitrile* (solution B).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution B.

(1) Mix, with the aid of ultrasound and shaking, a quantity of whole tablets containing 0.16 g of Simvastatin in a minimum volume of *water* until completely dispersed. Add a sufficient volume of solution B to produce 75 mL, mix with the aid of ultrasound and shaking for 15 minutes, allow to cool to room temperature, dilute to produce 100 mL and centrifuge. Dilute 1.5 volumes of the clear supernatant solution to 25 volumes.

(2) 0.01% w/v of *simvastatin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

7 volumes of a buffer solution prepared as described below and 13 volumes of *acetonitrile*.

To prepare the buffer solution dissolve 5.1 g of *sodium dihydrogen orthophosphate* in 900 mL of *water*, adjust the pH to 4.5 with either *orthophosphoric acid* or 1M *sodium hydroxide* and add sufficient *water* to produce 1000 mL.

When the chromatograms are recorded using the prescribed conditions the retention time of simvastatin is about 7 minutes.

SYSTEM SUITABILITY

The test is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{38}O_5$ in the tablets using the declared content of $C_{25}H_{38}O_5$ in *simvastatin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Simvastatin.

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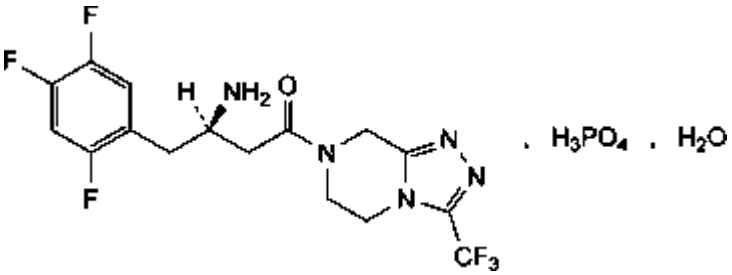
Sitagliptin Phosphate Monohydrate

General Notices

(Ph. Eur. monograph 2778)



$C_{16}H_{18}F_6N_5O_5P,H_2O$ 523.3 *654671-77-9*

Action and use

Dipeptidylpeptidase-4 inhibitor; treatment of diabetes mellitus.

Preparations

Sitagliptin Tablets

Metformin and Sitagliptin Tablets

Metformin and Sitagliptin Prolonged-release Tablets

Ph Eur

DEFINITION

(3*R*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sitagliptin phosphate monohydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Enantiomeric purity (see Tests).

C. Dissolve 0.200 g in *water R* and dilute to 5.0 mL with the same solvent. The solution gives reaction (a) of phosphates (2.3.1).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Solvent mixture *water R*, *methanol R* (10:90 *V/V*).

Test solution Dissolve 80 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 8 mg of *sitagliptin containing impurity A CRS* in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 35 °C.

Mobile phase *water for chromatography R*, *diethylamine R*, *heptane R*, *anhydrous ethanol R* (1:1:400:600 *V/V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 268 nm.

Injection 10 µL.

Run time 1.6 times the retention time of sitagliptin.

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Identification of impurities Use the chromatogram supplied with *sitagliptin containing impurity A CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to sitagliptin (retention time = about 15 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and sitagliptin.

Limit:

— *impurity A*: maximum 0.5 per cent;

— *reporting threshold*: 0.1 per cent (reference solution (a)).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, 0.1 per cent *V/V* solution of *phosphoric acid R* (5:95 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 250.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of *sitagliptin phosphate monohydrate CRS* in the solvent mixture and dilute to 250.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) In order to prepare the fumarate adduct *in situ*, heat 1 mL of *water R*, 1 mg of *sodium stearyl fumarate R* and 10 mg of the substance to be examined in a tightly closed vial at 80 °C for about 30 h. Dilute to 100 mL with the solvent mixture and stir for 1 h. Centrifuge a portion of the solution and use the clear supernatant.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped cyanosilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 15 volumes of *acetonitrile R1* and 85 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

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Run time 5.5 times the retention time of sitagliptin.

Relative retention With reference to sitagliptin (retention time = about 5.5 min): fumarate adduct = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to sitagliptin and the fumarate adduct.

Calculation of percentage contents:

— for each impurity, use the concentration of sitagliptin phosphate monohydrate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

3.3 per cent to 3.7 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

Run time Twice the retention time of sitagliptin.

Calculate the percentage content of $C_{16}H_{18}F_6N_5O_5P$ taking into account the assigned content of *sitagliptin phosphate monohydrate CRS*.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C.*

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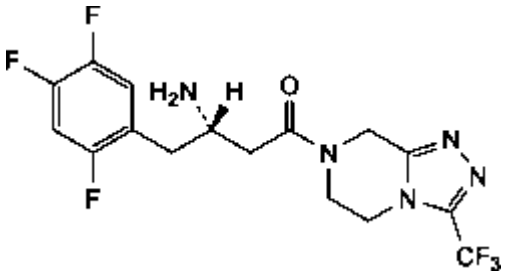
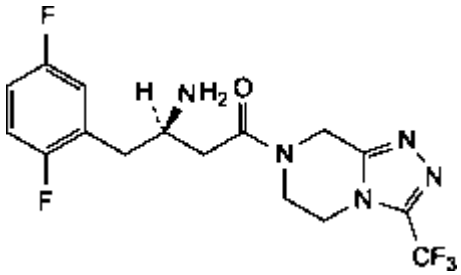
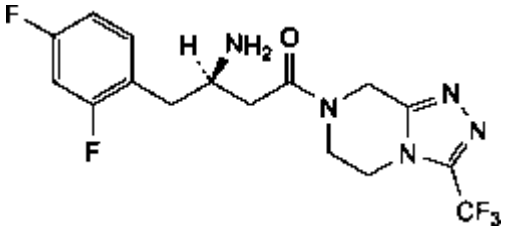


A. (3*S*)-3-amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one,



B. (3*R*)-3-amino-4-(2,5-difluorophenyl)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]butan-1-one,



C. (3*R*)-3-amino-4-(2,4-difluorophenyl)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]butan-1-one.

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Sitagliptin Tablets

General Notices

(Ph. Eur. monograph 2927)

Action and use

Dipeptidylpeptidase-4 inhibitor; treatment of diabetes mellitus.

Ph Eur

DEFINITION

Tablets containing *Sitagliptin phosphate monohydrate (2778)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of sitagliptin ($C_{16}H_{15}F_6N_5O$) stated on the label.

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Crush 1 tablet to a powder and homogenise.

Comparison *sitagliptin phosphate monohydrate CRS*.

Results The spectrum obtained shows absorption maxima at about 1669 cm^{-1}, 1513 cm^{-1}, 1425 cm^{-1}, 1207 cm^{-1}, 880 cm^{-1} and 844 cm^{-1}, similar to the spectrum obtained with *sitagliptin phosphate monohydrate CRS*. Other absorption maxima may be present in the spectra.

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TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, 0.1 per cent *V/V* solution of phosphoric acid R (5:95 *V/V*).

Test solution To 10 tablets, add a suitable volume of the solvent mixture to obtain a concentration of sitagliptin of 1 mg/mL. Stir vigorously for 1 h. Dilute 2.0 mL of the solution to 25.0 mL with the solvent mixture. Centrifuge a portion of the solution and use the clear supernatant.

Reference solution (a) Dissolve 25.0 mg of sitagliptin phosphate monohydrate CRS in the solvent mixture and dilute to 250.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) In order to prepare impurity FP-A (fumarate adduct) *in situ*, heat 1 mL of water R and either 1 sitagliptin tablet containing sodium stearyl fumarate as an excipient or 1 mg of sodium stearyl fumarate R and 10 mg of sitagliptin phosphate monohydrate CRS in a tightly closed vial at 80 °C for about 30 h. Dilute to 100 mL with the solvent mixture and stir for 1 h. Centrifuge a portion of the solution and use the clear supernatant.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped cyanosilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 15 volumes of acetonitrile R1 and 85 volumes of a 1.36 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 2.0 with phosphoric acid R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 7 times the retention time of sitagliptin.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity FP-A.

Relative retention With reference to sitagliptin (retention time = about 5.5 min): impurity FP-A = about 1.2.

System suitability Reference solution (c):

— resolution: minimum 1.5 between the peaks due to sitagliptin and impurity FP-A.

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Calculation of percentage contents:

— for each impurity, use the concentration of sitagliptin in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.1 per cent.

Disintegration[1] (2.9.1).

Medium water R.

Time 5 min.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

Run time Twice the retention time of sitagliptin.

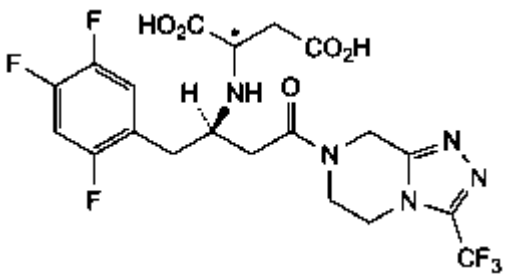
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the percentage content of sitagliptin ($C_{16}H_{15}F_6N_5O$) taking into account the assigned content of *sitagliptin phosphate monohydrate CRS* and applying a conversion factor of 0.806.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: FP-A, FP-B, FP-C, FP-D, FP-E.*



FP-A. 2-[[(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-yl]amino]butanedioic acid,

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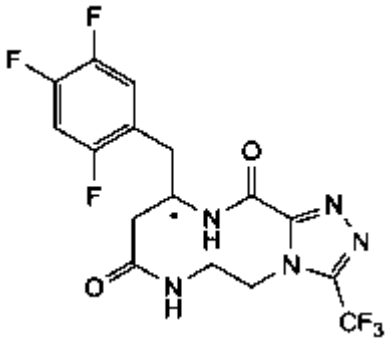
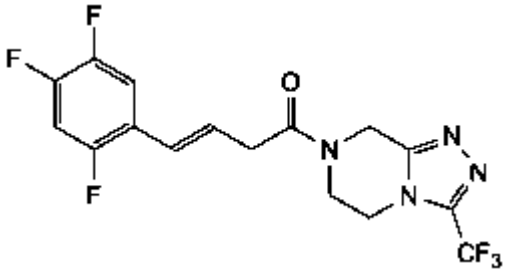
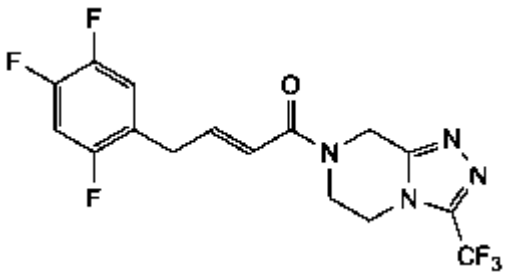


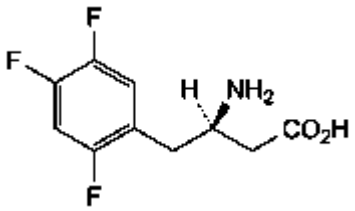
FP-B. 3-(trifluoromethyl)-10-[(2,4,5-trifluorophenyl)methyl]-6,7,10,11-tetrahydro[1,2,4]triazolo[3,4-*c*][1,4,7]triazecine-8,12(5*H*,9*H*)-dione,



FP-C. (3*E*)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-3-en-1-one,



FP-D. (2*E*)-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)but-2-en-1-one,



FP-E. (3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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Soap Spirit

General Notices

DEFINITION

Soft Soap	650 g
Ethanol (90 per cent)	Sufficient to produce 1000 mL

In making Soap Spirit, the Ethanol (90 per cent) may be replaced by Industrial Methylated Spirit[1] diluted so as to be of equivalent ethanolic strength.

Extemporaneous preparation

The following directions apply.

Dissolve the Soft Soap in 300 mL of Ethanol (90 per cent), add sufficient Ethanol (90 per cent) to produce 1000 mL, mix, allow to stand and decant.

The spirit complies with the requirements stated under Spirits and with the following requirements.

TESTS

Acidity or alkalinity

10 mL requires for neutralisation not more than 1.0 mL of *0.1M sodium hydroxide VS* or 0.2 mL of *0.1M hydrochloric acid VS* using *phenolphthalein solution R1* as indicator.

Weight per mL

0.945 to 0.970 g, Appendix V G.

Ethanol content

28 to 32% v/v, Appendix VIII F.

Content of fatty acids

Not less than 27.0% w/v when determined by the following method. To 10 mL add 20 mL of *water* and 20 mL of 1M *hydrochloric acid*, extract with two 20 mL quantities of *petroleum spirit* (*boiling range, 40° to 60°*), wash the combined extracts with two 10 mL quantities of *water*, evaporate the petroleum spirit, add 5 mL of *acetone*, again evaporate and dry the residue at 80° for 2 hours.

1 The law and the statutory regulations governing the use of Industrial Methylated Spirit must be observed.

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Soda Lime

General Notices

8006-28-8

Action and use

Used to absorb carbon dioxide.

DEFINITION

Soda Lime is a mixture of sodium hydroxide, or sodium hydroxide and potassium hydroxide, with calcium hydroxide.

CHARACTERISTICS

White or greyish white granules, or it may be coloured with an indicator to show when its absorptive capacity is exhausted. It absorbs about 20% of its weight of carbon dioxide.

Partially soluble in *water*; almost completely soluble in 1M *acetic acid*.

IDENTIFICATION

A. When moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

B. A solution in 1M *acetic acid* yields reaction C characteristic of *calcium salts*, Appendix VI.

C. A suspension in *water* is strongly alkaline to *litmus paper*.

TESTS

Hardness of granules

Shake 200 g on a sieve no. 2000 for 3 minutes using a mechanical sieve shaker that reproduces in a uniform manner the circular and tapping motion given to sieves in manual use and has a frequency of oscillation of 282 to 288 cycles per minute. Place 50 g of the retained material in a hardness pan 20 cm in diameter having a concave brass bottom, 7.9 mm thick at the circumference, 3.2 mm thick at the centre and with an inside spherical radius of curvature of 109 cm. Add 15 steel balls, 7.9 mm in diameter, and shake on the mechanical sieve shaker for 30 minutes. Remove the steel balls, transfer the contents of the pan to a sieve no. 2000 and again shake on the mechanical sieve shaker for 3 minutes. The material retained by the sieve weighs not less than 37.5 g.

Size of granules

Shake 500 g on a perforated plate of nominal pore size 6.70 mm; not more than 5 g is retained. Then shake on a sieve no. 4750; not more than 50 g is retained. Shake the unretained material on a sieve no. 1400; not more than 20 g passes through. Shake the unretained material on a sieve no. 600; not more than 7.5 g passes through.

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Loss on drying

When dried to constant weight at 105°, loses 14.0 to 21.0% of its weight. Use 1 g.

Moisture absorption

Place 10 g in an open glass dish about 50 mm in diameter and 30 mm high in a desiccator over *sulfuric acid (14%)* and allow it to remain for 24 hours. The increase in weight is not more than 7.5%.

Carbon dioxide absorption

The activity is not less than 120 minutes when determined by the following method.

Use a vertically-clamped tube of glass or other suitable transparent material about 25 cm long and 29 to 31 mm internal diameter with closely fitting rubber bungs at each end; the bungs are bored to receive polythene or glass tubing of about 8 mm external diameter, the tubing being flush with the inner ends of the bungs. With the lower bung in position, place sufficient nylon mesh support on top of the bung to produce a bed of mesh about 10 cm deep and press a closely fitting disc of stainless steel gauze of nominal mesh aperture about 500 µm on top of the nylon mesh so that its surface is at right angles to the axis of the tube. Introduce 59.8 to 60.2 g of the substance being examined onto the steel gauze in three portions, tamping lightly after the addition of each portion. Place a second disc of steel gauze on top, followed by a sufficient quantity of nylon mesh such that the soda lime is kept consolidated by slight pressure when the second bung has been inserted. The exit tube is connected to a condenser, consisting of two 50 mL separating funnels, leading to a drying tube packed with *anhydrous calcium chloride* and then to a carbon dioxide analyser sufficiently sensitive to detect 0.2% v/v of carbon dioxide. A katharometer, calibrated for carbon dioxide and preferably used in conjunction with a chart recorder, is suitable.

Using the gas analyser in accordance with the manufacturer's instructions, accurately determine the carbon dioxide content, *p*, as a percentage v/v, of a nominal 5% carbon dioxide mixture, the balance gas being oxygen, air or nitrogen as appropriate to the type of gas analyser being used. Suitable compressed gas mixtures are available commercially. Assemble the apparatus described above and pass the gas mixture downwards into the absorption tube at a rate of 900 cm^3 per minute until such time that the gas analyser shows the content of carbon dioxide in the effluent gas to have risen to 0.2% v/v. Steps should be taken to vent the effluent gas if an oxygen-carbon dioxide mixture is being used. Record the time taken, *t*, in minutes. The *activity* of the soda lime is given, in minutes, by the expression *tp*/5.

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Sodium (*S*)-Lactate Solution

General Notices

(Ph. Eur. monograph 2033)

Ph Eur

DEFINITION

Content

Minimum 50.0 per cent *m/m* of sodium (2*S*)-2-hydroxypropanoate ($C_3H_5NaO_3$; M_r 112.1); 96.0 per cent to 104.0 per cent of the content of sodium lactate stated on the label, not less than 95.0 per cent of which is the (*S*)-enantiomer.

CHARACTERS

Appearance

Clear, colourless, slightly syrupy liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. To 0.1 mL add 10 mL of *water R*. 5 mL of the solution gives the reaction of lactates (*2.3.1*).

B. It gives reaction (a) of sodium (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Solution S

Dilute a quantity of the substance to be examined corresponding to 40.0 g of sodium lactate to 200 mL with *distilled water R*.

Appearance of solution

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

pH (*2.2.3*)

6.5 to 9.0 for the substance to be examined.

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Reducing sugars and sucrose

To 5 mL of the substance to be examined add 2 mL of *dilute sodium hydroxide solution R* and 0.2 mL of *copper sulfate solution R*. The solution is clear and blue and remains so on boiling. Add to the hot solution 4 mL of *hydrochloric acid R*. Boil for 1 min. Add 6 mL of *strong sodium hydroxide solution R* and heat to boiling again. The solution is clear and blue.

Methanol

Gas chromatography (*2.4.24*).

Limit:

— *methanol*: maximum 50 ppm, calculated with reference to sodium lactate, if intended for use in the manufacture of parenteral preparations, dialysis, haemodialysis or haemofiltration solutions.

Chlorides (*2.4.4*)

Maximum 50 ppm calculated with reference to sodium lactate.

Dilute 5 mL of solution S to 15 mL with *water R*.

Oxalates and phosphates

To 1 mL of the substance to be examined add 15 mL of *ethanol (96 per cent) R* and 2 mL of *calcium chloride solution R*. Heat at 75 °C for 5 min. Any opalescence in the solution is not more intense than that of a standard prepared at the same time and in the same manner using a mixture of 1 mL of the substance to be examined, 15 mL of *ethanol (96 per cent) R* and 2 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm calculated with reference to sodium lactate.

To 7.5 mL of solution S, add 1.9 mL of *hydrochloric acid R1* and dilute to 15 mL with *distilled water R*. The solution complies with the limit test for sulfates without addition of 0.5 mL of *acetic acid R*. Acidify the standard solution with 0.05 mL of *hydrochloric acid R1* instead of 0.5 mL of *acetic acid R*.

Aluminium

Maximum 0.1 ppm, if intended for use in the manufacture of parenteral preparations, dialysis, haemodialysis or haemofiltration solutions.

Atomic absorption spectrometry (*2.2.23, Method I*). For the preparation of the solutions, use equipment that is aluminium-free or that will not release aluminium under the conditions of use (glass, polyethylene, etc).

Modifier solution Dissolve 100.0 g of *ammonium nitrate R* in a mixture of 50 mL of *water R* and 4 mL of *nitric acid R* and dilute to 200 mL with *water R*.

Blank solution Dilute 2.0 mL of the modifier solution to 25.0 mL with *water R*.

Test solution To 5.0 g add 2.0 mL of the modifier solution and dilute to 25.0 mL with *water R*.

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Reference solutions Prepare the reference solutions immediately before use (0.010 ppm to 0.050 ppm of aluminium) using *aluminium standard solution (200 ppm Al) R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Graphite furnace.

Carrier gas *argon R*.

Conditions The device is equipped with a non-specific absorption correction system. Heat the oven to 120 °C for as many seconds as there are microlitres of solution introduced into the apparatus, then heat at 1000 °C for 30 s and finally at 2700 °C for 6 s.

Iron (*2.4.9*)

Maximum 10 ppm calculated with reference to sodium lactate.

Dilute 5 mL of solution S to 10 mL with *water R*.

ASSAY

Dissolve a quantity of the substance to be examined corresponding to 75.0 mg of sodium lactate in a mixture of 10 mL of *glacial acetic acid R* and 20 mL of *acetic anhydride R*. Allow to stand for 15 min. Add 1 mL of *naphtholbenzein solution R* and titrate with *0.1 M perchloric acid*.

1 mL of *0.1 M perchloric acid* is equivalent to 11.21 mg of $C_3H_5NaO_3$.

(*S*)-enantiomer

Transfer a quantity of the substance to be examined corresponding to 2.50 g of sodium lactate into a 50 mL volumetric flask, dilute with about 30 mL of *water R* and add 5.0 g of *ammonium molybdate R*. Dissolve and dilute with *water R* to 50.0 mL. Measure the angle of optical rotation (*2.2.7*). Calculate the percentage content of (*S*)-enantiomer using the expression:

$$50 + \left(24.04 \times \alpha \times \frac{5.0}{m} \times \frac{50}{c}\right)$$

α	=	angle of optical rotation (absolute value);
m	=	mass of the substance to be examined, in grams;
c	=	percentage content *m/m* of $C_3H_5NaO_3$ in the substance to be examined.

The complex of sodium (*S*)-lactate formed under these test conditions is laevorotatory.

LABELLING

The label states:

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— where applicable, that the substance is suitable for use in the manufacture of dialysis, haemodialysis and haemofiltration solutions;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

— the declared content of sodium lactate.

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Sodium Acetate Sterile Concentrate

General Notices

Sterile Sodium Acetate Concentrate

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in Parenteral Nutrition Solutions.

DEFINITION

Sodium Acetate Sterile Concentrate is a sterile solution of Sodium Acetate Trihydrate in a suitable solvent.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements. Where appropriate, the concentrate also complies with the requirements stated under Unlicensed Medicines.

Content of anhydrous sodium acetate, $C_2H_3NaO_2$

95.0 to 105.0% of the stated amount.

Content of sodium, Na

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Yields the reactions characteristic *of sodium salts*, Appendix VI.

B. Yields reaction A characteristic *of acetates*, Appendix VI.

TESTS

Alkalinity

pH of the concentrate, diluted if necessary to produce a solution containing the equivalent of 5% w/v of anhydrous sodium acetate, 7.5 to 9.0, Appendix V L.

ASSAY

For sodium acetate

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Evaporate a volume of the concentrate containing the equivalent of 0.15 g of anhydrous sodium acetate to dryness; add 50 mL of *anhydrous acetic acid* and 10 mL of *acetic anhydride* and carry out Method I for non-aqueous titration, Appendix VIII A, using *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 8.20 mg of $C_2H_3NaO_2$.

For Na

Prepare a suitable dilution in *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm and using *sodium standard solution (200 ppm Na)*, suitably diluted with *water*, for the standard solutions.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous sodium acetate and in terms of the concentration of sodium ions (Na^+) in millimoles per mL.

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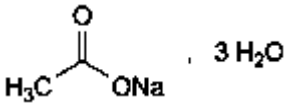
Sodium Acetate Trihydrate

General Notices

(Ph. Eur. monograph 0411)



$C_2H_3NaO_2,3H_2O$ 136.1 *6131-90-4*

Action and use

Used in solutions for dialysis; excipient.

Preparation

Sodium Acetate Sterile Concentrate

Ph Eur

DEFINITION

Sodium acetate trihydrate (sodium ethanoate trihydrate).

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. 1 mL of solution S (see Tests) gives reaction (b) of acetates (*2.3.1*).

B. 1 mL of solution S gives reaction (a) of sodium (*2.3.1*).

C. Loss on drying (see Tests).

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TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

7.5 to 9.0.

Dilute 5 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Reducing substances

Dissolve 5.0 g in 50 mL of *water R*, then add 5 mL of *dilute sulfuric acid R* and 0.5 mL of a 0.32 g/L solution of *potassium permanganate R*. The pink colour persists for at least 1 h. Prepare a blank in the same manner but without the substance to be examined.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Aluminium (*2.4.17*)

Maximum 0.2 ppm, if intended for use in the manufacture of dialysis solutions.

Prescribed solution Dissolve 20 g in 100 mL of *water R* and adjust to pH 6.0 with a 103 g/L solution of *hydrochloric acid R* (about 10 mL).

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Calcium and magnesium

Maximum 50 ppm, calculated as Ca.

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To 200 mL of *water R* add 10 mL of *ammonium chloride buffer solution pH 10.0 R*, 0.1 g of *mordant black 11 triturate R*, 2.0 mL of *0.05 M zinc chloride* and, dropwise, *0.02 M sodium edetate* until the colour changes from violet to blue. Add to the solution 10.0 g of the substance to be examined and shake to dissolve. Titrate with *0.02 M sodium edetate* until the blue colour is restored. Not more than 0.65 mL of *0.02 M sodium edetate* is required.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Loss on drying (*2.2.32*)

39.0 per cent to 40.5 per cent, determined on 1.000 g by drying in an oven at 130 °C. Introduce the substance to be examined into the oven while the latter is cold.

ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R*, add 5 mL of *acetic anhydride R*, mix and allow to stand for 30 min. Using 0.3 mL of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until a green colour is obtained.

1 mL of *0.1 M perchloric acid* is equivalent to 8.20 mg of $C_2H_3NaO_2$.

STORAGE

In an airtight container.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

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Sodium Acid Citrate

General Notices

Disodium Hydrogen Citrate

$C_6H_6Na_2O_7,1½H_2O$ 263.1 *144-33-2*

Action and use

Anticoagulant.

DEFINITION

Sodium Acid Citrate contains not less than 98.0% and not more than 104.0% of $C_6H_6Na_2O_7,1½\ H_2O$.

CHARACTERISTICS

A white powder.

Freely soluble in *water*; practically insoluble in *ethanol (96%)*.

IDENTIFICATION

Yields the reactions characteristic of *sodium salts* and of *citrates*, Appendix VI.

TESTS

Acidity

pH of a 3% w/v solution, 4.9 to 5.2, Appendix V L.

Arsenic

0.50 g dissolved in 25 mL of *water* complies with the *limit test for arsenic*, Appendix VII (2 ppm).

Chloride

Dissolve 1.0 g in 100 mL of *water*. 15 mL of the resulting solution complies with the *limit test for chlorides*, Appendix VII (330 ppm).

Oxalate

Dissolve 1.0 g in 4 mL of *water*, add 3 mL of *hydrochloric acid* and 1 g of granulated *zinc* and heat on a water bath for 1 minute. Allow to stand for 2 minutes, decant the liquid into a test tube containing 0.25 mL of a 1% w/v solution of *phenylhydrazine hydrochloride* and heat to

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boiling. Cool rapidly, transfer to a graduated measuring cylinder, add an equal volume of *hydrochloric acid* and 0.25 mL of *potassium hexacyanoferrate(III) solution*, shake and allow to stand for 30 minutes. Any red colour produced is not more intense than that produced by treating in the same manner 4 mL of a 0.005% w/v solution of *oxalic acid* (150 ppm, calculated as anhydrous oxalic acid).

Sulfate

Dissolve 0.50 g in 57 mL of *water* and add 3 mL of *2M hydrochloric acid*. 15 mL of the resulting solution complies with the *limit test for sulfates*, Appendix VII (0.12%).

Readily carbonisable substances

Heat 1.0 g, in powder, with 10 mL of *sulfuric acid* for 30 minutes in a water bath protected from light. Not more than a pale brown colour is produced.

ASSAY

Heat 2 g until carbonised, cool and boil the residue with 50 mL each of *water* and *0.5M hydrochloric acid VS*. Filter, wash the filter with *water* and titrate the excess of acid in the filtrate and washings with *0.5M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 65.78 mg of $C_6H_6Na_2O_7,1½H_2O$.

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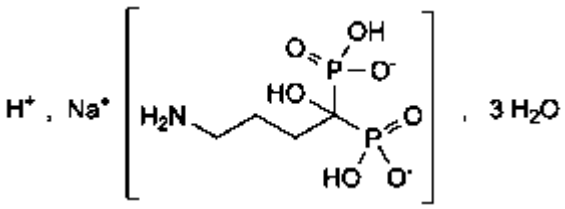
Sodium Alendronate Trihydrate

General Notices

Sodium Alendronate

(Ph. Eur. monograph 1564)



$C_4H_{12}NNaO_7P_2,3H_2O$ 325.1 *121268-17-5*

Preparation

Alendronic Acid and Colecalciferol Tablets

Ph Eur

DEFINITION

Monosodium trihydrogen (4-amino-1-hydroxybutylidene)bisphosphonate trihydrate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in methanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sodium alendronate trihydrate CRS*.

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B. Loss on drying (see Tests).

C. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

pH (2.2.3)

4.0 to 5.0 for solution S.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Solution A Dissolve 29.4 g of *sodium citrate R* in *water R* and dilute to 1.0 L with the same solvent.

Solution B Dissolve 19.1 g of *disodium tetraborate R* in *water R* and dilute to 1.0 L with the same solvent.

Solution C *Prepare immediately before use.* Dissolve 0.200 g of *(9-fluorenyl)methyl chloroformate R* in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Buffer solution Dissolve 2.84 g of *anhydrous disodium hydrogen phosphate R* and 5.88 g of *sodium citrate R* in 1.9 L of *water R*, adjust to pH 8.0 with either *phosphoric acid R* or a 42 g/L solution of *sodium hydroxide R* and dilute to 2.0 L with *water R*.

Test solution Dissolve 30 mg of the substance to be examined in solution A and dilute to 50 mL with solution A. Transfer 5 mL of the solution to a 50 mL polypropylene screw-cap centrifuge tube containing 5 mL of solution B. Add 5 mL of *acetonitrile R* and 5 mL of solution C. Shake for 45 s and allow to stand at room temperature for 30 min. Add 20 mL of *methylene chloride R* and shake vigorously for 1 min. Centrifuge for 5-10 min and use the clear upper layer.

Reference solution (a) Dissolve 15 mg of *4-aminobutanoic acid R* (impurity A) in solution A and dilute to 100 mL with solution A. Dilute 10 mL of the solution to 50 mL with solution A. Take 5 mL of this solution and proceed as described for the test solution, starting from ‘to a 50 mL polypropylene screw-cap centrifuge tube’.

Reference solution (b) Dissolve 3 mg of *sodium alendronate for system suitability CRS* (containing impurity D) in solution A and dilute to 5 mL with solution A. Take this solution and proceed as described for the test solution, starting from ‘to a 50 mL polypropylene screw-cap centrifuge tube’.

Blank solution Take 5 mL of solution A and proceed as described for the test solution, starting from ‘to a 50 mL polypropylene screw-cap centrifuge tube’.

Column:

— *size*: *l* = 0.25 m, Ø = 4.1 mm;

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— *stationary phase*: *styrene-divinylbenzene copolymer R* (10 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, buffer solution (15:85 *V/V*);

— *mobile phase B*: buffer solution, *acetonitrile R* (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 18	100 → 50	0 → 50
18 - 28	50 → 0	50 → 100

Flow rate 1.8 mL/min.

Detection Spectrophotometer at 266 nm.

Injection 20 µL of the test solution, reference solutions (a), (b) and the blank solution.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *sodium alendronate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to alendronate (retention time = about 7 min): impurity D = about 1.4; impurity A = about 1.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to alendronate and impurity D.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.4;

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Impurities B and C

Liquid chromatography (*2.2.29*).

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Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *sodium alendronate trihydrate CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dissolve 3.0 g of *phosphoric acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Reference solution (c) Dissolve 2.5 g of *phosphorous acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Reference solution (d) Mix 2.0 mL of reference solution (b) with 2.0 mL of reference solution (c) and dilute to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *anion-exchange resin R1* (7 µm);

— *temperature*: 35 °C.

Mobile phase Mix 0.2 mL of *anhydrous formic acid R* with 1 L of *water R*; adjust to pH 3.5 with *2 M sodium hydroxide R*.

Flow rate 1.2 mL/min.

Detection Differential refractometer.

Injection 100 µL of the test solution and reference solutions (b), (c) and (d).

Run time Twice the retention time of alendronate.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to alendronate (retention time = about 16 min): impurity B = about 1.3; impurity C = about 1.6.

Limits:

— *impurities B, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.5 per cent).

Loss on drying (*2.2.32*)

16.1 per cent to 17.1 per cent, determined on 1.000 g by drying in an oven at 140-145 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for impurities B and C with the following modification.

Injection Test solution and reference solution (a).

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Calculate the percentage content of $C_4H_{12}NNaO_7P_2$ taking into account the assigned content of *sodium alendronate trihydrate CRS*.

IMPURITIES

Specified impurities *A, B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*

A. 4-aminobutanoic acid (γ-aminobutyric acid),

B. phosphate,

C. phosphite,

D. unknown structure.

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Sodium Alginate

General Notices

(Ph. Eur. monograph 0625)

Action and use

Excipient.

Preparations

Alginate Raft-forming Oral Suspension

Compound Alginate Antacid Oral Suspension

Ph Eur

DEFINITION

Sodium alginate consists mainly of the sodium salt of alginic acid, which is a mixture of polyuronic acids $[(C_6H_8O_6)_n]$ composed of units of D-mannuronic acid and L-guluronic acid. Sodium alginate is obtained mainly from algae belonging to the Phaeophyceae.

CHARACTERS

Appearance

White or pale yellowish-brown powder.

Solubility

Slowly soluble in water forming a viscous, colloidal solution, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 0.2 g with shaking in 20 mL of *water R*. To 5 mL of this solution add 1 mL of *calcium chloride solution R*. A voluminous gelatinous mass is formed.

B. To 10 mL of the solution prepared in identification test A add 1 mL of *dilute sulfuric acid R*. A gelatinous mass is formed.

C. To 5 mg add 5 mL of *water R*, 1 mL of a freshly prepared 10 g/L solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and 5 mL of *hydrochloric acid R*. Boil for 3 min, cool, add 5 mL of *water R*, and shake with 15 mL of *di-isopropyl ether R*. Carry out a blank test. The upper layer obtained with the substance to be examined exhibits a deeper bluish-red colour than that obtained with the blank.

D. Sulfated ash (see Tests). The residue obtained, dissolved in 2 mL of *water R*, gives reaction (a) of sodium (*2.3.1*).

TESTS

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Solution S

Dissolve 0.10 g in *water R* with constant stirring, dilute to 30 mL with the same solvent and allow to stand for 1 h.

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dilute 1 mL of solution S to 10 mL with *water R*.

Chlorides

Maximum 1.0 per cent.

To 2.50 g add 50 mL of *dilute nitric acid R*, shake for 1 h and dilute to 100.0 mL with *dilute nitric acid R*. Filter. To 50.0 mL of the filtrate add 10.0 mL of *0.1 M silver nitrate* and 5 mL of *toluene R*. Titrate with *0.1 M ammonium thiocyanate*, using 2 mL of *ferric ammonium sulfate solution R2* as indicator and shaking vigorously towards the end point.

1 mL of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Calcium

Maximum 1.5 per cent.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dissolve 0.10 g in 50 mL of *dilute ammonia R2*, heating on a water-bath. Allow to cool and dilute to 100.0 mL with *distilled water R* (solution (a)). Dilute 3.0 mL of solution (a) to 100.0 mL with *distilled water R*.

Reference solutions Prepare 3 reference solutions in the same manner as the test solution but add 0.75 mL, 1.0 mL and 1.5 mL respectively of *calcium standard solution (100 ppm Ca) R* to the 3.0 mL of solution (a).

Set the zero of the instrument using a mixture of 1.5 volumes of *dilute ammonia R2* and 98.5 volumes of *distilled water R*.

Source Calcium hollow-cathode lamp.

Wavelength 422.7 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 0.1000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

30.0 per cent to 36.0 per cent (dried substance), determined on 0.1000 g.

Microbial contamination

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TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for sodium alginate used as viscosity-increasing agent or binder.

Apparent viscosity (2.2.10)

Carry out the test on a 10 g/L solution (dried substance). Determine the dynamic viscosity at 20 °C using a rotating viscometer at 20 r/min.

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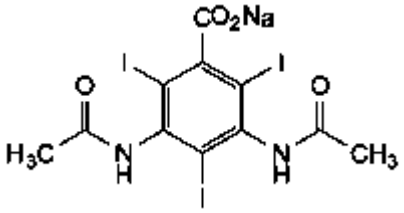
Sodium Amidotrizoate

General Notices

(Ph. Eur. monograph 1150)



$C_{11}H_8I_3N_2NaO_4$ 636 *737-31-5*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

Sodium amidotrizoate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of sodium 3,5-bis(acetylamino)-2,4,6-tri-iodobenzoate, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white powder, freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

It melts at about 261 °C with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *sodium amidotrizoate CRS*. Dry both the substance to be examined and the reference substance at 100 °C to 105 °C for 3 h.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (b).

C. Heat 50 mg gently in a small porcelain dish over a naked flame. Violet vapour is evolved.

D. It gives reaction (a) of sodium (*2.3.1*).

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TESTS

Solution S

Dissolve 10 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Dilute 1 mL of solution S to 10 mL with *water R*. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 7.5 to 9.5.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel GF_{254} plate R*. *Prepare the solutions in subdued light and develop the chromatograms protected from light*.

Test solution (a) Dissolve 0.50 g of the substance to be examined in a 3 per cent *V/V* solution of *ammonia R* in *methanol R* and dilute to 10 mL with the same solution.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a 3 per cent *V/V* solution of *ammonia R* in *methanol R*.

Reference solution (a) Dilute 1 mL of test solution (b) to 50 mL with a 3 per cent *V/V* solution of *ammonia R* in *methanol R*.

Reference solution (b) Dissolve 50 mg of *sodium amidotrizoate CRS* in a 3 per cent *V/V* solution of *ammonia R* in *methanol R* and dilute to 10 mL with the same solution.

Apply separately to the plate 2 µL of each solution. Develop over a path of 15 cm using a mixture of 20 volumes of *anhydrous formic acid R*, 25 volumes of *methyl ethyl ketone R* and 60 volumes of *toluene R*. Allow the plate to dry until the solvents have evaporated and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.2 per cent).

Free aromatic amines

Maintain the solutions and reagents in iced water, protected from light To 0.50 g in a 50 mL volumetric flask add 15 mL of *water R*. Shake and add 1 mL of *dilute sodium hydroxide solution R*. Cool in iced water, add 5 mL of a freshly prepared 5 g/L solution of *sodium nitrite R* and 12 mL of *dilute hydrochloric acid R*. Shake gently and allow to stand for exactly 2 min after adding the hydrochloric acid. Add 10 mL of a 20 g/L solution of *ammonium sulfamate R*. Allow to stand for 5 min, shaking frequently, and add 0.15 mL of a 100 g/L solution of *α-naphthol R* in *ethanol (96 per cent) R*. Shake and allow to stand for 5 min. Add 3.5 mL of *buffer solution pH 10.9 R*, mix and dilute to 50.0 mL with *water R*. The absorbance (*2.2.25*), measured within 20 min at 485 nm using as the compensation liquid a solution prepared at the same time and in the same manner but omitting the substance to be examined, is not greater than 0.30.

Free iodine and iodides

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Not more than 50 ppm. Dissolve 1.0 g in *distilled water R* and dilute to 10 mL with the same solvent. Add dropwise *dilute nitric acid R* until the precipitation is complete, then add 3 mL of *dilute nitric acid R*. Filter and wash the precipitate with 5 mL of *water R*. Collect the filtrate and washings. Add 1 mL of *strong hydrogen peroxide solution R* and 1 mL of *methylene chloride R*. Shake. The lower layer is not more intensely coloured than a reference solution prepared simultaneously and in the same manner, using a mixture of 5 mL of *iodide standard solution (10 ppm I) R*, 3 mL of *dilute nitric acid R* and 15 mL of *water R*.

Water (*2.5.12*)

Not more than 11.0 per cent, determined on 0.400 g by the semi-micro determination of water.

ASSAY

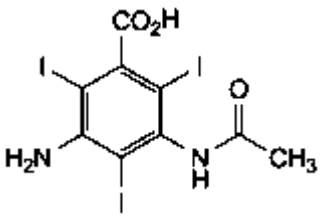
To 0.150 g in a 250 mL round-bottomed flask add 5 mL of *strong sodium hydroxide solution R*, 20 mL of *water R*, 1 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 30 min. Allow to cool and rinse the condenser with 20 mL of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (*2.1.2*) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 40 mL of *dilute sulfuric acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 21.20 mg of $C_{11}H_8I_3N_2NaO_4$.

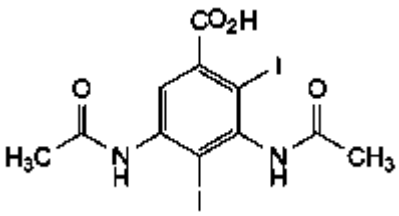
STORAGE

Store protected from light.

IMPURITIES



A. 3-acetylamino-5-amino-2,4,6-tri-iodobenzoic acid,



B. 3,5-bis(acetylamino)-2,4-di-iodobenzoic acid.

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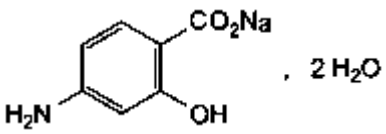
Sodium Aminosalicylate Dihydrate

General Notices

(Ph. Eur. monograph 1993)



$C_7H_6NNaO_3,2H_2O$ 211.1 *6018-19-5*

Action and use

Antituberculosis drug.

Ph Eur

DEFINITION

Sodium 4-amino-2-hydroxybenzoate dihydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals, slightly hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *sodium aminosalicylate dihydrate CRS*.

B. Introduce 0.3 g into a porcelain crucible. Cautiously heat on a small flame until vapour is evolved. Cover the crucible with a watch glass and collect the white sublimate. The melting point (*2.2.14*) of the sublimate is 120 °C to 124 °C.

C. To 0.1 mL of solution S (see Tests) add 5 mL of *water R* and 0.1 mL of *ferric chloride solution R1*. A reddish-brown colour develops.

D. 2 mL of solution S gives the reaction of primary aromatic amines (*2.3.1*).

E. 0.5 mL of solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

The freshly prepared solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_5 (*2.2.2, Method II*).

Dissolve 2.5 g in *water R* and dilute to 25 mL with the same solvent.

pH (*2.2.3*)

6.5 to 8.5 for solution S.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (b) Dissolve 5 mg of *3-aminophenol R* (impurity A) and 5 mg of *mesalazine R* (impurity B) in *water R* and dilute to 100 mL with the same solvent. Dilute 1 mL of the solution to 5 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 2.2 g of *perchloric acid R* and 1.0 g of *phosphoric acid R* in *water for chromatography R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: dissolve 1.7 g of *perchloric acid R* and 1.0 g of *phosphoric acid R* in *acetonitrile for chromatography R* and dilute to 1000 mL with the same solvent;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 30	100 → 40	0 → 60

Flow rate 1.25 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to 4-aminosalicylate (retention time = about 17 min): impurity A = about 0.31; impurity B = about 0.39.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurities A and B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.62;

— for each impurity, use the concentration of sodium aminosalicylate dihydrate in reference solution (a).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Loss on drying (*2.2.32*)

16.0 per cent to 17.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.150 g in 20 mL of *water R*. Add 10 mL of a 500 g/L solution of *sodium bromide R* and 25 mL of *glacial acetic acid R*. Add 5 mL of *0.1 M sodium nitrite* rapidly and continue the titration with the same titrant, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium nitrite* is equivalent to 17.51 mg of $C_7H_6NNaO_3$.

STORAGE

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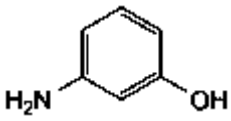
In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

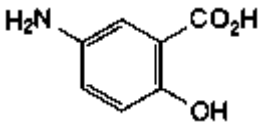
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. 3-aminophenol,



B. 5-amino-2-hydroxybenzoic acid (mesalazine).

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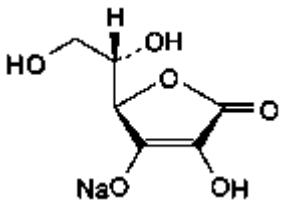
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Sodium Ascorbate

General Notices

(Ph. Eur. monograph 1791)



$C_6H_7NaO_6$ 198.1 *134-03-2*

Action and use

Excipient.

Ph Eur

DEFINITION

Sodium (2*R*)-2-[(1*S*)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder or crystals.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

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Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *sodium ascorbate CRS*.

C. To 1 mL of solution S (see Tests) add 0.2 mL of *dilute nitric acid R* and 0.2 mL of *silver nitrate solution R2*. A grey precipitate is formed.

D. 1 mL of solution S gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 or BY_6 (2.2.2, *Method II*); examine the colour immediately after preparation of the solution.

pH (2.2.3)

7.0 to 8.0, determined on freshly prepared solution S.

Specific optical rotation (2.2.7)

+ 103 to + 108 (dried substance), determined on freshly prepared solution S.

Impurity E

Maximum 0.2 per cent.

Test solution Dissolve 0.25 g in 5 mL of *water R*. Add 1 mL of *dilute acetic acid R* and 0.5 mL of *calcium chloride solution R*.

Reference solution Dissolve 70 mg of *oxalic acid R* (dihydrate of impurity E) in *water R* and dilute to 500 mL with the same solvent; to 5 mL of the solution add 1 mL of *dilute acetic acid R* and 0.5 mL of *calcium chloride solution R*.

Allow the solutions to stand for 1 h. Any opalescence in the test solution is not more intense than that in the reference solution.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Phosphate buffer solution Dissolve 6.8 g of *potassium dihydrogen phosphate R* in *water for chromatography R* and dilute to about 200 mL with the same solvent. Filter through a membrane filter (nominal pore size 0.45 µm) and dilute to 1000 mL with *water for chromatography R*.

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Test solution Dissolve 0.500 g of the substance to be examined in the phosphate buffer solution and dilute to 10.0 mL with the phosphate buffer solution.

Reference solution (a) Dissolve 10.0 mg of *ascorbic acid impurity C CRS* (impurity C) in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *ascorbic acid impurity D CRS* (impurity D) and 5.0 mg of *ascorbic acid CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1 mL of the test solution to 200 mL with the mobile phase. Mix 1 mL of this solution and 1 mL of reference solution (a).

Reference solution (d) Dilute 2.5 mL of reference solution (a) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Phosphate buffer solution, *acetonitrile R1* (25:75 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 2.5 times the retention time of ascorbic acid.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to ascorbic acid (retention time = about 9 min): impurity D = about 0.5; impurity C = about 1.45.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to ascorbic acid and impurity C in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 20 for the peak due to impurity C in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— for impurity C, use the concentration of impurity C in reference solution (d);

— for impurity D, use the concentration of impurity D in reference solution (b);

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— for impurities other than C and D, use the concentration of ascorbic acid in reference solution (b).

Limits:

— *impurities C, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than C and D*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Sulfates (2.4.13)

Maximum 150 ppm.

To 10 mL of solution S add 2 mL of *hydrochloric acid R1* and dilute to 15 mL with *distilled water R*.

Copper

Maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 2.0 g in *0.1 M nitric acid* and dilute to 25.0 mL with the same acid.

Reference solutions Prepare the reference solutions (0.2 ppm, 0.4 ppm and 0.6 ppm) using *copper standard solution (10 ppm Cu) R*, diluting with *0.1 M nitric acid*.

Source Copper hollow-cathode lamp.

Wavelength 324.8 nm.

Atomisation device Air-acetylene flame.

Iron

Maximum 2 ppm.

Atomic absorption spectrometry (*2.2.23*).

Test solution Dissolve 5.0 g in *0.1 M nitric acid* and dilute to 25.0 mL with the same acid.

Reference solutions Prepare the reference solutions (0.2 ppm, 0.4 ppm and 0.6 ppm) using *iron standard solution (20 ppm Fe) R*, diluting with *0.1 M nitric acid*.

Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

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Atomisation device Air-acetylene flame.

Loss on drying (2.2.32)

Maximum 0.25 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 80 mg in a mixture of 10 mL of *dilute sulfuric acid R* and 80 mL of *carbon dioxide-free water R*. Add 1 mL of *starch solution R*. Titrate with *0.05 M iodine* until a persistent violet-blue colour is obtained.

1 mL of *0.05 M iodine* is equivalent to 9.91 mg of $C_6H_7NaO_6$.

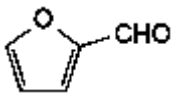
STORAGE

In a non-metallic container, protected from light.

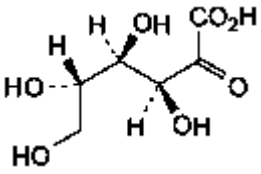
IMPURITIES

Specified impurities *C, D, E*.

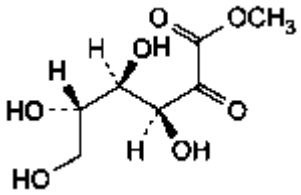
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, F, G, H*.



A. furan-2-carbaldehyde (furfural),



C. L-*xylo*-hex-2-ulosonic acid (L-sorbosonic acid),



D. methyl L-*xylo*-hex-2-ulosonate (methyl L-sorbosonate),

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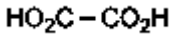
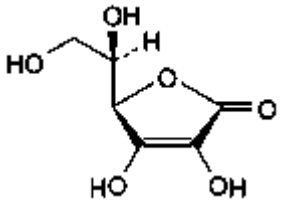
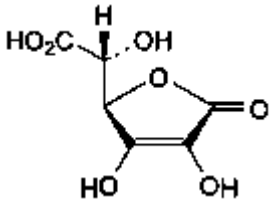


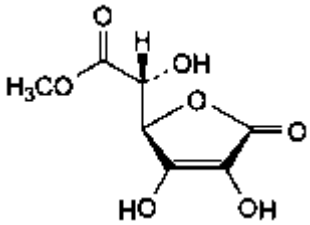
E. oxalic acid,



F. (5*R*)-5-[(1*R*)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one,



G. (*R*)-[(2*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]hydroxyacetic acid,



H. methyl (*R*)-[(2*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]hydroxyacetate.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Sodium Aurothiomalate

General Notices

(Ph. Eur. monograph 1994)

Action and use

Used in the treatment of rheumatoid arthritis.

Preparation

Sodium Aurothiomalate Injection

Ph Eur

DEFINITION

Mixture of monosodium and disodium salts of (2*RS*)-2-(aurosulfanyl)butanedioic acid.

Content

— *gold* (Au; A_r 197.0): 44.5 per cent to 46.0 per cent (dried substance);

— *sodium* (Na; A_r 22.99): 10.8 per cent to 11.8 per cent (dried substance).

CHARACTERS

Appearance

Fine, pale yellow, hygroscopic powder.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Dissolve 20 mg in *water R* and dilute to 2 mL with the same solvent. Add 2 mL of *strong hydrogen peroxide solution R* and 1 mL of *sodium hydroxide solution R*. Carefully heat to boiling and boil for 30 s. A precipitate is produced that appears brownish-black by reflected light and bluish-green by transmitted light.

B. To 20 mg add 2 mL of *water R*. The solution gives reaction (a) of sodium (*2.3.1*).

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C. Ignite 100 mg, dissolve the residue in *hydrochloric acid R* and dilute to 10 mL with the same acid. Allow to stand. 5 mL of the clear supernatant gives reaction (a) of sulfates (*2.3.1*).

TESTS

Appearance of solution

Dissolve 1.0 g in *water R* and dilute to 10 mL with the same solvent. Filter, seal in an ampoule and heat at 100 °C for 1 h. Cool and dilute the contents of the ampoule to 100 mL with *water R*. The solution remains clear and is not more intensely coloured than a 0.100 g/L solution of *potassium ferricyanide R*.

pH (*2.2.3*)

6.0 to 7.0.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.200 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *fumaric acid R* and 100.0 mg of *thiomalic acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 25.0 mL with *water R*.

Reference solution (b) Dissolve 12.0 mg of *thiomalic acid R* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dissolve 10.0 mg of *maleic acid R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 25.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 90 volumes of a 10.5 g/L solution of *phosphoric acid R*, 100 volumes of *methanol R2* and 810 volumes of *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL.

Run time Twice the retention time of impurity C.

Relative retention With reference to impurity C (retention time = about 8 min): impurity A = about 0.4; impurity B = about 0.6. Aurothiomalate does not elute under the chromatographic conditions described.

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System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurities B and C.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (6.0 per cent).

Glycerol

Maximum 8.0 per cent.

Test solution Dissolve 0.50 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 0.80 g of *glycerol R* to 100.0 mL with *water R*.

Reference solution (b) To 2.5 mL of reference solution (a) add 7.5 mL of *water R*.

Reference solution (c) To 5.0 mL of reference solution (a) add 5.0 mL of *water R*.

Reference solution (d) To 7.5 mL of reference solution (a) add 2.5 mL of *water R*.

Blank solution 10 mL of *water R*.

To the test solution, reference solutions (b), (c) and (d) and the blank solution, add 2.5 mL of a freshly prepared 235 g/L solution of *sodium hydroxide R* and mix. Add dropwise in 0.2 mL increments a 38.0 g/L solution of *cupric chloride R*, shaking vigorously after each addition, until the solutions become slightly turbid. Then add 0.2 mL of the 38.0 g/L solution of *cupric chloride R*. Stopper and shake vigorously for 1 min. Dilute to 25.0 mL with *water R* and mix. Centrifuge for 2 min. Measure the absorbance (*2.2.25*) of the supernatant of a 1 cm layer at 635 nm. Use the solution prepared from the blank solution as the compensation liquid. Draw a calibration curve and calculate the content of glycerol in the sample.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in a desiccator at a pressure not exceeding 0.7 kPa for 24 h.

ASSAY

Gold

Heat 0.2 g with 10 mL of *sulfuric acid R* and continue to boil gently until a clear, pale yellow liquid is produced. Cool, add about 1 mL of *nitric acid R* dropwise and boil for 1 h. Cool, dilute to 70 mL with *water R*, boil for 5 min and filter. Wash the residue of gold with *water R* at 60 °C. Dry and ignite at a temperature of at least 600 °C for 3 h. Weigh the residue and calculate the percentage content of Au.

Sodium

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Evaporate to dryness the filtrate and washings obtained in the assay for gold, moisten with *sulfuric acid R* and ignite at 600 ± 50 °C for 3 h.

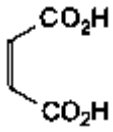
1.000 g of residue is equivalent to 0.324 g of Na.

STORAGE

In an airtight container.

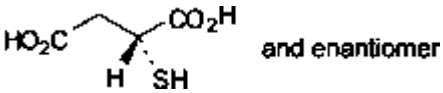
IMPURITIES

Specified impurities *A, B, C.*



A. (*Z*)-butenedioic acid (maleic acid),

B. (*E*)-butenedioic acid (fumaric acid),



C. (2*RS*)-2-sulfanylbutanedioic acid (thiomalic acid).

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Sodium Aurothiomalate Injection

General Notices

DEFINITION

Sodium Aurothiomalate Injection is a sterile solution of Sodium Aurothiomalate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of gold, Au

42.3 to 48.3% of the stated amount of Sodium Aurothiomalate.

CHARACTERISTICS

A pale yellow solution.

IDENTIFICATION

A. To a volume containing 20 mg of Sodium Aurothiomalate add 2 mL of *hydrogen peroxide solution* (*100 vol*) and 1 mL of 5M *sodium hydroxide* and boil for 30 seconds. A colloidal precipitate of gold is produced which appears bluish green by transmitted light.

B. To a volume containing 10 mg of Sodium Aurothiomalate add 0.1 mL of *potassium cyanide solution* and 0.1 mL of a 1.0% w/v solution of *sodium nitroprusside*. A deep magenta colour is produced.

Colour of solution

Dilute, if necessary, with *water* to give a solution containing 1.0% w/v of Sodium Aurothiomalate. The colour of the solution is not more intense than that of a 0.020% w/v solution of *potassium hexacyanoferrate*(III).

ASSAY

To a volume containing 0.1 g of Sodium Aurothiomalate, add 0.4 g of *potassium bromide* and 5 mL of *nitric acid*. Slowly evaporate the solution to dryness and continue heating until fumes cease to be evolved. Allow to cool, add 50 mL of *water*, warm, filter, wash the filter with hot *water*, dry and ignite the residue of gold, Au, for 3 hours at a temperature not lower than 600°.

STORAGE

Sodium Aurothiomalate Injection should be protected from light.

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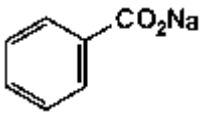
Sodium Benzoate

General Notices

(Ph. Eur. monograph 0123)



$C_7H_5NaO_2$ 144.1 *532-32-1*

Action and use

Excipient; treatment of hyperammonaemia due to urea cycle disorders; treatment of non-ketotic hyperglycinaemia.

Preparations

Sodium Benzoate Oral Solution

Sodium Benzoate Sterile Concentrate

Ph Eur

DEFINITION

Sodium benzenecarboxylate.

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or granular powder or flakes, slightly hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (90 per cent *V/V*).

IDENTIFICATION

A. It gives reactions (b) and (c) of benzoates (*2.3.1*).

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B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 10 mL of *carbon dioxide-free water R* and 0.2 mL of *phenolphthalein solution R*. Not more than 0.2 mL of *0.1 M sodium hydroxide* or *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Halogenated compounds

Maximum 200 ppm for ionised chlorine and maximum 300 ppm for total chlorine.

All glassware used must be chloride-free and may be prepared by soaking overnight in a 500 g/L solution of nitric acid R, rinsed with water R and stored full of water R. It is recommended that glassware be reserved exclusively for this test.

Test solution To 20.0 mL of solution S add 5 mL of *water R* and dilute to 50.0 mL with *ethanol (96 per cent) R*.

Determination of ionised chlorine

In three 25 mL volumetric flasks, prepare the following solutions.

Solution (a) To 4.0 mL of the test solution add 3 mL of *dilute sodium hydroxide solution R* and 3 mL of *ethanol (96 per cent) R*. This solution is used to prepare solution A.

Solution (b) To 3 mL of *dilute sodium hydroxide solution R* add 2 mL of *water R* and 5 mL of *ethanol (96 per cent) R*. This solution is used to prepare solution B.

Solution (c) To 4.0 mL of *chloride standard solution (8 ppm Cl) R* add 6.0 mL of *water R*. This solution is used to prepare solution C.

In a fourth 25 mL volumetric flask, place 10 mL of *water R*. To each flask add 5 mL of *ferric ammonium sulfate solution R5*, mix and add dropwise and with swirling 2 mL of *nitric acid R* and 5 mL of *mercuric thiocyanate solution R*. Shake. Dilute the contents of each flask to 25.0 mL with *water R* and allow the solutions to stand in a water-bath at 20 °C for 15 min. Measure at 460 nm in a 2 cm cell the absorbance (2.2.25) of solution A using solution B as the compensation liquid, and the absorbance of solution C using the solution obtained with 10 mL of *water R* as the compensation liquid. The absorbance of solution A is not greater than that of solution C.

Determination of total chlorine

Solution (a) To 10.0 mL of the test solution add 7.5 mL of *dilute sodium hydroxide solution R* and 0.125 g of *nickel-aluminium alloy R* and heat on a water-bath for 10 min. Allow to cool to room temperature, filter into a 25 mL volumetric flask and wash the filter with 3 quantities,

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each of 2 mL, of *ethanol (96 per cent) R* (a slight precipitate may form that disappears on acidification). Dilute the filtrate and washings to 25.0 mL with *water R*. This solution is used to prepare solution A.

Solution (b) In the same manner, prepare a similar solution replacing the test solution by a mixture of 5 mL of *ethanol (96 per cent) R* and 5 mL of *water R*. This solution is used to prepare solution B.

Solution (c) To 6.0 mL of *chloride standard solution (8 ppm Cl) R* add 4.0 mL of *water R*. This solution is used to prepare solution C.

In four 25 mL volumetric flasks, place separately 10 mL of solution (a), 10 mL of solution (b), 10 mL of solution (c) and 10 mL of *water R*. To each flask add 5 mL of *ferric ammonium sulfate solution R5*, mix and add dropwise and with swirling 2 mL of *nitric acid R* and 5 mL of *mercuric thiocyanate solution R*. Shake. Dilute the contents of each flask to 25.0 mL with *water R* and allow the solutions to stand in a water-bath at 20 °C for 15 min. Measure at 460 nm in a 2 cm cell the absorbance (*2.2.25*) of solution A using solution B as the compensation liquid, and the absorbance of solution C using the solution obtained with 10 mL of *water R* as the compensation liquid. The absorbance of solution A is not greater than that of solution C.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.00 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.250 g in 20 mL of *anhydrous acetic acid R*, heating to 50 °C if necessary. Cool. Using 0.05 mL of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until a green colour is obtained.

1 mL of *0.1 M perchloric acid* is equivalent to 14.41 mg of $C_7H_5NaO_2$.

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Sodium Benzoate Oral Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Treatment of hyperammonaemia due to urea cycle disorders; treatment of non-ketotic hyperglycinaemia.

DEFINITION

Sodium Benzoate Oral Solution is a solution of Sodium Benzoate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of sodium, Na

95.0 to 105.0% of the stated amount.

Content of sodium benzoate, $C_7H_5NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Yields reaction A characteristic of *benzoates*, Appendix VI.

B. Complies with the Assay for sodium.

TESTS

Acidity or alkalinity

pH, 7.0 to 7.5, Appendix V L.

ASSAY

For Na

Prepare a suitable dilution in *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm and using *sodium standard solution (100 ppm Na)*, suitably diluted with *water*, for the standard solutions.

For sodium benzoate

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Dilute a weighed quantity of the oral solution containing 0.250 g of Sodium Benzoate to 20 mL with *anhydrous acetic acid*. Titrate with 0.1M *perchloric acid* using 0.05 mL of *1-naphtholbenzein solution* as indicator, until a green colour is obtained.

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_7H_5NaO_2$, weight in volume. Each mL of 0.1M *perchloric acid* is equivalent to 14.41 mg of $C_7H_5NaO_2$.

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Sodium Benzoate Sterile Concentrate

General Notices

Sterile Sodium Benzoate Concentrate

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Treatment of hyperammonaemia due to urea cycle disorders; treatment of non-ketotic hyperglycinaemia.

DEFINITION

Sodium Benzoate Sterile Concentrate is a sterile solution of Sodium Benzoate in a suitable vehicle.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements. Where appropriate, the concentrate also complies with the requirements stated under Unlicensed Medicines.

Content of sodium, Na

95.0 to 105.0% of the stated amount.

Content of sodium benzoate, $C_7H_5NaO_2$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear and colourless solution.

IDENTIFICATION

A. Yields reaction A characteristic of *benzoates*, Appendix VI.

B. Complies with the Assay for sodium.

TESTS

Acidity or alkalinity

pH, 7.0 to 7.5, Appendix V L.

ASSAY

For Na

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Prepare a suitable dilution in *water* and determine by *atomic emission spectrophotometry*, Appendix II D, measuring at 589 nm and using *sodium standard solution* (*100 ppm Na*), suitably diluted with *water*, for the standard solutions.

For sodium benzoate

Dilute a quantity of the sterile concentrate containing 0.250 g of Sodium Benzoate to 20 mL with *anhydrous acetic acid*. Titrate with 0.1M *perchloric acid* using 0.05 mL of *1-naphtholbenzein* solution as indicator, until a green colour is obtained.

Each mL of 0.1M *perchloric acid* is equivalent to 14.41 mg of $C_7H_5NaO_2$.

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Sodium Bicarbonate

General Notices

(Sodium Hydrogen Carbonate, Ph. Eur. monograph 0195)

$NaHCO_3$ 84.0 *144-55-8*

Action and use

Antacid; used in treatment of electrolyte deficiency.

Preparations

Sodium Bicarbonate Ear Drops

Sodium Bicarbonate Eye Lotion

Sodium Bicarbonate Infusion

Sodium Bicarbonate Oral Solution

Compound Sodium Bicarbonate Tablets

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

When heated in the dry state or in solution, it gradually changes into sodium carbonate.

IDENTIFICATION

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A. To 5 mL of solution S (see Tests) add 0.1 mL of *phenolphthalein solution R*. A pale pink colour is produced. Heat; gas is evolved and the solution becomes red.

B. It gives the reaction of carbonates and bicarbonates (*2.3.1*).

C. Solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in 90 mL of *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Carbonates

The pH (*2.2.3*) of freshly prepared solution S is not greater than 8.6.

Chlorides (*2.4.4*)

Maximum 150 ppm.

To 7 mL of solution S add 2 mL of *nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 150 ppm.

To a suspension of 1.0 g in 10 mL of *distilled water R* add *hydrochloric acid R* until neutral and about 1 mL in excess. Dilute to 15 mL with *distilled water R*.

Ammonium (*2.4.1*)

Maximum 20 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*. Prepare the standard using a mixture of 5 mL of *water R* and 10 mL of *ammonium standard solution (1 ppm NH_4) R*.

Calcium (*2.4.3*)

Maximum 100 ppm.

To a suspension of 1.0 g in 10 mL of *distilled water R* add *hydrochloric acid R* until neutral and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

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Dissolve 0.5 g in 5 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*.

ASSAY

Dissolve 0.750 g in 50 mL of *carbon dioxide-free water R*. Titrate with *1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*). Read the volume added at the 2nd point of inflection, or at the point of inflection if only 1 point is detected.

1 mL of *1 M hydrochloric acid* is equivalent to 84.0 mg of $NaHCO_3$.

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Sodium Bicarbonate Ear Drops

General Notices

DEFINITION

Sodium Bicarbonate	5 g
Glycerol	30 mL
Purified Water, freshly boiled and cooled	Sufficient to produce 100 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Sodium Bicarbonate in about 60 mL of Purified Water, add the Glycerol and sufficient Purified Water to produce 100 mL and mix.

Sodium Bicarbonate Ear Drops should be recently prepared.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of sodium bicarbonate, $NaHCO_3$

4.75 to 5.25% w/v.

Weight per mL

1.10 to 1.12 g, Appendix V G.

ASSAY

To 5 mL add 20 mL of *water* and titrate with *0.1M hydrochloric acid VS* using *methyl orange-xylene cyanol FF solution* as indicator. Each mL of *0.1M hydrochloric acid VS* is equivalent to 8.401 mg of $NaHCO_3$.

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Sodium Bicarbonate Eye Lotion

General Notices

DEFINITION

Sodium Bicarbonate Eye Lotion is a sterile aqueous solution of Sodium Bicarbonate.

Extemporaneous preparation

The following directions apply.

Dissolve the Sodium Bicarbonate in sufficient Purified Water, clarify by filtration, transfer the filtered solution into the final container, close the container so as to exclude micro-organisms and sterilise by *heating in an autoclave*.

The eye lotion complies with the requirements stated under Eye Preparations and with the following requirements.

Content of sodium bicarbonate, $NaHCO_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The residue on evaporation, when moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

B. Yields reaction A characteristic of *sodium salts* and the reactions characteristic of *bicarbonates*, Appendix VI.

ASSAY

Titrate a volume containing 1 g of Sodium Bicarbonate with *0.5M hydrochloric acid VS* using *methyl orange solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$.

Containers

Sodium Bicarbonate Eye Lotion is supplied in suitable containers with a nominal volume of not more than 1 litre.

STORAGE

Containers that have previously been subjected to heating in an autoclave should not be re-used to keep Sodium Bicarbonate Eye Lotion.

When Sodium Bicarbonate Eye Lotion is prescribed or demanded no strength being stated, a lotion containing 2% w/v of Sodium Bicarbonate shall be dispensed or supplied.

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Sodium Bicarbonate Infusion

General Notices

Sodium Bicarbonate Injection; Sodium Bicarbonate Intravenous Infusion

DEFINITION

Sodium Bicarbonate Infusion is a sterile solution containing Sodium Bicarbonate. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sodium bicarbonate, $NaHCO_3$

94.0 to 106.0% of the stated amount.

IDENTIFICATION

A. The residue on evaporation, when moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

B. Yields reaction A characteristic of *sodium salts* and the reactions characteristic of *bicarbonates*, Appendix VI.

TESTS

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 1.7 IU per mL of Sodium Bicarbonate Infusion.

ASSAY

Titrate a volume containing 1 g of Sodium Bicarbonate with *0.5M hydrochloric acid VS* using *methyl orange solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$.

STORAGE

Containers that have previously been subjected to heating in an autoclave should not be re-used to keep Sodium Bicarbonate Infusion.

LABELLING

The strength is stated as the percentage w/v of Sodium Bicarbonate.

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The label states (1) that containers containing visible particles must not be used; (2) the approximate concentrations, in millimoles per litre, of the sodium ions and the bicarbonate ions.

For a preparation containing 1.4% w/v of Sodium Bicarbonate the concentration of each ion is stated as 167 millimoles per litre.

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Sodium Bicarbonate Oral Solution

General Notices

Action and use

Treatment of dyspepsia; treatment of uraemic acidosis and renal tubular acidosis.

DEFINITION

Sodium Bicarbonate Oral Solution is a solution containing Sodium Bicarbonate in Purified Water. It is supplied as a ready-to-use solution or it is prepared by dissolving Sodium Bicarbonate Powder for Oral Solution in the requisite volume of Purified Water just before issue for use.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

STORAGE

The oral solution should be stored at the temperature and used within the period stated on the label.

When supplied as a ready-to-use solution, the oral solution complies with the following requirements.

Content of sodium bicarbonate, $NaHCO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The residue on evaporation, when moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

B. Yields reaction A characteristic of *sodium salts* and the reactions characteristic of *bicarbonates*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 7.0 to 8.5, Appendix V L.

ASSAY

Titrate a volume containing 1 g of Sodium Bicarbonate with *0.5M hydrochloric acid VS* using *methyl orange solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$.

LABELLING

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LABELLING

The label states that the solution is for oral administration.

SODIUM BICARBONATE POWDER FOR ORAL SOLUTION

DEFINITION

Sodium Bicarbonate Powder for Oral Solution is a dry powder consisting of Sodium Bicarbonate with or without excipients. It is supplied in a sealed container.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids and with the following requirements. Where appropriate, the dry ingredients also comply with the requirements stated under Unlicensed Medicines.

Content of sodium bicarbonate, $NaHCO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. When moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

B. Yield reaction A characteristic of *sodium salts* and the reactions characteristic of *bicarbonates*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a solution containing 5% w/v of Sodium Bicarbonate, 7.0 to 8.5, Appendix V L.

ASSAY

Dissolve a quantity of the contents of the sealed container containing 1 g of Sodium Bicarbonate in 50 mL of *carbon-dioxide free water* and titrate with *0.5M hydrochloric acid VS* using *methyl orange solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$.

LABELLING

The label states that the preparation is for oral administration.

When Sodium Bicarbonate Oral Solution for paediatric or neonatal use is prescribed or demanded, a solution containing 1 mmol/mL shall usually be dispensed or supplied.

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Sodium Bromide

General Notices

(Ph. Eur. monograph 0190)

NaBr 102.9 *7647-15-6*

Ph Eur

DEFINITION

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, granular powder or small, colourless, transparent or opaque crystals, slightly hygroscopic.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives reaction (a) of bromides (*2.3.1*).

B. Solution S (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

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Bromates

To 10 mL of solution S add 1 mL of *starch solution R*, 0.1 mL of a 100 g/L solution of *potassium iodide R* and 0.25 mL of *0.5 M sulfuric acid* and allow to stand protected from light for 5 min. No blue or violet colour develops.

Chlorides and sulfates

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 0.400 g of the substance to be examined in 50 mL of *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 25.0 mL of test solution (a) to 50.0 mL with *water for chromatography R*.

Reference solution (a) To 25.0 mL of test solution (a) add 1.0 mL of *sulfate standard solution (10 ppm SO_4) R* and 12.0 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (b) Dilute 10 mL of test solution (a) to 100 mL with *water for chromatography R*. To 2 mL of this solution add 8 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 20 mL with *water for chromatography R*.

Blank solution *water for chromatography R*.

Column:

— *size*: *l* = 0.25 m, Ø = 2 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R2* (13 µm).

Mobile phase Dissolve 0.600 g of *potassium hydroxide R* in *water for chromatography R* and dilute to 1000 mL with the same solvent.

Flow rate 0.4 mL/min.

Detection Conductivity detector equipped with a suitable ion suppressor.

Injection 50 µL of test solution (b), reference solutions (a) and (b) and the blank solution.

Run time 2.5 times the retention time of bromide.

Retention time Chloride = about 5 min; bromide = about 8 min; sulfate = about 16 min.

System suitability Reference solution (b):

— *resolution*: minimum 8.0 between the peaks due to chloride and bromide.

Calculation of percentage contents:

— for chlorides, use the concentration of chloride in reference solution (a); correct the area of the peak due to chloride in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to chloride in the chromatogram obtained with test solution (b);

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— for sulfates, use the concentration of sulfate in reference solution (a); correct the area of the peak due to sulfate in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to sulfate in the chromatogram obtained with test solution (b).

Limits:

— *chlorides*: maximum 0.6 per cent;

— *sulfates*: maximum 0.01 per cent.

Iodides

To 5 mL of solution S add 0.15 mL of *ferric chloride solution R1* and 2 mL of *methylene chloride R*. Shake and allow to separate. The lower layer is colourless (*2.2.2, Method I*).

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium and alkaline-earth metals (*2.4.7*)

Maximum 200 ppm, calculated as Ca.

10.0 g complies with the test for magnesium and alkaline-earth metals. The volume of *0.01 M sodium edetate* used does not exceed 5.0 mL.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 85.0 mg in *water R*, add 5 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 10.29 mg of NaBr.

Calculate the percentage content of NaBr using the following expression:

$$a - 2.902\,b$$

a	=	percentage content of NaBr and NaCl obtained in the assay and calculated as NaBr;
b	=	percentage content of Cl obtained in the test for chlorides.

STORAGE

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In an airtight container.

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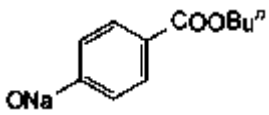
Sodium Butyl Hydroxybenzoate

General Notices

Sodium Butylparaben



$C_{11}H_{13}NaO_3$ 216.2 *36457-20-2*

Action and use

Antimicrobial preservative.

DEFINITION

Sodium Butyl Hydroxybenzoate is the sodium salt of butyl 4-hydroxybenzoate. It contains not less than 99.0% and not more than 102.0% of $C_{11}H_{13}NaO_3$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white powder; hygroscopic.

Freely soluble in *water* and in *ethanol (96%)*.

IDENTIFICATION

A. Dissolve 0.5 g in 5 mL of *water* and acidify to *litmus paper* with *hydrochloric acid*. A white precipitate is produced. Wash the precipitate with *water* and dry. The *infrared absorption spectrum* of the precipitate, Appendix II A, is concordant with the *reference spectrum* of butyl hydroxybenzoate *(RS 036)*.

B. The residue on ignition yields the reactions characteristic of *sodium salts*, Appendix VI.

TESTS

Alkalinity

pH of a 0.1% w/v solution, 9.5 to 10.5, Appendix V L.

Clarity of solution

Dissolve 1.0 g in 10 mL of *water*. The solution is *clear*, Appendix IV A.

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Chloride

Dissolve 1.0 g in 100 mL of *water*, add 1 mL of *nitric acid* and filter. 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII (330 ppm).

Sulfate

Dissolve 0.50 g in 40 mL of *water*, add 3.5 mL of *2M hydrochloric acid*, dilute to 60 mL with *water* and filter. 15 mL of the filtrate complies with the *limit test for sulfates*, Appendix VII (0.12%).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a 2.0% w/v solution of the substance being examined in *water* with an equal volume of *acetone*.

(2) Dilute 1 volume of solution (1) to 25 volumes with a mixture of equal volumes of *acetone* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F_{254} the surface of which has been modified with chemically-bonded octadecylsilyl groups (Whatman KC18F plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 30 volumes of *water* and 70 volumes of *methanol*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Water

Not more than 5.0% w/w, Appendix IX C. Use 1 g.

ASSAY

Gently boil 0.1 g under a reflux condenser with 25 mL of 1.25M *sodium hydroxide* for 30 minutes. Allow to cool, add 25 mL of *0.0333M potassium bromate VS*, 5 mL of a 12.5% w/v solution of *potassium bromide* and 10 mL of *hydrochloric acid* and immediately stopper the flask. Shake for 15 minutes and allow to stand for 15 minutes. Add 25 mL of *dilute potassium iodide solution* and shake vigorously. Titrate the liberated iodine with *0.1M sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of potassium bromate required. The volume of *0.0333M potassium bromate VS* used is equivalent to half of the volume of *0.1M sodium thiosulfate VS* required for the titration. Each mL of *0.0333M potassium bromate VS* is equivalent to 7.207 mg of $C_{11}H_{13}NaO_3$.

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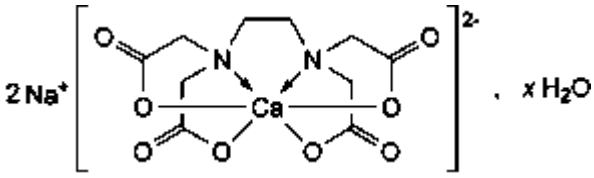
Sodium Calcium Edetate[1]

General Notices

(Ph. Eur. monograph 0231)



$C_{10}H_{12}CaN_2Na_2O_8,xH_2O$ 374.3 (anhydrous substance) *62-33-9*

Action and use

Chelating agent.

Preparation

Sodium Calcium Edetate Infusion

Ph Eur

DEFINITION

Disodium [(ethylenedinitrilo)tetraacetato]calciate(2-).

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water of crystallisation.

♦ CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).♦

IDENTIFICATION

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First identification: ♦ *A,* ♦ ◊ *C,* ◊ *D.*

◊ *Second identification: B, C, D.*◊

♦ A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *sodium calcium edetate CRS*.♦

B. Dissolve 2 g in 10 mL of *water R*, add 6 mL of *lead nitrate solution R*, shake and add 3 mL of *potassium iodide solution R*. No yellow precipitate is formed. Make alkaline to *red litmus paper R* by the addition of *dilute ammonia R2* and add 3 mL of *ammonium oxalate solution R*. A white precipitate is formed.

◊ C. Ignite. The residue gives reaction (b) of calcium (2.3.1).◊

D. Dissolve 0.5 g in 10 mL of *water R* and add 10 mL of *potassium pyroantimonate solution R*. A white, crystalline precipitate is formed. The formation of the precipitate is accelerated by rubbing the wall of the tube with a glass rod.

TESTS

♦ Solution S

Dissolve 5.0 g in *water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).♦

pH (2.2.3)

6.5 to 8.0.

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

♦ Impurity A

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture Dissolve 10.0 g of *ferric sulfate pentahydrate R* in 20 mL of *0.5 M sulfuric acid* and add 780 mL of *water R*. Adjust to pH 2.0 with *1 M sodium hydroxide* and dilute to 1000 mL with *water R*.

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution Dissolve 40.0 mg of *nitrilotriacetic acid R* (impurity A) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. To 1.0 mL of this solution add 0.1 mL of the test solution and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

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— *stationary phase*: *graphitised carbon for chromatography R* (5 µm).

Mobile phase Dissolve 50.0 mg of *ferric sulfate pentahydrate R* in 50 mL of *0.5 M sulfuric acid* and add 750 mL of *water for chromatography R*; adjust to pH 1.5 with *0.5 M sulfuric acid* or *1 M sodium hydroxide*, add 20 mL of *ethylene glycol R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 20 µL; filter the solutions and inject immediately.

Run time 4 times the retention time of the iron complex of impurity A.

Retention time Iron complex of impurity A = about 5 min; iron complex of edetic acid = about 10 min.

System suitability Reference solution:

— *resolution*: minimum 7 between the peaks due to the iron complex of impurity A and the iron complex of edetic acid;

— *signal-to-noise ratio*: minimum 50 for the peak due to impurity A.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).♦

Disodium edetate

Maximum 1.0 per cent.

Dissolve 5.0 g in 250 mL of *water R*. Add 10 mL of *ammonium chloride buffer solution pH 10.0 R* and about 50 mg of *mordant black 11 triturate R*. Not more than 1.5 mL of *0.1 M magnesium chloride* is required to change the colour of the indicator to violet.

Chlorides

Maximum 0.1 per cent.

Dissolve 0.7 g in *water R* and dilute to 20 mL with the same solvent. Add 30 mL of *dilute nitric acid R*, allow to stand for 30 min and filter. Dilute 10 mL of the filtrate to 50 mL with *water R*. Use this solution as the test solution. Prepare the reference solution using 0.40 mL of *0.01 M hydrochloric acid*, add 6 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Filter both solutions if necessary. Add 1 mL of *silver nitrate solution R2* to the test solution and to the reference solution and mix. After standing for 5 min protected from light, any opalescence in the test solution is not more intense than that in the reference solution.

♦ Iron (*2.4.9*)

Maximum 80 ppm.

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Dilute 2.5 mL of solution S to 10 mL with *water R*. Add 0.25 g of *calcium chloride R* to the test solution and the standard before the addition of the *thioglycollic acid R*.◊

Water (*2.5.12*)

5.0 per cent to 13.0 per cent, determined on 0.200 g.

ASSAY

Dissolve 0.500 g in *water R* and dilute to 200 mL with the same solvent. To 20.0 mL of this solution, add 80 mL of *water R* and adjust to pH 2 with *dilute nitric acid R*. Titrate with *0.01 M bismuth nitrate*, using 0.1 mL of a 1 g/L solution of *xylenol orange R* as indicator. The colour of the solution changes from yellow to red.

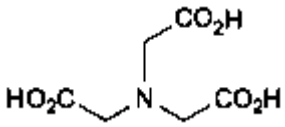
1 mL of *0.01 M bismuth nitrate* is equivalent to 3.74 mg of $C_{10}H_{12}CaN_2Na_2O_8$.

♦ STORAGE

In an airtight container, protected from light.♦

IMPURITIES

Specified impurities A.



A. nitrilotriacetic acid.

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

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Sodium Calcium Edetate Infusion

General Notices

Sodium Calcium Edetate Injection; Sodium Calcium Edetate Intravenous Infusion

Action and use

Chelating agent.

DEFINITION

Sodium Calcium Edetate Infusion is a sterile solution containing Sodium Calcium Edetate. It is prepared by diluting Sodium Calcium Edetate Sterile Concentrate with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

LABELLING

The strength is stated in terms of the equivalent amount of anhydrous sodium calcium edetate in a suitable dose-volume.

SODIUM CALCIUM EDETATE STERILE CONCENTRATE

DEFINITION

Sodium Calcium Edetate Sterile Concentrate is a sterile solution of Sodium Calcium Edetate in Water for Injections containing the equivalent of 20% w/v of anhydrous sodium calcium edetate.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of anhydrous sodium calcium edetate, $C_{10}H_{12}CaN_2Na_2O_8$

19.0 to 21.0% w/v.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Dilute 2.5 mL with 7.5 mL of *water*, make alkaline to *litmus paper* with 5M *ammonia* and add 5 mL of a 2.5% w/v solution of *ammonium oxalate*. Not more than a trace of precipitate is produced.

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B. To 10 mL add 2 mL of a 10% w/v solution of *lead(II) nitrate*, shake and add 5 mL of *dilute potassium iodide solution*; no yellow precipitate is produced. Make alkaline to *litmus paper* with 5M *ammonia* and add 5 mL of a 2.5% w/v solution of *ammonium oxalate*; a white precipitate is produced.

C. Evaporate to dryness and ignite. The residue yields the reactions characteristic of *sodium salts* and *calcium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 6.5 to 8.0, Appendix V L.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit is not more than 0.125 IU per mg of sodium calcium edetate.

ASSAY

To 2.5 mL add 90 mL of *water*, 7 g of *hexamine* and 5 mL of *2M hydrochloric acid* and titrate with 0.05M *lead nitrate VS* using *xylenol orange solution* as indicator. Each mL of 0.05M *lead nitrate VS* is equivalent to 18.71 mg of $C_{10}H_{12}CaN_2Na_2O_8$.

STORAGE

Sodium Calcium Edetate Sterile Concentrate should be kept in containers made from lead-free glass.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous sodium calcium edetate.

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Sodium Caprylate

General Notices

Sodium Octanoate

(Ph. Eur. monograph 1471)

$C_8H_{15}NaO_2$ 166.2 *1984-06-1*

Action and use

Excipient.

Ph Eur

DEFINITION

Sodium octanoate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble or freely soluble in water, freely soluble in acetic acid, sparingly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

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B. To 0.2 mL of solution S (see Tests) add 0.3 mL of *water R*. The solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

8.0 to 10.5 for solution S.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 0.116 g in *water R* and dilute to 5 mL with the same solvent. Add 1 mL of a 2.8 per cent *V/V* solution of *sulfuric acid R* and shake with 10 mL of *ethyl acetate R*. Separate the organic layer and dry over *anhydrous sodium sulfate R*.

Reference solution (a) Dissolve 0.10 g of *caprylic acid CRS* in *ethyl acetate R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1 mL of the test solution to 100 mL with *ethyl acetate R*. Dilute 5 mL of this solution to 50 mL with *ethyl acetate R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 2-nitroterephthalate R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.5 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	100

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	Time (min)	Temperature (°C)
	1 - 25	100 → 220
	25 - 35	220
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 5 for the principal peak.

Limits:

— *any impurity*: for each impurity, maximum 0.3 per cent;

— *total*: maximum 0.5 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

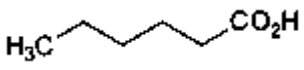
Maximum 3.0 per cent, determined on 1.000 g.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 16.62 mg of $C_8H_{15}NaO_2$.

IMPURITIES



A. hexanoic acid,

B. heptanoic acid,

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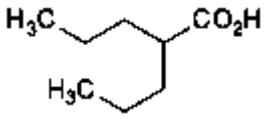
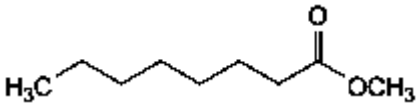
C. nonanoic acid,

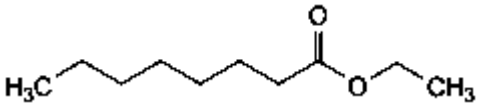
D. decanoic acid,



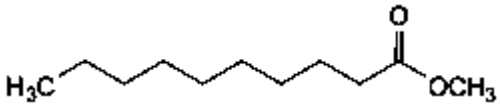
E. 2-propylpentanoic acid (valproic acid),



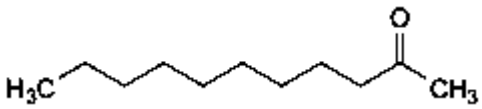
F. methyl octanoate,



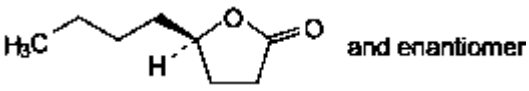
G. ethyl octanoate,



H. methyl decanoate,



I. undecan-2-one,



J. (*RS*)-5-butyltetrahydrofuran-2-one (γ-hydroxyoctanoic acid lactone).

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Sodium Carbonate

General Notices

Anhydrous Sodium Carbonate

(Ph. Eur. monograph 0773)

Na_2CO_3 106.0 *497-19-8*

Ph Eur

DEFINITION

Content

99.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, slightly granular powder, hygroscopic.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in *water R* and dilute to 10 mL with the same solvent. The solution is strongly alkaline (*2.2.4*).

B. The solution prepared for identification test A gives the reaction of carbonates (*2.3.1*).

C. The solution prepared for identification test A gives reaction (a) of sodium (*2.3.1*).

D. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 2.0 g in portions in a mixture of 5 mL of *hydrochloric acid R* and 25 mL of *distilled water R*. Heat to boiling and cool. Add *dilute sodium hydroxide solution R* until the solution is neutral and dilute to 50 mL with *distilled water R*.

Appearance of solution

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The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method I).

Dissolve 2.0 g in 10 mL of water R.

Alkali hydroxides and bicarbonates

Dissolve 0.4 g in 20 mL of water R. Add 20 mL of barium chloride solution R1 and filter. To 10 mL of the filtrate add 0.1 mL of phenolphthalein solution R. The solution does not become red. Boil the remainder of the filtrate for 2 min. The solution remains clear (2.2.1).

Chlorides (2.4.4)

Maximum 125 ppm.

Dissolve 0.4 g in water R, add 4 mL of dilute nitric acid R and dilute to 15 mL with water R.

Sulfates (2.4.13)

Maximum 250 ppm, determined on solution S.

Iron (2.4.9)

Maximum 50 ppm.

Dilute 5 mL of solution S to 10 mL with water R.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 300 ± 15 °C.

ASSAY

Dissolve 0.400 g in 50 mL of carbon dioxide-free water R. Titrate with 1 M hydrochloric acid, determining the end-point potentiometrically (2.2.20). Read the volume added at the 2nd point of inflection.

1 mL of 1 M hydrochloric acid is equivalent to 52.99 mg of Na_2CO_3.

STORAGE

In an airtight container.

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Sodium Carbonate Decahydrate

General Notices

(Ph. Eur. monograph 0191)

$Na_2CO_3,10H_2O$ 286.1 *6132-02-1*

Ph Eur

DEFINITION

Content

36.7 per cent to 40.0 per cent of Na_2CO_3.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless, transparent crystals, efflorescent.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in *water R* and dilute to 10 mL with the same solvent. The solution is strongly alkaline (*2.2.4*).

B. The solution prepared for identification test A gives the reaction of carbonates (*2.3.1*).

C. The solution prepared for identification test A gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in portions in a mixture of 5 mL of *hydrochloric acid R* and 25 mL of *distilled water R*. Heat the solution to boiling and cool. Add *dilute sodium hydroxide solution R* until the solution is neutral and dilute to 50 mL with *distilled water R*.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method I*).

Dissolve 4.0 g in 10 mL of *water R*.

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Alkali hydroxides and bicarbonates

Dissolve 1.0 g in 20 mL of *water R*, add 20 mL of *barium chloride solution R1* and filter. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. The solution does not become red. Heat the remainder of the filtrate to boiling for 2 min. The solution remains clear (*2.2.1*).

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dissolve 1.0 g in *water R*, add 4 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

ASSAY

Dissolve 1.000 g in 50 mL of *carbon dioxide-free water R*. Titrate with *1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*). Read the volume added at the 2nd point of inflection.

1 mL of *1 M hydrochloric acid* is equivalent to 52.99 mg of Na_2CO_3.

STORAGE

In an airtight container.

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Sodium Carbonate Monohydrate

General Notices

(Ph. Eur. monograph 0192)

Na_2CO_3,H_2O 124.0 *5968-11-6*

Ph Eur

DEFINITION

Content

83.0 per cent to 87.5 per cent of Na_2CO_3.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in *water R* and dilute to 10 mL with the same solvent. The solution is strongly alkaline (2.2.4).

B. The solution prepared for identification test A gives the reaction of carbonates (2.3.1).

C. The solution prepared for identification test A gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in portions in a mixture of 5 mL of *hydrochloric acid R* and 25 mL of *distilled water R*. Heat the solution to boiling and cool. Add *dilute sodium hydroxide solution R* until the solution is neutral and dilute to 50 mL with *distilled water R*.

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method I*).

Dissolve 2.0 g in 10 mL of *water R*.

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Alkali hydroxides and bicarbonates

Dissolve 0.4 g in 20 mL of *water R*, add 20 mL of *barium chloride solution R1* and filter. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. The solution does not become red. Heat the remainder of the filtrate to boiling for 2 min. The solution remains clear (*2.2.1*).

Chlorides (*2.4.4*)

Maximum 125 ppm.

Dissolve 0.4 g in *water R*, add 4 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 250 ppm, determined on solution S.

Iron (*2.4.9*)

Maximum 50 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

ASSAY

Dissolve 0.500 g in 50 mL of *carbon dioxide-free water R*. Titrate with *1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*). Read the volume added at the 2nd point of inflection.

1 mL of *1 M hydrochloric acid* is equivalent to 52.99 mg of Na_2CO_3.

STORAGE

In an airtight container.

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Sodium Cetostearyl Sulfate

General Notices

Sodium Cetostearyl Sulphate

(Ph. Eur. monograph 0847)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of sodium cetyl sulfate (sodium hexadecyl sulfate, $C_{16}H_{33}NaO_4S$; M_r 344.5) and sodium stearyl sulfate (sodium octadecyl sulfate, $C_{18}H_{37}NaO_4S$; M_r 372.5). A suitable buffer may be added.

Content

— *sodium cetostearyl sulfate*: minimum 90.0 per cent (anhydrous substance);

— *sodium cetyl sulfate*: minimum 40.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow, amorphous or crystalline powder.

Solubility

Soluble in hot water giving an opalescent solution, practically insoluble in cold water, partly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D, F.

Second identification: A, C, D, E, F.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in 10 mL of *ethanol (70 per cent V/V) R*, heating on a water-bath.

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Reference solution Dissolve 50 mg of *sodium cetostearyl sulfate CRS* in 10 mL of *ethanol (70 per cent V/V) R*, heating on a water-bath.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *water R*, *acetone R*, *methanol R* (20:40:40 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 50 g/L solution of *phosphomolybdic acid R* in *ethanol (96 per cent) R*; heat at 120 °C until spots appear (about 5 min).

Results The principal spots in the chromatogram obtained with the test solution are similar in position and colour to the principal spots in the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results The 2 principal peaks in the chromatogram obtained with test solution (b) are similar in retention time to the 2 principal peaks in the chromatograms obtained with reference solutions (a) and (b).

C. Dissolve 0.1 g in 10 mL of *water R* and shake. A foam is formed.

D. It gives a yellow colour to a non-luminous flame.

E. To 0.1 mL of the solution prepared for identification test C add 0.1 mL of a 1 g/L solution of *methylene blue R* and 2 mL of *dilute sulfuric acid R*. Add 2 mL of *methylene chloride R* and shake. The methylene chloride layer has an intense blue colour.

F. Mix about 10 mg with 10 mL of *anhydrous ethanol R*. Heat to boiling on a water-bath, shaking frequently. Filter immediately and evaporate to dryness. Dissolve the residue in 7 mL of *water R*, add 3 mL of *dilute hydrochloric acid R* and evaporate the solution to half its volume. Allow to cool. Filter. To the filtrate add 1 mL of *barium chloride solution R1*. A white, crystalline precipitate is formed.

TESTS

Acidity or alkalinity

Dissolve 0.5 g with heating in a mixture of 10 mL of *water R* and 15 mL of *ethanol (90 per cent V/V) R*. Add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Add 0.1 mL of *0.1 M sodium hydroxide*. The solution is red.

Sodium chloride and sodium sulfate

Maximum 8.0 per cent for the sum of the percentage contents.

Sodium chloride Dissolve 5.00 g in 50 mL of *water R*, add *dilute nitric acid R* dropwise until the solution is neutral to *blue litmus paper R*. Titrate with *0.1 M silver nitrate* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

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Sodium sulfate Dissolve 0.500 g in 20 mL of *water R*, warming gently if necessary, and add 1 mL of a 0.5 g/L solution of *dithizone R* in *acetone R*. If the solution is red, add *1 M nitric acid* dropwise until a bluish-green colour is obtained. Add 2.0 mL of *dichloroacetic acid solution R* and 80 mL of *acetone R*. Titrate with *0.01 M lead nitrate* until a persistent orange-red colour is obtained.

1 mL of *0.01 M lead nitrate* is equivalent to 1.420 mg of Na_2SO_4.

Free cetostearyl alcohol

Maximum 4.0 per cent.

From the chromatogram obtained with test solution (a) in the assay, calculate the percentage content of free cetostearyl alcohol in the substance to be examined using the following expression and taking into account the assigned content of the chemical reference substances:

$$\frac{A_1}{A_2} \times \frac{m_2}{m_1} \times \frac{2}{100} \times 100$$

A_1	=	sum of the areas of the peaks due to cetyl alcohol and stearyl alcohol in the chromatogram obtained with test solution (a);
A_2	=	area of the peak due to the internal standard in the chromatogram obtained with test solution (a);
m_1	=	mass of the substance to be examined in test solution (a), in milligrams;
m_2	=	mass of the internal standard in the internal standard solution, in milligrams.

Water (*2.5.12*)

Maximum 1.5 per cent, determined on 1.00 g.

ASSAY

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 0.200 g of *1-nonadecanol CRS* in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent.

Test solution (a) Dissolve 0.300 g of the substance to be examined in 50.0 mL of *anhydrous ethanol R* and add 2.0 mL of the internal standard solution and 48.0 mL of *water R*. Shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers. Reserve the lower layer for the preparation of test solution (b). Wash the combined upper layers with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Test solution (b) Transfer 25.0 mL of the lower layer obtained in the preparation of test solution (a) to a 200 mL flask that can be fitted with a reflux condenser. Add 10.0 mL of the internal standard solution and 20 mL of *hydrochloric acid R*. Boil under a reflux condenser for 2 h. Allow to cool and shake with 4 quantities, each of 20 mL, of *pentane R*. Combine the upper layers, wash with 2 quantities, each of 20 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Reference solution (a) Dissolve 0.100 g of *cetyl alcohol CRS* in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers.

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Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Reference solution (b) Dissolve 0.100 g of *stearyl alcohol CRS* in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 20	150 → 250
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Elution order Cetyl alcohol, stearyl alcohol, 1-nonadecanol.

Calculate the percentage content of sodium cetyl sulfate in the substance to be examined using the following expression and taking into account the assigned content of *cetyl alcohol CRS*:

$$A_x \times \frac{A_2}{A_1} \times \frac{m_{x,y}}{A_{x,y}} \times \frac{1}{m} \times 100 \times 4 \times \frac{1}{2.5} \times F_x$$

A_x = area of the peak due to cetyl alcohol in the chromatogram obtained with test solution (b);

$A_{x,y}$ = area of the peak due to *cetyl alcohol CRS* in the chromatogram obtained with reference solution (a);

A_1 = area of the peak due to the internal standard in the chromatogram obtained with test solution (b);

A_2 = area of the peak due to the internal standard in the chromatogram obtained with reference solution (a);

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F_x = conversion factor from cetyl alcohol to sodium cetyl sulfate (1.421);

m = mass of the substance to be examined in test solution (a), in milligrams;

$m_{x,y}$ = mass of *cetyl alcohol CRS* in reference solution (a), in milligrams.

Calculate the percentage content of sodium stearyl sulfate in the substance to be examined using the following expression and taking into account the assigned content of *stearyl alcohol CRS*:

$$A_z \times \frac{A_3}{A_1} \times \frac{m_{z,y}}{A_{z,y}} \times \frac{1}{m} \times 100 \times 4 \times \frac{1}{2.5} \times F_z$$

A_z = area of the peak due to stearyl alcohol in the chromatogram obtained with test solution (b);

$A_{z,y}$ = area of the peak due to *stearyl alcohol CRS* in the chromatogram obtained with reference solution (b);

A_1 = area of the peak due to the internal standard in the chromatogram obtained with test solution (b);

A_3 = area of the peak due to the internal standard in the chromatogram obtained with reference solution (b);

F_z = conversion factor from stearyl alcohol to sodium stearyl sulfate (1.377);

m = mass of the substance to be examined in test solution (a), in milligrams;

$m_{z,y}$ = mass of *stearyl alcohol CRS* in reference solution (b), in milligrams.

The percentage content of sodium cetostearyl sulfate corresponds to the sum of the percentage contents of sodium cetyl sulfate and sodium stearyl sulfate.

LABELLING

The label states, where appropriate, the name and concentration of any added buffer.

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Sodium Chloride[1]

General Notices

(Ph. Eur. monograph 0193)

NaCl 58.44 *7647-14-5*

Action and use

Used in treatment of electrolyte deficiency.

Preparations

Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution

Compound Sodium Chloride Mouthwash

Magnesium Sulfate, Potassium Chloride and Sodium Chloride Infusion

Oral Rehydration Salts

Potassium Chloride and Sodium Chloride Infusion

Potassium Chloride, Sodium Chloride and Glucose Infusion

Sodium Chloride Eye Drops

Sodium Chloride Eye Lotion

Sodium Chloride Eye Ointment

Sodium Chloride and Glucose Infusion

Sodium Chloride Infusion

Sodium Chloride Irrigation Solution

Sodium Chloride Nebuliser Solution

Sodium Chloride Oral Solution

Sodium Chloride Solution

Sodium Chloride Soluble Tablets

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DEFINITION

Content

99.0 per cent to 100.5 per cent (dried substance).

♦ CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals or white or almost white pearls.

Solubility

Freely soluble in water, practically insoluble in anhydrous ethanol.♦

IDENTIFICATION

A. It gives reaction (a) of chlorides (*2.3.1*).

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

◊ *If the substance is in the form of pearls, crush before use*.◊

Solution S

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent.

♦ Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).♦

Acidity or alkalinity

To 20 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromides

Maximum 100 ppm.

To 0.5 mL of solution S add 4.0 mL of *water R*, 2.0 mL of *phenol red solution R2* and 1.0 mL of a 0.1 g/L solution of *chloramine R* and mix immediately. After exactly 2 min, add 0.15 mL of *0.1 M sodium thiosulfate*, mix and dilute to 10.0 mL with *water R*. The absorbance (*2.2.25*) of the solution measured at 590 nm, using *water R* as the compensation liquid, is not greater than that of a standard prepared at the same time and in the same manner, using 5.0 mL of a 3.0 mg/L solution of *potassium bromide R*.

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Ferrocyanides

Dissolve 2.0 g in 6 mL of *water R*. Add 0.5 mL of a mixture of 5 mL of a 10 g/L solution of *ferric ammonium sulfate R* in a 2.5 g/L solution of *sulfuric acid R* and 95 mL of a 10 g/L solution of *ferrous sulfate R*. No blue colour develops within 10 min.

Iodides

Moisten 5 g by the dropwise addition of a freshly prepared mixture of 0.15 mL of *sodium nitrite solution R*, 2 mL of *0.5 M sulfuric acid*, 25 mL of *iodide-free starch solution R* and 25 mL of *water R*. After 5 min, examine in daylight. The mixture shows no blue colour.

Nitrites

To 10 mL of solution S add 10 mL of *water R*. The absorbance (*2.2.25*) is not greater than 0.01 at 354 nm.

Phosphates (*2.4.11*)

Maximum 25 ppm.

Dilute 2 mL of solution S to 100 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 7.5 mL of solution S to 30 mL with *distilled water R*.

Aluminium (*2.4.17*)

Maximum 0.2 ppm, if intended for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions or haemofiltration solutions.

Prescribed solution Dissolve 20.0 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

♦ Arsenic (*2.4.2, Method A*)

Maximum 1 ppm, determined on 5 mL of solution S.♦

Barium

To 5 mL of solution S add 5 mL of *distilled water R* and 2 mL of *dilute sulfuric acid R*. After 2 h, any opalescence in the solution is not more intense than that in a mixture of 5 mL of solution S and 7 mL of *distilled water R*.

Iron (*2.4.9*)

Maximum 2 ppm, determined on solution S.

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Prepare the standard using a mixture of 4 mL of *iron standard solution (1 ppm Fe) R* and 6 mL of *water R*.

Magnesium and alkaline-earth metals (*2.4.7*)

Maximum 100 ppm, calculated as Ca and determined on 10.0 g.

Use 0.150 g of *mordant black 11 triturate R*. The volume of *0.01 M sodium edetate* used is not more than 2.5 mL.

Potassium

Maximum 500 ppm, if intended for use in the manufacture of parenteral preparations or haemodialysis, haemofiltration or peritoneal dialysis solutions.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Dissolve 1.144 g of *potassium chloride R*, previously dried at 100-105 °C for 3 h, in *water R* and dilute to 1000.0 mL with the same solvent (600 µg of K per millilitre). Dilute as required.

Wavelength 766.5 nm.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

♦ Bacterial endotoxins (*2.6.14*)

Less than 5 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.♦

ASSAY

Dissolve 50.0 mg in *water R* and dilute to 50 mL with the same solvent. Titrate with *0.1 M silver nitrate* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

♦ LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

— where applicable, that the substance is suitable for use in the manufacture of peritoneal dialysis solutions, haemodialysis solutions or haemofiltration solutions.♦

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Sodium Chloride and Glucose Infusion

General Notices

Sodium Chloride and Dextrose Infusion; Sodium Chloride and Dextrose Injection; Sodium Chloride and Dextrose Intravenous Infusion; Sodium Chloride and Glucose Injection; Sodium Chloride and Glucose Intravenous Infusion

DEFINITION

Sodium Chloride and Glucose Infusion is a sterile solution containing Sodium Chloride and either Glucose or Glucose Monohydrate. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

Content of anhydrous glucose, $C_6H_{12}O_6$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or faintly straw-coloured solution.

IDENTIFICATION

A. When heated with *cupri-tartaric solution R1*, a copious precipitate of copper(I) oxide is produced.

B. Yields reaction B characteristic of *sodium salts* and reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 3.5 to 6.5, Appendix V L.

5-Hydroxymethylfurfural and related substances

Dilute a volume containing 1.0 g of glucose, $C_6H_{12}O_6$, to 500 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 284 nm, Appendix II B. The *absorbance* is not more than 0.25.

Bacterial endotoxins

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The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C. Dilute infusions containing more than 0.9% w/v of Sodium Chloride with *water BET* to contain 0.9% w/v.

ASSAY

For sodium chloride

Titrate a quantity containing 0.1 g of Sodium Chloride with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

For glucose

To a quantity containing the equivalent of 2 to 5 g of glucose, $C_6H_{12}O_6$, add 0.2 mL of 5M *ammonia* and sufficient *water* to produce 100 mL. Mix well, allow to stand for 30 minutes and measure the *optical rotation* in a 2-dm tube, Appendix V F. The observed rotation in degrees multiplied by 0.9477 represents the weight in g of glucose, $C_6H_{12}O_6$, in the volume of the injection taken for assay.

LABELLING

The strength is stated as the percentages w/v of Sodium Chloride and of glucose, $C_6H_{12}O_6$. The label states that solutions containing visible particles must not be used.

When the preparation is intended for intravenous infusion, the label states the approximate concentrations, in millimoles per litre, of the sodium ions and the chloride ions and the number of grams per litre of glucose, $C_6H_{12}O_6$. For a preparation containing 0.18% w/v of Sodium Chloride, the concentration of each ion is stated as 30 millimoles per litre.

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Sodium Chloride Eye Drops

General Notices

DEFINITION

Sodium Chloride Eye Drops are a sterile solution of Sodium Chloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of sodium chloride, NaCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Yield the reactions characteristic of *sodium salts*, Appendix VI.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

ASSAY

Titrate a volume containing 0.1 g of Sodium Chloride with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

When Sodium Chloride Eye Drops are prescribed or demanded no strength being stated, eye drops containing 0.9% w/v of Sodium Chloride shall be dispensed or supplied.

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Sodium Chloride Eye Lotion

General Notices

DEFINITION

Sodium Chloride Eye Lotion is a sterile aqueous solution containing 0.9% w/v of Sodium Chloride.

Extemporaneous preparation

The following directions apply.

Dissolve the Sodium Chloride in sufficient Purified Water, clarify by filtration, transfer the filtered solution into the final container, close the container so as to exclude micro-organisms and sterilise by *heating in an autoclave*.

The eye lotion complies with the requirements stated under Eye Preparations and with the following requirements.

Content of sodium chloride, NaCl

0.85 to 0.95% w/v.

IDENTIFICATION

Yields the reactions characteristic of *sodium salts* and reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Sterility

Complies with the *test for sterility*, Appendix XVI A.

ASSAY

To 25 mL add 75 mL of *acetate buffer pH 5.0* and titrate with *0.1M silver nitrate VS*, stirring constantly and determining the end point potentiometrically. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

Containers

Sodium Chloride Eye Lotion is supplied in suitable containers with a nominal volume of not more than 1 litre.

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Sodium Chloride Eye Ointment

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used for corneal protection.

DEFINITION

Sodium Chloride Eye Ointment is a sterile preparation containing Sodium Chloride in a suitable basis.

The eye ointment complies with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye ointment also complies with the requirements stated under Unlicensed Medicines.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of the eye ointment in *water*, heating if necessary. The resulting solution yields the reactions characteristic of *sodium salts* and reaction A characteristic of *chlorides*, Appendix VI.

ASSAY

Dissolve a quantity of the eye ointment containing 50 mg of Sodium Chloride in *water*, heating if necessary; add sufficient *water* to produce 50 mL and titrate with *0.1M silver nitrate VS*, determining the end point potentiometrically. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

STORAGE

Sodium Chloride Eye Ointment should be stored at a temperature not exceeding 30°.

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Sodium Chloride Infusion

General Notices

Sodium Chloride Injection; Sodium Chloride Intravenous Infusion

DEFINITION

Sodium Chloride Infusion is a sterile solution containing Sodium Chloride. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields the reactions characteristic of *sodium salts* and reaction A characteristic of *chlorides*, Appendix VI.

Bacterial endotoxins

The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C. Dilute infusions containing more than 0.9% w/v of Sodium Chloride with *water BET* to contain 0.9% w/v.

ASSAY

Titrate a volume containing 0.2 g of Sodium Chloride with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

LABELLING

The strength is stated as the percentage w/v of Sodium Chloride. The label states that solutions containing visible solid particles must not be used.

When the preparation is intended for intravenous infusion, the label states the approximate concentrations, in millimoles per litre, of the sodium ions and the chloride ions. For a preparation containing 0.9% w/v of Sodium Chloride the concentration of each ion is stated as 150 millimoles per litre.

For concentrated solutions supplied for the preparation of Sodium Chloride Infusion by dilution, the label states ‘Sterile Sodium Chloride Concentrate’ as the title of the preparation.

When Sodium Chloride Infusion or Sodium Chloride Injection is prescribed or demanded and no strength is stated, Sodium Chloride Infusion (0.9% w/v) shall be dispensed or supplied.

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When Sodium Chloride Injection is required as a diluent for Parenteral Preparations of the Pharmacopoeia, Sodium Chloride Infusion (0.9% w/v) shall be used.

When normal saline solution for injection is prescribed or demanded, Sodium Chloride Infusion (0.9% w/v) shall be dispensed or supplied.

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Sodium Chloride Irrigation Solution

General Notices

DEFINITION

Sodium Chloride Irrigation Solution is a solution of Sodium Chloride in Water for Irrigation.

The irrigation solution complies with the requirements stated under Preparations for Irrigation and with the following requirements.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Yields the reactions characteristic of *sodium salts*, Appendix VI.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

ASSAY

Titrate a volume containing 0.2 g of Sodium Chloride with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

When normal saline is prescribed or demanded for use as an irrigation solution, Sodium Chloride Irrigation Solution containing 0.9% w/v of Sodium Chloride shall be dispensed or supplied.

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Sodium Chloride Nebuliser Solution

General Notices

Action and use

Diluent; moisturiser; mucolytic.

DEFINITION

Sodium Chloride Nebuliser Solution is a sterile solution of Sodium Chloride in a suitable vehicle, intended to be converted into aerosols by a nebuliser.

When used as a mucolytic, the solution is hypertonic. The hypertonic solution is not currently licensed in the United Kingdom.

The nebuliser solution complies with the requirements stated under Preparations for Inhalation and with the following requirements. Where appropriate, the nebuliser solution also complies with the requirements stated under Unlicensed Medicines.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields the reactions characteristic of *sodium salts* and reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Sterility

Complies with the *test for sterility*, Appendix XVI A.

ASSAY

For hypertonic solutions

Dilute a suitable volume of the nebuliser solution with sufficient *water* to produce a solution containing about 1% w/v of Sodium Chloride.

Titrate a volume containing 0.2 g of Sodium Chloride with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

For isotonic solutions

Use the undiluted nebuliser solution.

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Titrate a volume containing 0.2 g of Sodium Chloride with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

LABELLING

The strength is stated as the percentage w/v of Sodium Chloride.

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Sodium Chloride Oral Solution

General Notices

Action and use

Used in the treatment of electrolyte deficiency.

DEFINITION

Sodium Chloride Oral Solution is a hypertonic solution of Sodium Chloride in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution which is free from visible particles.

IDENTIFICATION

A. When introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

ASSAY

Titrate a volume containing 0.2 g of Sodium Chloride with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

LABELLING

The label states, where applicable, that the contents of the container are sterile.

If the label states that the contents of the container are sterile, the solution complies with the following additional requirements.

Sterility

Complies with the *test for sterility*, Appendix XVI A.

LABELLING

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The label states (1) ‘Sterile Sodium Chloride Oral Solution’; (2) that the solution is for oral administration; (3) the conditions under which it should be stored.

When Sodium Chloride Oral Solution for paediatric or neonatal use is prescribed or demanded, a solution containing either 1 mmol/mL or 5 mmol/mL shall usually be dispensed or supplied.

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Sodium Chloride Soluble Tablets

General Notices

Soluble Sodium Chloride Tablets

DEFINITION

Sodium Chloride Soluble Tablets contain Sodium Chloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sodium chloride, NaCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The powdered tablets yield the reactions characteristic of *sodium salts* and the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Clarity of solution

Dissolve a quantity of the tablets containing 0.6 g of Sodium Chloride in 100 mL of *water*. The solution is *clear*, Appendix IV A.

Disintegration

The tablets dissolve completely within 15 minutes when examined by the *disintegration test for tablets and capsules*, Appendix XII A1, but using *water* at 19° to 21°.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.2 g of Sodium Chloride in 35 mL of *water*, add 15 mL of 2M *nitric acid*, 5 mL of *dibutyl phthalate* and 50 mL of *0.1M silver nitrate VS* and shake vigorously for about 1 minute. Add 5 mL of *ammonium iron(III) sulfate solution R2* and titrate with *0.1M ammonium thiocyanate VS* until a reddish brown colour is obtained which, after shaking, does not fade within 5 minutes. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

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Sodium Chloride Solution

General Notices

Sodium Chloride Cutaneous Solution

DEFINITION

Sodium Chloride Solution is a 0.9% w/v *cutaneous solution* of Sodium Chloride in Purified Water. The solution may be clarified by filtration.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of sodium chloride, NaCl

0.85 to 0.95% w/v.

IDENTIFICATION

A. When introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

ASSAY

Titrate 20 mL with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.844 mg of NaCl.

LABELLING

When normal saline is prescribed or demanded, Sodium Chloride Solution shall be dispensed or supplied.

If the label states that the contents of the container are sterile, the solution complies with the following additional requirements.

Sterility

Complies with the *test for sterility*, Appendix XVI A.

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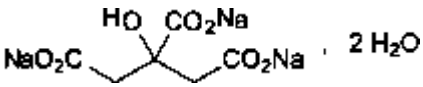
Sodium Citrate

General Notices

Trisodium Citrate

(Ph. Eur. monograph 0412)



$C_6H_5Na_3O_7,2H_2O$ 294.1 *6132-04-3*

Action and use

Systemic alkalinising substance.

Preparations

Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution

Sodium Citrate Eye Drops

Sodium Citrate Irrigation Solution

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DEFINITION

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or white or almost white, granular crystals, slightly deliquescent in moist air.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

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IDENTIFICATION

A. To 1 mL of solution S (see Tests) add 4 mL of *water R*. The solution gives the reaction of citrates (*2.3.1*).

B. 1 mL of solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. Not more than 0.2 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Readily carbonisable substances

To 0.20 g of the powdered substance to be examined add 10 mL of *sulfuric acid R* and heat in a water-bath at 90 ± 1 °C for 60 min. Cool rapidly. The solution is not more intensely coloured than reference solution Y_2 or GY_2 (*2.2.2, Method II*).

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Oxalates

Maximum 300 ppm.

Dissolve 0.50 g in 4 mL of *water R*, add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules and heat on a water-bath for 1 min. Allow to stand for 2 min, decant the liquid into a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of *potassium ferricyanide solution R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 4 mL of a 50 mg/L solution of *oxalic acid R*.

Sulfates (*2.4.13*)

Maximum 150 ppm.

To 10 mL of solution S add 2 mL of *hydrochloric acid R1* and dilute to 15 mL with *distilled water R*.

Water (*2.5.12*)

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11.0 per cent to 13.0 per cent, determined on 0.300 g. Use as the solvent a mixture of 20 mL of *methanol R*, 30 mL of *formamide R* and 5 g of *salicylic acid R*.

Pyrogens (*2.6.8*)

If intended for use in the manufacture of large-volume parenteral preparations, the competent authority may require that it comply with the test for pyrogens. Inject per kilogram of the rabbit's mass 10 mL of a freshly prepared solution in *water for injections R* containing per millilitre 10.0 mg of the substance to be examined and 7.5 mg of pyrogen-free *calcium chloride R*.

ASSAY

Dissolve 0.150 g in 20 mL of *anhydrous acetic acid R*, heating to about 50 °C. Allow to cool. Titrate with *0.1 M perchloric acid*, using 0.25 mL of *naphtholbenzein solution R* as indicator until a green colour is obtained.

1 mL of *0.1 M perchloric acid* is equivalent to 8.602 mg of $C_6H_5Na_3O_7$.

STORAGE

In an airtight container.

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Sodium Citrate Eye Drops

General Notices

DEFINITION

Sodium Citrate Eye Drops are a sterile solution of Sodium Citrate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of sodium citrate, $C_6H_5Na_3O_7,2H_2O$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Yield reaction A characteristic of *sodium salts*, Appendix VI.

B. Yield reaction A characteristic of *citrates*, Appendix VI.

Acidity or alkalinity

pH, 7.0 to 7.5, Appendix V L.

ASSAY

Evaporate a volume containing 0.15 g of Sodium Citrate to dryness and dissolve the residue in *anhydrous acetic acid*, warming to about 50°. Allow to cool and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.25 mL of *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 9.803 mg of $C_6H_5Na_3O_7,2H_2O$.

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Sodium Citrate Irrigation Solution

General Notices

Sterile Sodium Citrate Solution for Bladder Irrigation

DEFINITION

Sodium Citrate Irrigation Solution is a sterile, solution of Sodium Citrate in Water for Irrigation containing Citric Acid or Citric Acid Monohydrate.

The irrigation solution complies with the requirements stated under Preparations for Irrigation and with the following requirements.

Content of sodium citrate, $C_6H_5Na_3O_7,2H_2O$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

Yields reaction A characteristic of *sodium salts* and reaction A characteristic of *citrates*, Appendix VI.

Acidity or alkalinity

pH, 6.0 to 7.5, Appendix V L.

ASSAY

Evaporate a volume containing 0.15 g of Sodium Citrate to dryness and dissolve the residue in *anhydrous acetic acid*, warming to about 50°. Allow to cool and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.25 mL of *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 9.803 mg of $C_6H_5Na_3O_7,2H_2O$.

When Sodium Citrate Irrigation Solution is prescribed or demanded, no strength being stated, a solution containing 3.0% w/v of Sodium Citrate shall be dispensed or supplied.

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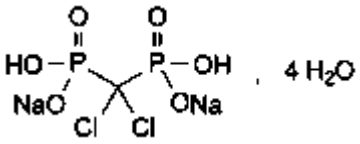
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Sodium Clodronate Tetrahydrate

General Notices

(Clodronate Disodium Tetrahydrate, Ph. Eur. monograph 1777)



$CH_2Cl_2Na_2O_6P_2,4H_2O$ 360.9

Ph Eur

DEFINITION

Disodium dihydrogen (dichloromethylene)bis(phosphonate) tetrahydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent), slightly soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *clodronate disodium tetrahydrate CRS*.

B. Dissolve 0.5 g in 10 mL of *water R*. The solution gives reaction (a) of sodium (2.3.1).

TESTS

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Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

3.0 to 4.5 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.125 g of the substance to be examined in 30 mL of *water R*, sonicate for 10 min and dilute to 50.0 mL with *water R* (*test stock solution*). Dilute 10.0 mL of the test stock solution to 20.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 50.0 mL with *water R*.

Reference solution (b) Dissolve 1 mg of *clodronate impurity D CRS* in 10 mL of *water R*, sonicate for 10 min and dilute to 20 mL with *water R*. Mix 2 mL of this solution with 10 mL of the test stock solution and dilute to 20 mL with *water R*.

Reference solution (c) Dilute 1 mL of a 0.3 g/L solution of *phosphoric acid R* (impurity B) to 100 mL with *water R*.

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R2* (13 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R2* (7.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 0.21 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R*; close immediately, mix and use under helium pressure;

— *mobile phase B*: 4.2 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R*; close immediately, mix and use under helium pressure;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.1	90	10
0.1 - 10	90 → 60	10 → 40
10 - 22	60 → 50	40 → 50
22 - 23	50 → 20	50 → 80
23 - 25	20	80

Flow rate 1.0 mL/min.

Detection Conductivity detector; use a self-regenerating anion suppressor.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Relative retention With reference to clodronate (retention time = about 20 min): impurities A and B = about 0.7; impurity D = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to clodronate and impurity D.

Calculation of percentage contents:

— for each impurity, use the concentration of clodronate disodium tetrahydrate in reference solution (a).

Limits:

— *sum of impurities A and B*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.03 per cent.

Water (2.5.12)

18.5 per cent to 21.0 per cent, determined on 0.100 g.

ASSAY

Dissolve 0.140 g in 10 mL of *water R*. Add 10 mL of *strong sodium hydroxide solution R* and some glass beads. Boil until the solution is completely decolourised (about 10 min). Cool in an ice-bath and add 30 mL of *water R* and 10 mL of *nitric acid R*. Titrate with *0.1 M silver*

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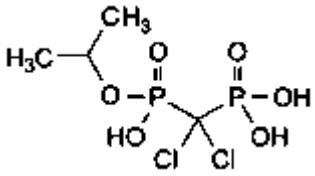
nitrate, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 14.44 mg of $CH_2Cl_2Na_2O_6P_2$.

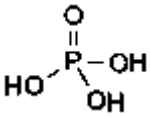
IMPURITIES

Specified impurities *A, B.*

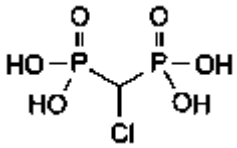
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



A. [dichloro[hydroxy[(propan-2-yl)oxy]phosphinoyl]methyl]phosphonic acid,



B. phosphoric acid,



D. (chloromethylene)bis(phosphonic acid).

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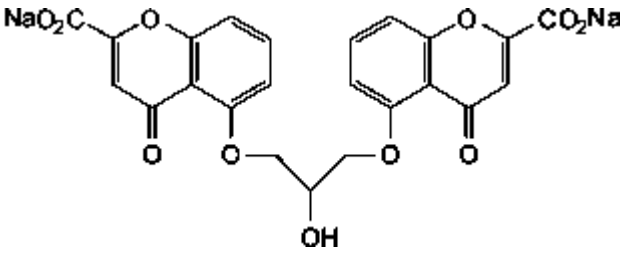
Sodium Cromoglicate

General Notices

(Ph. Eur. monograph 0562)



$C_{23}H_{14}Na_2O_{11}$ 512.3 *15826-37-6*

Action and use

Prophylaxis of allergic conditions.

Preparation

Sodium Cromoglicate Eye Drops

Ph Eur

DEFINITION

Disodium 5,5′-[(2-hydroxypropane-1,3-diyl)bis(oxy)]bis(4-oxo-4*H*-1-benzopyran-2-carboxylate).

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

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First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 10.0 mg in *phosphate buffer solution pH 7.4 R* and dilute to 100.0 mL with the same buffer solution. Dilute 10.0 mL of the solution to 100.0 mL with *phosphate buffer solution pH 7.4 R*.

Spectral range 230-350 nm.

Absorption maxima 239 nm and 327 nm.

Absorbance ratio A_{327}/A_{239} = 0.25 to 0.30.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *sodium cromoglicate CRS*.

C. Dissolve about 5 mg in 0.5 mL of *methanol R*. Add 3 mL of a 5 g/L solution of *4-aminoantipyrine R* in *methanol R* containing 1 per cent *V/V* of *hydrochloric acid R*. Allow to stand for 5 min. An intense yellow colour develops.

D. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Add 0.2 mL of a 0.40 g/L solution of *sodium hydroxide R*. The solution is pink. Add 0.4 mL of a 1.03 g/L solution of *hydrochloric acid R*. The solution is colourless. Add 0.25 mL of *methyl red solution R*. The solution is red.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *acetonitrile R* (40:60 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 7 mg of *sodium cromoglicate for system suitability CRS* (containing impurity C) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, 10 g/L solution of *tetrabutylammonium hydrogen sulfate R* (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R*, 10 g/L solution of *tetrabutylammonium hydrogen sulfate R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100 → 0	0 → 100
15 - 20	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 330 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *sodium cromoglicate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to cromoglicate (retention time = about 11 min): impurity C = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to cromoglicate and impurity C.

Limits:

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

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— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Oxalates

Maximum 0.35 per cent.

Dissolve 0.10 g in 20 mL of *water R*, add 5.0 mL of *iron salicylate solution R* and dilute to 50.0 mL with *water R*. Measure the absorbance (*2.2.25*) at 480 nm. The absorbance is not less than that of a reference solution prepared in the same manner using 0.35 mg of *oxalic acid R* instead of the substance to be examined.

Water (*2.5.12*)

Maximum 10.0 per cent, determined on 0.250 g. Use as the solvent a mixture of 10 mL of *anhydrous methanol R* and 20 mL of *formamide R*.

ASSAY

Dissolve 0.200 g with heating in a mixture of 5 mL of *2-propanol R* and 25 mL of *ethylene glycol R*. Cool and add a mixture of 6 mL of *tetrahydrofuran R* and 24 mL of *acetonitrile R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.62 mg of $C_{23}H_{14}Na_2O_{11}$.

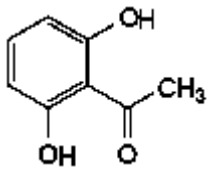
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



A. 1-(2,6-dihydroxyphenyl)ethan-1-one,

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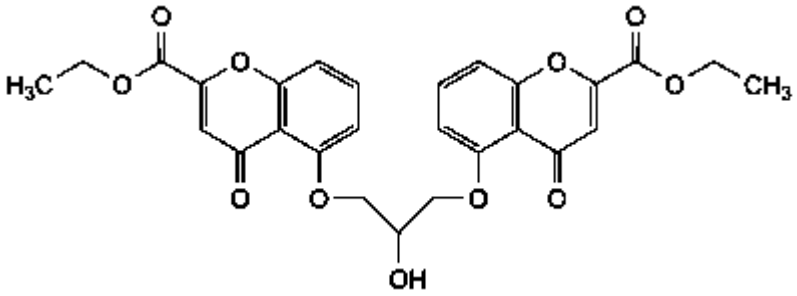

B. diethyl 5,5′-[(2-hydroxypropane-1,3-diyl)bis(oxy)]bis(4-oxo-4*H*-1-benzopyran-2-carboxylate),

C. unknown structure.

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Sodium Cromoglicate Eye Drops

General Notices

DEFINITION

Sodium Cromoglicate Eye Drops are a sterile solution of Sodium Cromoglicate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of sodium cromoglicate, $C_{23}H_{14}Na_2O_{11}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 400 nm of a solution of the eye drops diluted to contain 0.002% w/v of Sodium Cromoglicate exhibits two maxima at 239 and 326 nm, and a shoulder at about 260 nm.

B. To 1 mL of the eye drops add 2.5 mL of 1M *sodium hydroxide* and boil for 1 minute; a yellow colour is produced. Add 0.5 mL of *diazobenzenesulfonic acid solution*; a deep red colour is produced.

TESTS

Acidity or alkalinity

pH, 4.0 to 7.0, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a precoated silica gel F_{254} plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 5 volumes of *glacial acetic acid*, 50 volumes of *ethyl acetate* and 50 volumes of *toluene* as the mobile phase but allowing the solvent front to ascend 10 cm above the line of application. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) use the eye drops, diluted, if necessary with *water*, to contain 2% w/v of Sodium Cromoglicate. Solution (2) contains 0.01% w/v of *1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-propanol* in *dichloromethane*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Dilute the eye drops with *phosphate buffer pH 7.4* to give a solution containing 0.004% w/v of Sodium Cromoglicate and measure the *absorbance* of the resulting solution at the maximum at 326 nm, Appendix II B. Calculate the content of $C_{23}H_{14}Na_2O_{11}$ in the eye drops taking 164 as the value of A(1%, 1 cm) at the maximum at 326 nm.

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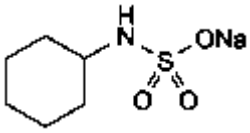
Sodium Cyclamate

General Notices

(Ph. Eur. monograph 0774)



$C_6H_{12}NNaO_3S$ 201.2 *139-05-9*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

Sodium *N*-cyclohexylsulfamate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *sodium cyclamate CRS*.

B. Examine the chromatograms obtained in the test for impurity A.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 1 mL of solution S (see Tests), add 1 mL of *water R* and 2 mL of *silver nitrate solution R1*, then shake. A white, crystalline precipitate is formed.

D. To 1 mL of solution S add 5 mL of *water R*, 2 mL of *dilute hydrochloric acid R* and 4 mL of *barium chloride solution R1* and mix. The solution is clear. Add 2 mL of *sodium nitrite solution R*. A voluminous white precipitate is formed and gas is given off.

E. A mixture of 1 mL of solution S and 1 mL of *water R* gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.5 to 7.5 for solution S.

Absorbance (*2.2.25*)

Maximum 0.10, determined at 270 nm on solution S.

Impurity A

Thin-layer chromatography (*2.2.27*).

Test solution (a) Solution S.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *water R*.

Reference solution (a) Dissolve 0.10 g of *sodium cyclamate CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *sulfamic acid R* (impurity A) in *water R* and dilute to 100 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *water R*, *ethyl acetate R*, *propanol R* (10:10:20:70 *V/V/V/V*).

Application 2 µL.

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Development Over a path of 12 cm.

Drying In a current of warm air, then heat at 105 °C for 5 min.

Detection Spray the hot plate with *strong sodium hypochlorite solution R* diluted to a concentration of 5 g/L of active chlorine. Place in a current of cold air until an area of coating below the points of application gives at most a faint blue colour with a drop of *potassium iodide and starch solution R*; avoid prolonged exposure to cold air. Spray with *potassium iodide and starch solution R* and examine the chromatograms within 5 min.

Limit Test solution (a):

— *impurity A*: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.1 per cent).

Impurities B, C and D

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 2 µL of *tetradecane R* in *methylene chloride R* and dilute to 100 mL with the same solvent.

Test solution Dissolve 2.00 g of the substance to be examined in 20 mL of *water R*, add 0.5 mL of *strong sodium hydroxide solution R* and shake with 30 mL of *toluene R*. Shake 20 mL of the upper layer with 4 mL of a mixture of equal volumes of *dilute acetic acid R* and *water R*. Separate the lower layer, add 0.5 mL of *strong sodium hydroxide solution R* and 0.5 mL of the internal standard solution and shake. Use the lower layer immediately after separation.

Reference solution Dissolve 10.0 mg (about 12 µL) of *cyclohexylamine R* (impurity C), 1.0 mg (about 1.1 µL) of *dicyclohexylamine R* (impurity D) and 1.0 mg (about 1 µL) of *aniline R* (impurity B) in *water R*, then dilute to 1000 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *water R* (solution A). To 20.0 mL of solution A, add 0.5 mL of *strong sodium hydroxide solution R* and extract with 30 mL of *toluene R*. Shake 20 mL of the upper layer with 4 mL of a mixture of equal volumes of *dilute acetic acid R* and *water R*. Separate the lower layer, add 0.5 mL of *strong sodium hydroxide solution R* and 0.5 mL of the internal standard solution and shake. Use the lower layer immediately after separation.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.51 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.8 mL/min.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 1	85
	1 - 9	85 → 150
	9 - 13	150
Injection port		250
Detector		270

Detection Flame ionisation.

Injection 1.5 µL; use a split vent at a flow rate of 20 mL/min.

Relative retention With reference to impurity C (retention time = about 2.3 min): impurity B = about 1.4; tetradecane = about 4.3; impurity D = about 4.5.

Limits:

— *impurity C*: maximum 10 ppm;

— *impurities B, D*: for each impurity, maximum 1 ppm.

Sulfates (2.4.13)

Maximum 0.1 per cent.

Dilute 1.5 mL of solution S to 15 mL with *distilled water R*.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

ASSAY

Dissolve without heating 0.150 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 20.12 mg of $C_6H_{12}NNaO_3S$.

IMPURITIES

Specified impurities *A, B, C, D.*

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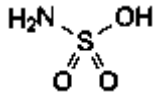
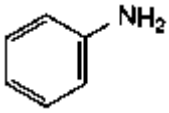
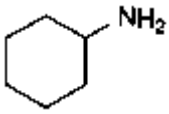


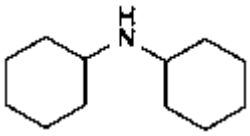
A. sulfamic acid,



B. aniline (phenylamine),



C. cyclohexanamine,



D. *N*-cyclohexylcyclohexanamine.

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Sodium Dihydrogen Phosphate

General Notices

Anhydrous Sodium Dihydrogen Phosphate

NaH_2PO_4 120.0 *7558-80-7*

Action and use

Excipient.

Preparation

Phosphates Enema

DEFINITION

Sodium Dihydrogen Phosphate contains not less than 98.0% and not more than 100.5% of NaH_2PO_4, calculated with reference to the dried substance.

CHARACTERISTICS

White, slightly deliquescent crystals or granules.

Very soluble in *water*; very slightly soluble in *ethanol (96%)*.

Dissolve 10.0 g in sufficient *carbon dioxide-free water* prepared from *distilled water* to produce 100 mL (solution S).

IDENTIFICATION

A. Solution S is *slightly acid,* Appendix V K.

B. Solution S yields the reactions characteristic of *phosphates*, Appendix VI.

C. Solution S neutralised with a 10% w/v solution of *potassium hydroxide* yields reaction A characteristic of *sodium salts*, Appendix VI.

D. Complies with the test for Loss on drying.

TESTS

Acidity

pH of a mixture of 5 mL of solution S and 5 mL of *carbon dioxide-free water*, 4.2 to 4.5, Appendix V L.

Clarity and colour of solution

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Solution S is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

Arsenic

0.5 g complies with the *limit test for arsenic*, Appendix VII (2 ppm).

Iron

10 mL of solution S complies with the *limit test for iron*, Appendix VII (10 ppm).

Chloride

Dilute 2.5 mL of solution S to 15 mL with *water*. The resulting solution complies with the *limit test for chlorides*, Appendix VII (200 ppm).

Sulfate

To 5 mL of solution S add 0.5 mL of *hydrochloric acid* and dilute to 15 mL with *distilled water*. The resulting solution complies with the *limit test for sulfates*, Appendix VII (300 ppm).

Reducing substances

To 5 mL of solution S add 0.25 mL of 0.02M *potassium permanganate* and 5 mL of 1M *sulfuric acid* and heat in a water bath for 5 minutes. The solution retains a slight red colour.

Loss on drying

When dried to constant weight at 130°, loses not more than 1.0% of its weight. Use 1 g.

ASSAY

Dissolve 2 g in 50 mL of *water* and titrate with carbonate-free *1M sodium hydroxide VS* determining the end point potentiometrically.

Each mL of *1M sodium hydroxide VS* is equivalent to 0.120 g of NaH_2PO_4.

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Sodium Dihydrogen Phosphate Dihydrate

General Notices

Sodium Acid Phosphate

(Ph. Eur. monograph 0194)

$NaH_2PO_4,2H_2O$ 156.0 *13472-35-0*

Action and use

Excipient.

Preparation

Phosphates Enema

Ph Eur

DEFINITION

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals.

Solubility

Very soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly acid (*2.2.4*).

B. Solution S gives the reactions of phosphates (*2.3.1*).

C. Solution S previously neutralised using a 100 g/L solution of *potassium hydroxide R* gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

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Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.2 to 4.5.

To 5 mL of solution S add 5 mL of *carbon dioxide-free water R*.

Reducing substances

To 5 mL of solution S add 0.25 mL of a 3.2 g/L solution of *potassium permanganate R* and 5 mL of *dilute sulfuric acid R* and heat in a water-bath for 5 min. The colour of the permanganate is not completely discharged.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

To 5 mL of solution S add 0.5 mL of *hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Loss on drying (*2.2.32*)

21.5 per cent to 24.0 per cent, determined on 0.500 g by drying in an oven at 130 °C.

ASSAY

Dissolve 2.500 g in 40 mL of *water R*. Titrate with carbonate-free *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 0.120 g of NaH_2PO_4.

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Sodium Dihydrogen Phosphate Monohydrate

General Notices

NaH_2PO_4,H_2O 138.0 *10049-21-5*

Action and use

Excipient.

Preparation

Phosphates Enema

DEFINITION

Sodium Dihydrogen Phosphate Monohydrate contains not less than 98.0% and not more than 100.5% of NaH_2PO_4, calculated with reference to the dried substance.

CHARACTERISTICS

Colourless crystals or a white powder.

Very soluble in *water*; very slightly soluble in *ethanol (96%)*.

Dissolve 10.0 g in sufficient *carbon dioxide-free water* prepared from *distilled water* to produce 100 mL (solution S).

IDENTIFICATION

A. Solution S is *slightly acid,* Appendix V K.

B. Solution S yields the reactions characteristic of *phosphates*, Appendix VI.

C. Solution S neutralised with a 10% w/v solution of *potassium hydroxide* yields reaction A characteristic of *sodium salts*, Appendix VI.

D. Complies with the test for Loss on drying.

TESTS

Acidity

pH of a mixture of 5 mL of solution S and 5 mL of *carbon dioxide-free water*, 4.2 to 4.5, Appendix V L.

Clarity and colour of solution

Solution S is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

Arsenic

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0.5 g complies with the *limit test for arsenic*, Appendix VII (2 ppm).

Iron

10 mL of solution S complies with the *limit test for iron*, Appendix VII (10 ppm).

Chloride

Dilute 2.5 mL of solution S to 15 mL with *water*. The resulting solution complies with the *limit test for chlorides*, Appendix VII (200 ppm).

Sulfate

To 5 mL of solution S add 0.5 mL of *hydrochloric acid* and dilute to 15 mL with *distilled water*. The resulting solution complies with the *limit test for sulfates*, Appendix VII (300 ppm).

Reducing substances

To 5 mL of solution S add 0.25 mL of 0.02M *potassium permanganate* and 5 mL of 1M *sulfuric acid* and heat in a water bath for 5 minutes. The solution retains a slight red colour.

Loss on drying

When dried to constant weight at 130°, loses 11.5 to 14.5% of its weight. Use 0.5 g.

ASSAY

Dissolve 2.2 g in 50 mL of *water* and titrate with carbonate-free *1M sodium hydroxide VS* determining the end point potentiometrically. Each mL of *1M sodium hydroxide VS* is equivalent to 0.120 g of NaH_2PO_4.

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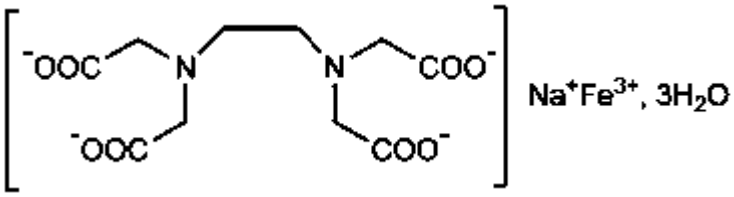
Sodium Feredetate

General Notices



$C_{10}H_{12}N_2O_8FeNa,3H_2O$ 421.1 *15708-41-5 (anhydrous)*

Action and use

Source of iron.

Preparation

Sodium Feredetate Oral Solution

DEFINITION

Sodium Feredetate is iron(III) sodium ethylenediaminetetra-acetate trihydrate. It contains not less than 98.0% and not more than 102.0% of $C_{10}H_{12}N_2O_8FeNa$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A yellow or yellowish brown, crystalline powder.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of sodium feredetate *(RS 378)*.

B. Ignite 0.5 g and allow to cool. Dissolve the residue in 2 mL of *hydrochloric acid*, add sufficient *water* to produce 20 mL and filter. The filtrate yields reaction C characteristic of *iron salts*, Appendix VI. Dilute 1 volume of the filtrate to 10 volumes with *water*; the solution yields reaction B characteristic of *iron salts*, Appendix VI.

C. Dissolve 2 g in 30 mL of *water*, slowly add 6.5 mL of a 20% w/v solution of *potassium hydroxide*, shake and filter the resulting suspension. Evaporate 8 mL of the filtrate to dryness, ignite and dissolve the residue in 4 mL of *water*. The solution yields reaction B characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity

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pH of a 1% w/v solution, 3.5 to 5.5, Appendix V L.

Free iron

Not more than 500 ppm, when determined by the following method. Dissolve 0.2 g in sufficient *water* to produce 20 mL and filter. Label three tubes A, B and C. Place 5 mL of the filtrate into each of tubes A and B and 4 mL of *water* and 1 mL of an iron standard solution prepared in the following manner in tube C. For the iron standard solution dilute 25 volumes of a 0.1726% w/v solution of *ammonium iron(III) sulfate* in 0.05M *sulfuric acid* to 200 volumes with *water* (25 ppm of Fe(III)). Add 1 mL of a 1.0% w/v solution of *disodium catechol-3,5-disulfonate* into each of tubes A and C and 1 mL of *water* to tube B. Measure the *absorbance* of solution A at 670 nm, Appendix II B, using solution B in the reference cell and of solution C using *water* in the reference cell. The absorbance of solution A is not greater than that of solution C.

Free sodium edetate

To 4 mL of a 1.0% w/v solution add 2 mL of an iron standard solution prepared in the following manner and 1 mL of a 1.0% w/v solution of *disodium catechol-3,5-disulfonate* and mix. For the iron standard solution dilute 50 volumes of a 0.1726% w/v solution of *ammonium iron(III) sulfate* in 0.05M *sulfuric acid* to 200 volumes with *water* (50 ppm of Fe(III)). Prepare a standard in the same manner using 4 mL of a 0.010% w/v solution of *disodium edetate* in place of the solution of the substance being examined. Measure the *absorbance* of the solutions at 670 nm, Appendix II B, using *water* in the reference cell. The absorbance of the solution of the substance being examined is not less than that of the standard solution (1%).

Nitrilotriacetic acid

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

Solvent A To 10 volumes of a 50% w/v solution of *iron(III) sulfate pentahydrate* in 0.5M *sulfuric acid* add 390 volumes of *water*, adjust to a pH of 2.0 with 1M *sodium hydroxide* and dilute to 500 volumes with *water*.

(1) 0.4% w/v of the substance being examined in solvent A. Mix with the aid of ultrasound.
(2) 0.0004% w/v of *nitrilotriacetic acid* in solvent A.
(3) 0.0004% w/v of *nitrilotriacetic acid* in solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with spherical *graphitised carbon for chromatography R* (5 µm) with a specific surface area of 120 m^2/g and a pore size of 25 nm (Hypercarb is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 273 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

To 50 volumes of a 0.01% w/v solution of *iron(III) sulfate pentahydrate* in 0.5M *sulfuric acid*, add 750 volumes of *water*. Adjust to a pH of 1.5 with 0.5M *sulfuric acid* or 1M *sodium hydroxide* and add 20 volumes of *ethylene glycol*. Dilute to 1000 volumes with *water*.

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When the chromatograms are recorded under the prescribed conditions the retention of sodium feredetate relative to nitrilotriacetic acid (retention time, about 5 minutes) is about 2.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nitrilotriacetic acid and sodium feredetate is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to nitrilotriacetic acid is not greater than the area of the principal peak in the chromatogram obtained with solution 2 (0.1%).

Chlorides

Dissolve 1 g in 100 mL of *water* and filter. 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII (350 ppm).

Sulfates

Dissolve 2 g in 40 mL of *water*, add 5 mL of a 20% w/v solution of *sodium hydroxide* and sufficient *water* to produce 50 mL, shake and filter. Evaporate 6.2 mL of this solution to dryness and ignite until no trace of carbon remains. Cool and dissolve the residue in 10 mL of *distilled water*. Neutralise the solution with *2M hydrochloric acid* using *litmus paper* as external indicator and add 2 mL in excess. Boil the solution, cool, dilute to 15 mL with *distilled water* and filter. The filtrate complies with the *limit test for sulfates*, Appendix VII (600 ppm).

Water

12.0% to 13.5% w/w, Appendix IX C, Method I. Use 0.1 g.

ASSAY

Dissolve 1 g in 40 mL of *water* in an iodine flask, add 20 mL of *hydrochloric acid* and 3 g of *potassium iodide*, close the flask and allow to stand for 5 minutes. Titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Repeat the procedure without the substance being examined. The difference between the titrations represents the amount of sodium thiosulfate required.
Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 36.71 mg of $C_{10}H_{12}N_2O_8FeNa$.

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Sodium Feredetate Oral Solution

General Notices

Action and use

Source of iron.

DEFINITION

Sodium Feredetate Oral Solution contains Sodium Feredetate in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ferric iron, Fe(III)

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Evaporate a quantity of the oral solution containing the equivalent of about 30 mg of ferric iron to dryness, ignite the residue and cool. Mix the cooled residue with 2 mL of *hydrochloric acid*, add sufficient *water* to produce 20 mL and filter. The filtrate yields reaction C characteristic of *iron salts* and a one in five dilution of the filtrate yields reaction B characteristic of *iron salts*, Appendix VI.

B. To a quantity of the oral solution containing the equivalent of 55 mg of ferric iron add sufficient 5M *ammonia* to make it alkaline to *litmus paper*, followed by 5 mL of a 2.5% w/v solution of *ammonium oxalate*. Not more than a trace of a precipitate is produced.

TESTS

Acidity

pH, 2.6 to 3.5, Appendix V L.

Free iron

Not more than 0.72% w/v of the content of ferric iron when determined in the following manner. Label three tubes A, B and C. Place a quantity of the oral solution containing the equivalent of 55 mg of ferric iron into each tube. Add 1 mL of a 1.0% w/v solution of *disodium catechol-3,5-disulfonate* into each of tubes A and B, add 4 mL of an iron standard solution prepared in the following manner to tube A and dilute each of solutions A, B and C to 25 mL with *water*. For the iron standard solution dilute 10 volumes of a 0.1726% w/v solution of *ammonium iron(III) sulfate* in 0.05M *sulfuric acid* to 20 volumes with *water* (100 ppm of Fe(III)). Measure the *absorbance* of solutions A and B at 670 nm, Appendix II B, using solution C in the reference cell using a 4-cm pathlength. The absorbance of solution A is not less than twice that of solution B.

ASSAY

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Mix a quantity of the oral solution containing the equivalent of 0.137 g of ferric iron with 20 mL of *water* and 20 mL of *hydrochloric acid*. Cool to room temperature and add 3 g of *potassium iodide*, stopper the flask and allow to stand for 5 minutes. Titrate the liberated iodine with 0.1 M *sodium thiosulfate VS* using 0.5 mL of *starch mucilage*, added just before the end point, as indicator. Repeat the procedure without the substance being examined. The difference between the titrations represents the amount of iodine liberated. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 5.585 mg of Fe.

LABELLING

The quantity of the active ingredient is stated both as the amount of Sodium Feredetate and in terms of the equivalent amount of ferric iron.

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Sodium Fluoride

General Notices

(Ph. Eur. monograph 0514)

NaF 41.99 *7681-49-4*

Action and use

Used in prevention of dental caries.

Preparations

Sodium Fluoride Mouthwash

Sodium Fluoride Oral Drops

Sodium Fluoride Oral Solution

Sodium Fluoride Tablets

Ph Eur

DEFINITION

Content

98.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. To 2 mL of solution S (see Tests) add 0.5 mL of *calcium chloride solution R*. A gelatinous white precipitate is formed that dissolves on adding 5 mL of *ferric chloride solution R1*.

B. To about 4 mg add a mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R* and mix. The colour changes from red to yellow.

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C. Solution S gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* without heating and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

Dissolve 2.5 g of *potassium nitrate R* in 40 mL of solution S and dilute to 50 mL with *carbon dioxide-free water R*. Cool to 0 °C and add 0.2 mL of *phenolphthalein solution R*. If the solution is colourless, not more than 1.0 mL of *0.1 M sodium hydroxide* is required to produce a red colour that persists for at least 15 s. If the solution is red, not more than 0.25 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Fluorosilicates

Heat to boiling the neutralised solution obtained in the test for acidity or alkalinity and titrate whilst hot. Not more than 0.75 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to red.

Sulfates (2.4.13)

Maximum 200 ppm.

Dissolve 0.25 g in 10 mL of a 223 g/L solution of *aluminium nitrate R*. Add 5 mL of *distilled water R* and 0.6 mL of *hydrochloric acid R1*. Prepare the standard by mixing 0.6 mL of *hydrochloric acid R1*, 5 mL of *sulfate standard solution (10 ppm SO_4) R* and 10 mL of a 223 g/L solution of *aluminium nitrate R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 130 °C for 3 h.

ASSAY

Dissolve 0.100 g in *water R* and dilute to 60 mL with the same solvent. Titrate with *0.1 M lanthanum nitrate*, determining the end-point potentiometrically (2.2.20) using a fluoride-selective indicator electrode and a silver-silver chloride reference electrode.

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1 mL of *0.1 M lanthanum nitrate* is equivalent to 12.60 mg of NaF.

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Sodium Fluoride Mouthwash

General Notices

DEFINITION

Sodium Fluoride Mouthwash is a solution of Sodium Fluoride in a suitable aqueous vehicle.

The mouthwash complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of sodium fluoride, NaF

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake 5 mL of the mouthwash with *activated charcoal* and filter. To 0.2 mL of the filtrate add 0.2 mL of a freshly prepared mixture of equal volumes of *alizarin S solution* and *zirconyl nitrate solution*. A yellow colour is produced.

B. The filtrate obtained in test A yields reaction A characteristic of *sodium salts*, Appendix VI.

ASSAY

Carry out Method I for *potentiometric determination of ionic concentration* *using ion-selective electrodes*, Appendix VIII E, using a fluoride selective electrode.

Prepare and store all solutions in plastic containers.

For solution (1) dilute a volume of the mouthwash containing 50 mg of Sodium Fluoride to 1000 mL. Solutions (2), (3), (4) and (5) contain 0.0110% w/v, 0.00550% w/v, 0.00220% w/v and 0.00110% w/v of *sodium fluoride* respectively. To 20 mL of each solution add 20 mL of a buffer solution prepared by mixing 57 mL of *glacial acetic acid*, 58 g of *sodium chloride* and 4 g of *cyclohexylenedinitrilotetra-acetic acid* in 500 mL of *water*, adjusting the pH to 5.2 with a 50% w/v solution of *sodium hydroxide* and diluting to 1000 mL with *water*.

In turn, stir each solution, immerse the electrodes and allow to stand for 5 minutes with constant stirring. Determine the potential difference between the electrodes for each of solutions (2), (3), (4) and (5) and plot on semi-logarithmic graph paper the potential difference obtained as a function of concentration of sodium fluoride. Using exactly the same conditions, determine the potential difference obtained with solution (1) and hence calculate the content of sodium fluoride in the mouthwash.

LABELLING

The label states the concentration of sodium fluoride and of fluoride ion in a suitable volume.

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Sodium Fluoride Oral Drops

General Notices

DEFINITION

Sodium Fluoride Oral Drops are a solution of Sodium Fluoride in a suitable aqueous vehicle.

The oral drops comply with the requirements stated under Oral Liquids and with the following requirements.

Content of sodium fluoride, NaF

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To 0.2 mL add 0.2 mL of a freshly prepared mixture of equal volumes of *alizarin S solution* and *zirconyl nitrate solution*. A yellow colour is produced.

B. Yield reaction A characteristic of *sodium salts*, Appendix VI.

ASSAY

Carry out Method I for *potentiometric determination of ionic concentration* *using ion-selective electrodes*, Appendix VIII E, using a fluoride selective electrode.

Prepare and store all solutions in plastic containers.

For solution (1) dilute a volume of the oral drops containing 11 mg of Sodium Fluoride to 200 mL. Solutions (2), (3), (4) and (5) contain 0.0110% w/v, 0.00550% w/v, 0.00220% w/v and 0.00110% w/v of *sodium fluoride* respectively. To 20 mL of each solution add 20 mL of a buffer solution prepared by mixing 57 mL of glacial acetic acid, 58 g of sodium chloride and 4 g of cyclohexylenedinitrilotetra-acetic acid in 500 mL of water, adjusting the pH to 5.2 with a 50% w/v solution of sodium hydroxide and diluting to 1000 mL with water.

In turn, stir each solution, immerse the electrodes and allow to stand for 5 minutes with constant stirring. Determine the potential difference between the electrodes for each of solutions (2), (3), (4) and (5) and plot on semi-logarithmic graph paper the potential difference obtained as a function of concentration of sodium fluoride. Using exactly the same conditions, determine the potential difference obtained with solution (1) and hence calculate the content of sodium fluoride in the oral drops.

LABELLING

The label states the concentration of sodium fluoride and of fluoride ion in a suitable dose-volume.

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Sodium Fluoride Oral Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in the prevention of dental caries.

DEFINITION

Sodium Fluoride Oral Solution is a solution of Sodium Fluoride in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of sodium fluoride, NaF

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To 0.2 mL add 0.2 mL of a freshly prepared mixture of equal volumes of *alizarin S solution* and *zirconyl nitrate solution*. A yellow colour is produced.

B. Yields reaction A characteristic of *sodium salts*, Appendix VI.

ASSAY

Carry out Method I for *potentiometric determination of ionic concentration* *using ion-selective electrodes*, Appendix VIII E, using a fluoride selective electrode.

Prepare and store all solutions in plastic containers.

For solution (1) dilute a volume of the oral solution containing 11 mg of Sodium Fluoride to 200 mL. Solutions (2), (3), (4) and (5) contain 0.0110% w/v, 0.00550% w/v, 0.00220% w/v and 0.00110% w/v of *sodium fluoride* respectively. To 20 mL of each solution add 20 mL of a buffer solution prepared by mixing 57 mL of *glacial acetic acid*, 58 g of *sodium chloride* and 4 g of *cyclohexylenedinitrilotetra-acetic acid* in 500 mL of *water*, adjusting the pH to 5.2 with a 50% w/v solution of *sodium hydroxide* and diluting to 1000 mL with *water*.

In turn, stir each solution, immerse the electrodes and allow to stand for 5 minutes with constant stirring. Determine the potential difference between the electrodes for each of solutions (2), (3), (4) and (5) and plot on semi-logarithmic graph paper the potential difference obtained as a function of concentration of sodium fluoride. Using exactly the same conditions, determine the potential difference obtained with solution (1) and hence calculate the content of sodium fluoride in the oral solution.

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Sodium Fluoride Tablets

General Notices

DEFINITION

Sodium Fluoride Tablets contain Sodium Fluoride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sodium fluoride, NaF

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 5 mg of Sodium Fluoride with 5 mL of *water* for 5 minutes and filter (Solution A). To 2 mL of the filtrate add 0.2 mL of a freshly prepared mixture of equal volumes of *alizarin S solution* and *zirconyl nitrate solution*. A yellow colour is produced.

B. Solution A yields reaction A characteristic of *sodium salts*, Appendix VI.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Sodium Fluoride comply with the requirements stated under Tablets using the following method of analysis. Carry out Method I for *potentiometric determination of ionic concentration* *using ion-selective electrodes*, Appendix VIII E, using a fluoride selective electrode.

Prepare and store all solutions in plastic containers.

For solution (1) add a sufficient quantity of *water* to one tablet to produce a solution containing 0.0055% w/v of Sodium Fluoride, heat at 80° and mix with the aid of ultrasound until dissolved, cool to room temperature and filter. Solutions (2), (3), (4) and (5) contain 0.0110% w/v, 0.00550% w/v, 0.00220% w/v and 0.00110% w/v of *sodium fluoride* respectively. To 15 mL of each solution add 20 mL of a buffer solution prepared by mixing 57 mL of *glacial acetic acid*, 58 g of *sodium chloride* and 4 g of *cyclohexylenedinitrilotetra-acetic acid* in 500 mL of *water*, adjusting the pH to 5.2 with a 50% w/v solution of *sodium hydroxide* and diluting to 1000 mL with *water*.

In turn, stir each solution, immerse the electrodes and allow to stand for 5 minutes with constant stirring. Determine the potential difference between the electrodes for solutions (2), (3), (4) and (5) and plot on semi-logarithmic graph paper the potential difference obtained for each solution as a function of concentration of sodium fluoride. Using exactly the same conditions, determine the potential difference obtained with solution (1) and calculate the content of sodium fluoride in each tablet.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Sodium Fluoride

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Use the average of the individual results obtained in the test for Uniformity of content.

LABELLING

The label states the quantity of sodium fluoride and of fluoride ion per tablet.

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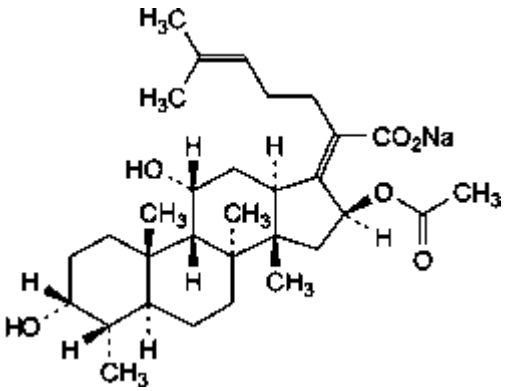
Sodium Fusidate

General Notices

(Ph. Eur. monograph 0848)



$C_{31}H_{47}NaO_6$ 538.7 *751-94-0*

Action and use

Antibacterial.

Preparation

Sodium Fusidate Ointment

Ph Eur

DEFINITION

Sodium *ent*-(17*Z*)-16α-(acetyloxy)-3β,11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oate.

Antimicrobial substance produced by fermentation of certain strains of *Fusidium coccineum* or by any other means.

Content

97.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, slightly hygroscopic.

Solubility

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Freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sodium fusidate CRS*.

B. Ignite 1 g. The residue gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution B_6 (2.2.2, *Method II*).

Dissolve 1.5 g in 10 mL of *water R*.

pH (2.2.3)

7.5 to 9.0.

Dissolve 0.125 g in 10 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture *methanol R*, 5 g/L solution of *phosphoric acid R*, *acetonitrile R* (10:40:50 *V/V/V*).

Test solution Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *fusidic acid for peak identification CRS* (containing impurities A, B, C, D, F, G, H and N) in the solvent mixture and dilute to 1.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve the contents of a vial of *fusidic acid impurity mixture CRS* (containing impurities I, K, L and M) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 30 °C.

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Mobile phase:

— *mobile phase A*: *methanol R*, *acetonitrile R*, 5 g/L solution of *phosphoric acid R* (20:40:40 *V/V/V*);

— *mobile phase B*: 5 g/L solution of *phosphoric acid R*, *methanol R*, *acetonitrile R* (10:20:70 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 28	100 → 0	0 → 100
28 - 33	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *fusidic acid for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, F, G, H and N; use the chromatogram supplied with *fusidic acid impurity mixture CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities I, K, L and M.

Relative retention With reference to fusidic acid (retention time = about 18 min): impurity A = about 0.4; impurity B = about 0.5; impurity C = about 0.6; impurity D = about 0.63; impurity N = about 0.65; impurity F = about 0.7; impurity G = about 0.82; impurity H = about 0.85; impurity I = about 0.96; impurity K = about 1.18; impurity L = about 1.23; impurity M = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities G and H.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.7; impurity D = 0.7; impurity F = 0.3; impurity I = 0.6; impurity K = 0.6;

— *impurity M*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity G*: not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *impurity L*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.4 per cent);

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— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities C, D, F, I, K, N*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.500 g.

ASSAY

Dissolve 0.400 g in 30 mL of *water R* and add 40 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 53.87 mg of $C_{31}H_{47}NaO_6$.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A, B, C, D, F, G, I, K, L, M, N.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, H, J, O.*

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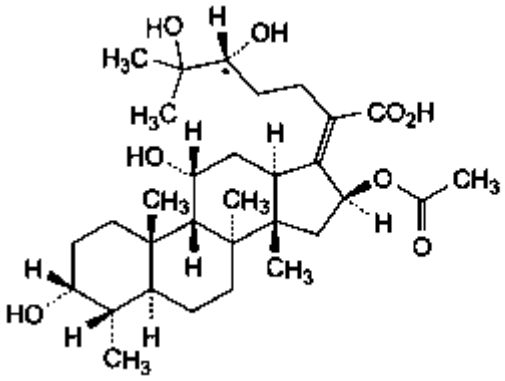
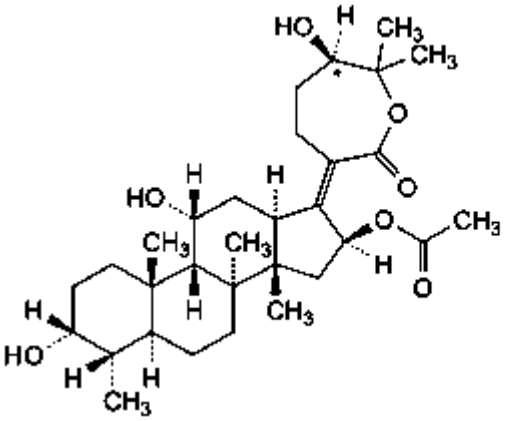


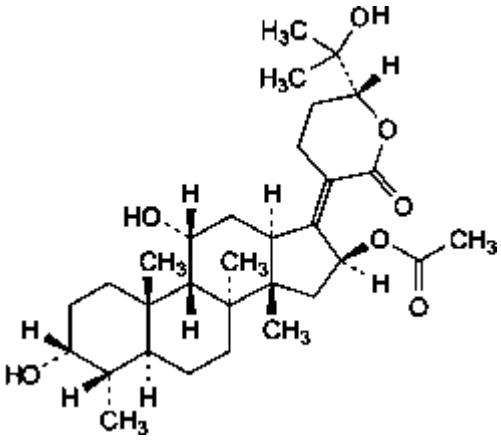
and epimer at C*

A. *ent*-(24*SR*,17*Z*)-16α-(acetyloxy)-3β,11β,24,25-tetrahydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholest-17(20)-en-21-oic acid (24,25-dihydro-24,25-dihydroxyfusidic acid),



and epimer at C*

B. *ent*-(17*Z*)-3β,11β-dihydroxy-17-[(6*SR*)-6-hydroxy-7,7-dimethyl-2-oxooxepan-3-ylidene]-4β,8,14-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate (24,25-dihydro-24,25-dihydroxyfusidic acid 21,25-lactone),



C. *ent*-(17*Z*)-3β,11β-dihydroxy-17-[(6*S*)-6-(1-hydroxy-1-methylethyl)-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene]-4β,8,14-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate ((24*R*)-24,25-dihydro-24,25-dihydroxyfusidic acid 21,24-lactone),

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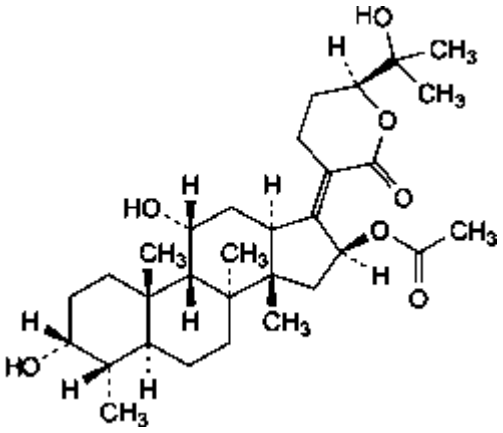
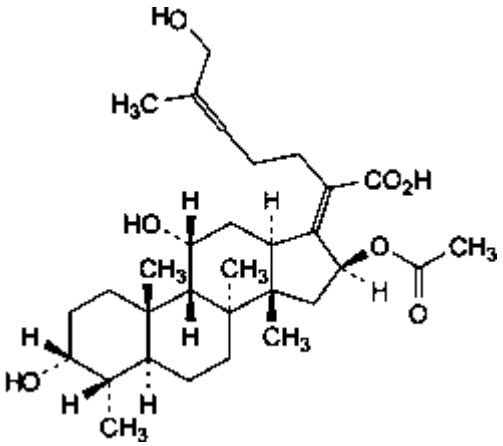
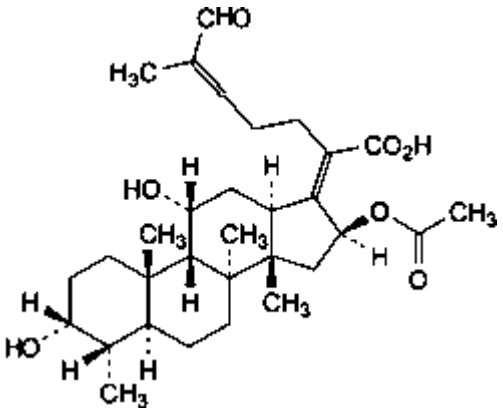


D. *ent*-(17*Z*)-3β,11β-dihydroxy-17-[(6*R*)-6-(1-hydroxy-1-methylethyl)-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene]-4β,8,14-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate ((24*S*)-24,25-dihydro-24,25-dihydroxyfusidic acid 21,24-lactone),



E. *ent*-(17*Z*,24*EZ*)-16α-(acetyloxy)-3β,11β,26-trihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (26-hydroxyfusidic acid),



F. *ent*-(17*Z*,24*EZ*)-16α-(acetyloxy)-3β,11β-dihydroxy-4β,8,14-trimethyl-26-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (26-oxofusidic acid),

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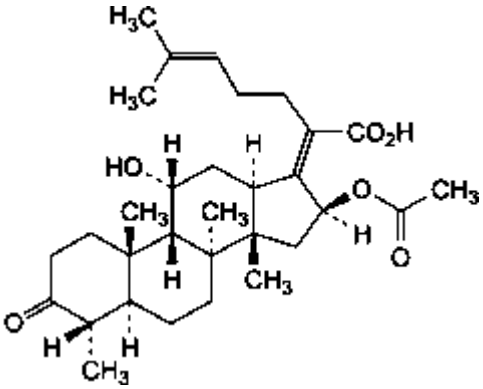
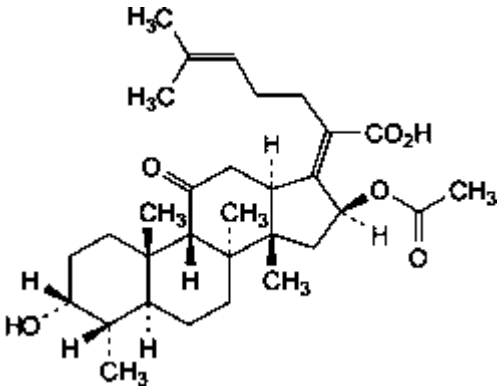
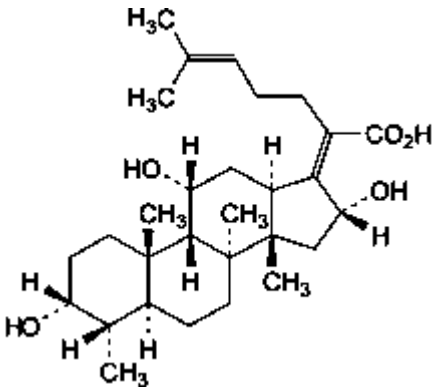


G. *ent*-(17*Z*)-16α-(acetyloxy)-11β-hydroxy-4β,8,14-trimethyl-3-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (3-didehydrofusidic acid),



H. *ent*-(17*Z*)-16α-(acetyloxy)-3β-hydroxy-4β,8,14-trimethyl-11-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (11-didehydrofusidic acid),



I. *ent*-(17*Z*)-3β,11β,16β-trihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (16-*epi*-deacetylfusidic acid),

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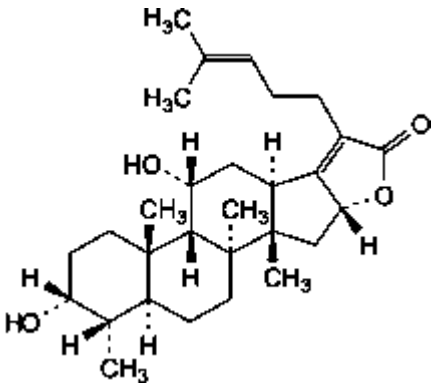
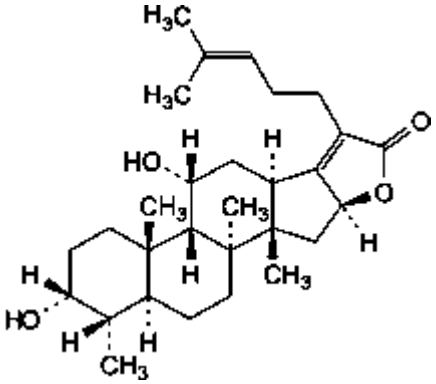
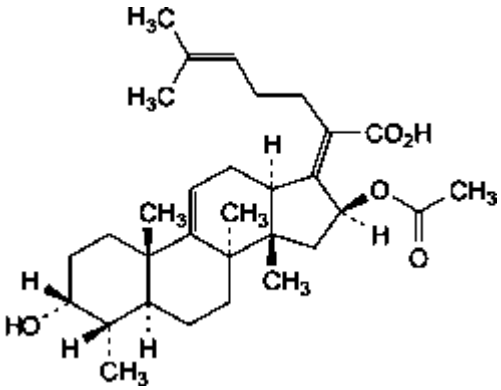


J. *ent*-(17*Z*)-3β,11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dieno-21(16β)-lactone (16-*epi*-deacetylfusidic acid 21,16-lactone),



K. *ent*-(17*Z*)-3β,11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dieno-21(16α)-lactone (deacetylfusidic acid 21,16-lactone),



L. *ent*-(17*Z*)-16α-(acetyloxy)-3β-hydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-9(11),17(20),24-trien-21-oic acid (9,11-anhydrofusidic acid),

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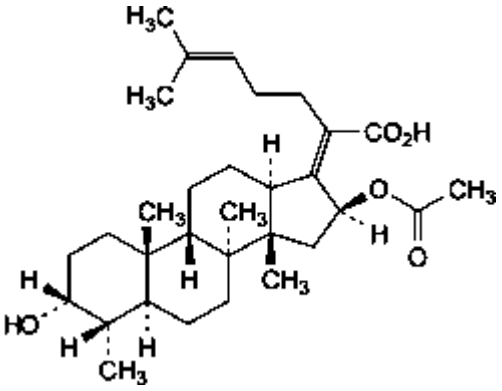
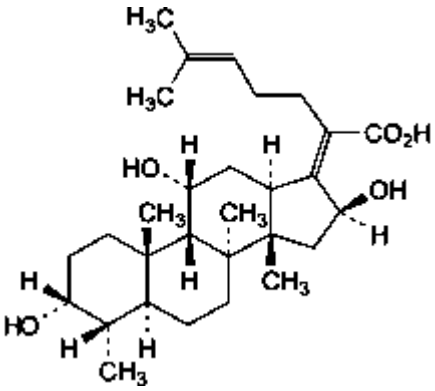


M. *ent*-(17*Z*)-16α-(acetyloxy)-3β-hydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (11-deoxyfusidic acid),

N. unknown structure,



O. *ent*-(17*Z*)-3β,11β,16α-trihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (deacetylfusidic acid).

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Sodium Fusidate Ointment

General Notices

Action and use

Antibacterial

DEFINITION

Sodium Fusidate Ointment contains Sodium Fusidate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of sodium fusidate, $C_{31}H_{47}NaO_6$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Disperse a quantity of the ointment containing 60 mg of Sodium Fusidate in 30 mL of *hexane* and shake with 6 mL of *water*. Allow to separate, remove the aqueous layer and add to it 5 mL of 0.2M *orthophosphoric acid*. Extract with two 10-mL quantities of *dichloromethane*, dry the combined extracts with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 0.6 mL of *dichloromethane IR*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of fusidic acid (*RS 166*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 10 volumes of *methanol*, 40 volumes of 0.05M *orthophosphoric acid* and 50 volumes of *acetonitrile*.

(1) Add 25 mL of *hexane* to a quantity of the ointment containing 26 mg of Sodium Fusidate, stir, extract with 10 mL of *ethanol* (*70%*) and allow the layers to separate. Use the ethanol layer.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dissolve the contents of a vial of *fusidic acid impurity mixture EPCRS* in 1.0 mL of solution A.

(4) 0.2% w/v of *fusidic acid for peak identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *methanol*, 40 volumes of *acetonitrile* and 40 volumes of 0.05M *orthophosphoric acid*.

Mobile phase B 20 volumes of *methanol*, 70 volumes of *acetonitrile*, and 10 volumes of 0.05M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-33	0	100	isocratic
33-34	0→100	100→0	linear gradient
34-40	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to fusidic acid (retention time about 18 minutes) are: impurity A, about 0.4; impurity B, about 0.5; impurity C, about 0.6; impurity D, about 0.63; impurity N about 0.65; impurity F, about 0.7; impurity G, about 0.8; impurity H, about 0.9; impurity I, about 0.96; impurity K, about 1.18; impurity L, about 1.23 and impurity M, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurities G and H is at least 1.5.

LIMITS

Identify any peaks due to impurities C, D, F, G, I, K and M using relative retentions and the chromatograms obtained with solutions (3) and (4). Multiply the area of the peaks by the following correction factors: impurities C and D, 0.7; impurity F, 0.3; and impurities I and K, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity G or M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak due to impurity A is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

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the area of any peak due to impurity B, C, D, or F is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A as described under Related substances.

(1) Add 25 mL of *hexane* to a quantity of the ointment containing 26 mg of Sodium Fusidate, stir, extract with 10 mL of *ethanol* (*70%*) and allow the layers to separate. Use the ethanol layer and dilute to 100 mL with solution A.
(2) 0.03% w/v of *diethanolamine fusidate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with the following modification.

MOBILE PHASE

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-29	0→100	100→0	linear gradient
29-35	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the retention time of fusidic acid is about 18 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{31}H_{47}NaO_6$ in the ointment using the chromatograms obtained and the declared content of $C_{31}H_{48}O_6$ in *diethanolamine fusidate BPCRS*. Each mg of $C_{31}H_{48}O_6$ is equivalent to 1.043 mg of $C_{31}H_{47}NaO_6$

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sodium Fusidate.

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Sodium Fusidate Tablets

General Notices

Action and use

Antibacterial

DEFINITION

Sodium Fusidate Tablets contain Sodium Fusidate.

The Tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sodium fusidate, $C_{31}H_{47}NaO_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of powdered tablets containing the equivalent of 0.1 g of sodium fusidate add 5 mL of *water* and extract with three 10-mL quantities of *dichloromethane*. Wash the combined extracts with two 10-mL quantities of *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 1 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of fusidic acid *(RS 166)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 10 volumes of *methanol*, 40 volumes of 0.05M *orthophosphoric acid* and 50 volumes of *acetonitrile*.

(1) Disperse a quantity of the powdered tablets corresponding to 250 mg of Sodium Fusidate in 80 mL of *ethanol* (*70%*). Dilute to 100 mL with *ethanol* (70%) and filter (0.7-µm Whatman GFC filter is appropriate).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dissolve the contents of a vial of *fusidic acid impurity mixture EPCRS* in 1.0 mL of solution A.
(4) 0.2% w/v of *fusidic acid for peak identification EPCRS*.
(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Symmetry C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *methanol*, 40 volumes of *acetonitrile* and 40 volumes of 0.05M *orthophosphoric acid*.

Mobile phase B 20 volumes of *methanol*, 70 volumes of *acetonitrile*, and 10 volumes of 0.05M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-33	0	100	isocratic
33-34	0→100	100→0	linear gradient
34-40	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to Fusidic acid (retention time about 18 minutes) are: impurity A, about 0.4; impurity B, about 0.5; impurity C, about 0.6; impurity D, about 0.63; impurity N about 0.65; impurity F, about 0.7; impurity G, about 0.8; impurity H, about 0.9; impurity I, about 0.96; impurity K, about 1.18; impurity L, about 1.23 and impurity M, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurities G and H is at least 1.5.

LIMITS

Identify any peaks due to impurities C, D, F, G, I, K and M using relative retentions and the chromatograms obtained with solutions (3) and (4). Multiply the area of the peaks by the following correction factors: impurities C and D, 0.7; impurity F, 0.3; and impurities I and K, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak due to impurity G is not greater than 0.9 times the area of the principal peak in the chromatogram obtained with solution (2) (0.9%);

the area of any peak due to impurity K is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

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the area of any peak due to impurity C, D, F, I or L is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity B is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak due to impurity A is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 4.0 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in Solution A as described under Related substances.

(1) Disperse a quantity of the powdered tablets corresponding to 250 mg of Sodium Fusidate in 80 mL of *ethanol* (*70%*), dilute to 100 mL with ethanol (70%) and filter (0.7-µm Whatman GFC filter is appropriate). Dilute a suitable volume of the filtrate to produce a final solution containing 0.025% w/v sodium fusidate.
(2) 0.03% w/v of *diethanolamine fusidate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used with the following modification.

MOBILE PHASE

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-29	0→100	100→0	linear gradient
29-35	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the retention time of fusidic acid is about 18 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{31}H_{47}NaO_6$ in the tablets using the declared content of $C_{31}H_{48}O_6$ in *diethanolamine fusidate BPCRS*. Each mg of $C_{31}H_{48}O_6$ is equivalent to 1.04 mg of $C_{31}H_{47}NaO_6$.

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IMPURITIES

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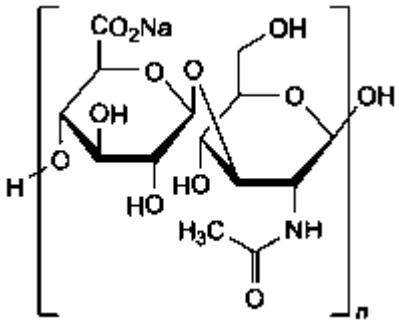
Sodium Hyaluronate

General Notices

(Ph. Eur. monograph 1472)



$(C_{14}H_{20}NNaO_{11})_n$ *9067-32-7*

Action and use

High viscosity mucopolysaccharide.

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DEFINITION

Sodium salt of hyaluronic acid, a glycosaminoglycan consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide units. It is extracted from cocks' combs or obtained by fermentation from *Streptococci*, Lancefield Groups A and C.

Content

95.0 per cent to 105.0 per cent (dried substance).

Intrinsic viscosity: 90 per cent to 120 per cent of the value stated on the label.

PRODUCTION

Where applicable, the animals from which sodium hyaluronate is derived must fulfil the requirements for the health of animals suitable for human consumption.

When produced by fermentation of gram-positive bacteria, the process must be shown to reduce or eliminate pyrogenic or inflammatory components of the cell wall.

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CHARACTERS

Appearance

White or almost white, very hygroscopic powder or fibrous aggregate.

Solubility

Sparingly soluble or soluble in water, practically insoluble in acetone and in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of sodium hyaluronate*.

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Weigh a quantity of the substance to be examined equivalent to 0.10 g of the dried substance and add 30.0 mL of a 9 g/L solution of *sodium chloride R*. Mix gently on a shaker until dissolved (about 12 h).

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 600 nm is not greater than 0.01.

pH (2.2.3)

5.0 to 8.5.

Dissolve the substance to be examined in *carbon dioxide-free water R* to obtain a solution containing a quantity equivalent to 5 mg of the dried substance per millilitre.

Intrinsic viscosity

Sodium hyaluronate is very hygroscopic and must be protected from moisture during weighing.

Buffer solution (0.15 M sodium chloride in 0.01 M phosphate buffer solution pH 7.0) Dissolve 0.78 g of *sodium dihydrogen phosphate R* and 4.50 g of *sodium chloride R* in *water R* and dilute to 500.0 mL with the same solvent (solution A). Dissolve 1.79 g of *disodium hydrogen phosphate dodecahydrate R* and 4.50 g of *sodium chloride R* in *water R* and dilute to 500.0 mL with the same solvent (solution B). Mix solutions A and B until a pH of 7.0 is reached. Filter through a sintered-glass filter (4) (2.1.2).

Test solution (a) Weigh 0.200 g (m_{0p}) *(NOTE: this value is only indicative and should be adjusted after an initial measurement of the viscosity of test solution (a))* of the substance to be examined and dilute with 50.0 g (m_{0s}) of buffer solution at 4 °C. Mix the solution by

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shaking at 4 °C during 24 h. Weigh 5.00 g (m_{1p}) of the solution and dilute with 100.0 g (m_{1s}) of buffer solution at 25 °C. Mix this solution by shaking for 20 min. Filter the solution through a sintered-glass filter (100) (2.1.2), and discard the first 10 mL.

Test solution (b) Weigh 30.0 g (m_{2p}) of test solution (a) and dilute with 10.0 g (m_{2s}) of buffer solution at 25 °C. Mix this solution by shaking for 20 min. Filter the solution through a sintered-glass filter (100) (2.1.2) and discard the first 10 mL.

Test solution (c) Weigh 20.0 g (m_{3p}) of test solution (a) and dilute with 20.0 g (m_{3s}) of buffer solution at 25 °C. Mix this solution by shaking for 20 min. Filter the solution through a sintered-glass filter (100) (2.1.2) and discard the first 10 mL.

Test solution (d) Weigh 10.0 g (m_{4p}) of test solution (a) and dilute with 30.0 g (m_{4s}) of buffer solution at 25 °C. Mix this solution by shaking for 20 min. Filter the solution through a sintered-glass filter (100) (2.1.2) and discard the first 10 mL.

Determine the flow-times (2.2.9) for the buffer solution (t_0) and for the 4 test solutions (t_1, t_2, t_3 and t_4), at 25.00 ± 0.03 °C. Use an appropriate suspended level viscometer (specifications: viscometer constant about 0.005 mm^2/s^2, kinematic viscosity of 1-5 mm^2/s, internal diameter of tube *R* 0.53 mm, volume of bulb *C* 5.6 mL, internal diameter of tube *N* 2.8-3.2 mm) with a funnel-shaped lower capillary end. Use the same viscometer for all measurements; measure all outflow times in triplicate. The test is not valid unless the results do not differ by more than 0.35 per cent from the mean and unless the flow time t_1 is not less than 1.6 times and not more than 1.8 times t_0 $\left(1.6t_0 \leq t_1 \leq 1.8t_0\right)$. If this is not the case, adjust the value of m_{0p} and repeat the procedure.

Calculation of the relative viscosities

Since the densities of the sodium hyaluronate solutions and of the solvent are almost equal, the relative viscosities η_{ri} (being η_{r1}, η_{r2}, η_{r3} and η_{r4}) can be calculated from the ratio of the flow times for the respective solutions t_i (being t_1, t_2, $t_3$and t_4) to the flow time of the solvent t_0, but taking into account the kinetic energy correction factor for the capillary (*B* = 30 800 s^3), using the following expression:

$$\frac{t_i - \frac{B}{t_i^2}}{t_0 - \frac{B}{t_0^2}}$$

Calculation of the concentrations

Calculate the concentration c_1 (expressed in kg/m^3) of sodium hyaluronate in test solution (a) using the following expression:

$$\frac{m_{0p} \times x \times (100 - h) \times m_{1p} \times \rho_{25}}{100 \times 100 \times \left(m_{0p} + m_{0s}\right) \times \left(m_{1p} + m_{1s}\right)}$$

x	=	percentage content of sodium hyaluronate as determined under Assay;
h	=	percentage loss on drying;
ρ_{25}	=	1005 kg/m^3 (density of the test solution at 25 °C).

Calculate the concentration c_2 (expressed in kg/m^3) of sodium hyaluronate in test solution (b) using the following expression:

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$$c_1 \times \frac{m_{2p}}{m_{2s}+m_{2p}}$$

Calculate the concentration c_3 (expressed in kg/m^3) of sodium hyaluronate in test solution (c) using the following expression:

$$c_1 \times \frac{m_{3p}}{m_{3s}+m_{3p}}$$

Calculate the concentration c_4 (expressed in kg/m^3) of sodium hyaluronate in test solution (d) using the following expression:

$$c_1 \times \frac{m_{4p}}{m_{4s}+m_{4p}}$$

Calculation of the intrinsic viscosity

Calculate the intrinsic viscosity [η] by linear least-squares regression analysis using the Martin equation:

$$\log_{10}\left(\frac{\eta_r - 1}{c}\right) = \log_{10}[\eta] + k[\eta]c$$

The decimal antilogarithm of the intercept is the intrinsic viscosity expressed in m^3/kg.

Sulfated glycosaminoglycans

Maximum 1 per cent, if the product is extracted from cocks' combs.

Appropriate safety precautions are to be taken when handling perchloric acid at elevated temperature.

Test solution Introduce a quantity of the substance to be examined equivalent to 50.0 mg of the dried substance into a test-tube 150 mm long and 16 mm in internal diameter and dissolve in 1.0 mL of *perchloric acid R*.

Reference solution Dissolve 0.149 g of *anhydrous sodium sulfate R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *water R*. Evaporate 1.0 mL in a test-tube 150 mm long and 16 mm in internal diameter in a heating block at 90-95 °C, and dissolve the residue in 1.0 mL of *perchloric acid R*.

Plug each test-tube with a piece of glass wool. Place the test-tubes in a heating block or a silicone oil bath maintained at 180 °C and heat until clear, colourless solutions are obtained (about 12 h). Remove the test-tubes and cool to room temperature. Add to each test-tube 3.0 mL of a 33.3 g/L solution of *barium chloride R*, cap and shake vigorously. Allow the test-tubes to stand for 30 min. Shake each test-tube once again, and determine the absorbance (*2.2.25*) at 660 nm, using *water R* as a blank.

The absorbance obtained with the test solution is not greater than the absorbance obtained with the reference solution.

Nucleic acids

The absorbance (*2.2.25*) of solution S at 260 nm is maximum 0.5.

Protein

Maximum 0.3 per cent; maximum 0.1 per cent, if intended for use in the manufacture of parenteral preparations.

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Test solution (a) Dissolve the substance to be examined in *water R* to obtain a solution containing a quantity equivalent to about 10 mg of the dried substance per millilitre.

Test solution (b) Mix equal volumes of test solution (a) and *water R*.

Reference solutions Prepare a 0.5 mg/mL stock solution of *bovine albumin R* in *water R*. Prepare 5 dilutions of the stock solution containing between 5 µg/mL and 50 µg/mL of *bovine albumin R*.

Add 2.5 mL of freshly prepared *cupri-tartaric solution R3* to test-tubes containing respectively 2.5 mL of *water R* (blank), 2.5 mL of test solution (a), 2.5 mL of test solution (b), as well as to test-tubes containing 2.5 mL of each dilution in the series of reference solutions prepared as described above. Mix after each addition. After about 10 min, add to each test-tube 0.50 mL of a mixture of equal volumes of *phosphomolybdotungstic reagent R* and *water R* prepared immediately before use. Mix after each addition. After 30 min, measure the absorbance (*2.2.25*) of each solution at 750 nm against the blank. From the calibration curve obtained with the 5 reference solutions determine the content of protein in test solutions (a) and (b).

Chlorides (*2.4.4*)

Maximum 0.5 per cent.

Dissolve 67 mg in 100 mL of *water R*.

Iron

Maximum 80 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dissolve a quantity of the substance to be examined equivalent to 0.25 g of the dried substance in 1 mL of *nitric acid R* by heating on a water-bath. Cool and dilute to 10.0 mL with *water R*.

Reference solutions Prepare 2 reference solutions in the same manner as the test solution, adding 1.0 mL and 2.0 mL respectively of *iron standard solution (10 ppm Fe) R* to the dissolved substance to be examined.

Source Iron hollow-cathode lamp using a transmission band of 0.2 nm.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 20.0 per cent, determined on 0.500 g by drying at 100-110 °C over *diphosphorus pentoxide R* for 6 h.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*). Use 1 g of the substance to be examined.

Bacterial endotoxins (*2.6.14*)

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Less than 0.5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins; less than 0.05 IU/mg, if intended for use in the manufacture of intra-ocular preparations or intra-articular preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Determine the glucuronic acid content by reaction with carbazole as described below.

Reagent A Dissolve 0.95 g of *disodium tetraborate R* in 100.0 mL of *sulfuric acid R*.

Reagent B Dissolve 0.125 g of *carbazole R* in 100.0 mL of *anhydrous ethanol R*.

Test solution Prepare this solution in triplicate. Dissolve 0.170 g of the substance to be examined in *water R* and dilute to 100.0 g with the same solvent. Dilute 10.0 g of this solution to 200.0 g with *water R*.

Reference stock solution Dissolve 0.100 g of *D-glucuronic acid R*, previously dried to constant mass in vacuum over *diphosphorus pentoxide R* (2.2.32), in *water R* and dilute to 100.0 g with the same solvent.

Reference solutions Prepare 5 dilutions of the reference stock solution containing between 6.5 µg/g and 65 µg/g of *D-glucuronic acid R*.

Place 25 test-tubes, numbered 1 to 25, in iced water. Add 1.0 mL of the 5 reference solutions in triplicate to the test-tubes 1 to 15 (reference tubes), 1.0 mL of the 3 test solutions in triplicate to the test-tubes 16 to 24 (sample tubes), and 1.0 mL of *water R* to test-tube 25 (blank). Add to each test-tube 5.0 mL of freshly prepared reagent A, previously cooled in iced water. Tightly close the test-tubes with plastic caps, shake the contents, and place on a water bath for exactly 15 min. Cool in iced water, and add to each test tube 0.20 mL of reagent B. Recap the tubes, shake, and put them again on a water-bath for exactly 15 min. Cool to room temperature and measure the absorbance (2.2.25) of the solutions at 530 nm, against the blank.

From the calibration curve obtained with the mean absorbances read for each reference solution, determine the mean concentrations of D-glucuronic acid in the test solutions.

Calculate the percentage content of sodium hyaluronate using the following expression:

$$\frac{c_g}{c_s} \times Z \times \frac{100}{100 - h} \times \frac{401.3}{194.1}$$

c_g	=	mean of concentrations of D-glucuronic acid in the test solutions, in milligrams per gram;
c_s	=	mean of concentrations of the substance to be examined in the test solutions, in milligrams per gram;
Z	=	determined percentage content of $C_6H_{10}O_7$ in *D-glucuronic acid R*;
h	=	percentage loss on drying;
401.3	=	relative molecular mass of the disaccharide fragment;
194.1	=	relative molecular mass of glucuronic acid.

STORAGE

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In an airtight container, protected from light and humidity. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states:

— the intrinsic viscosity;

— the origin of the substance;

— the intended use of the substance;

— where applicable, that the substance is suitable for parenteral administration other than intra-articular administration;

— where applicable, that the substance is suitable for parenteral administration, including intra-articular administration;

— where applicable that the material is suitable for intra-ocular use.

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Sodium Hydroxide

General Notices

Caustic Soda

(Ph. Eur. monograph 0677)

NaOH 40.00 *1310-73-2*

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DEFINITION

Content

97.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline masses, supplied as pellets, sticks or slabs, deliquescent, readily absorbing carbon dioxide.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. pH (2.2.3): minimum 11.0.

Dissolve 0.1 g in 10 mL of *water R*. Dilute 1 mL of the solution to 100 mL with *water R*.

B. 2 mL of solution S (see Tests) gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Carry out the procedure described below with caution Dissolve 5.0 g in 12 mL of *water R*. Add 17 mL of *hydrochloric acid R1*, adjust to pH 7 with a 103 g/L solution of *hydrochloric acid R* and dilute to 50 mL with *water R*.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

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Dissolve 1.0 g in 10 mL of *water R*.

Carbonates

Maximum 2.0 per cent, calculated as Na_2CO_3 as determined in the assay.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dissolve 0.25 g in 5 mL of *water R*, acidify the solution with about 4 mL of *nitric acid R* and dilute to 15 mL with *water R*. The solution, without addition of *dilute nitric acid R*, complies with the test.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dissolve 0.75 g in 6 mL of *distilled water R*, adjust to pH 7 with *hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

ASSAY

Dissolve 2.000 g in about 80 mL of *carbon dioxide-free water R*. Add 0.3 mL of *phenolphthalein solution R* and titrate with *1 M hydrochloric acid*. Add 0.3 mL of *methyl orange solution R* and continue the titration with *1 M hydrochloric acid*.

1 mL of *1 M hydrochloric acid* used in the 2nd part of the titration is equivalent to 0.1060 g of Na_2CO_3.

1 mL of *1 M hydrochloric acid* used in the combined titrations is equivalent to 40.00 mg of total alkali, calculated as NaOH.

STORAGE

In an airtight, non-metallic container.

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Sodium Iodide

General Notices

(Ph. Eur. monograph 0196)

NaI 149.9 *7681-82-5*

Preparation

Sodium Iodide Injection

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DEFINITION

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives the reactions of iodides (*2.3.1*).

B. Solution S gives the reactions of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

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Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Alkalinity

To 12.5 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.7 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Iodates

To 10 mL of solution S add 0.25 mL of *iodide-free starch solution R* and 0.2 mL of *dilute sulfuric acid R* and allow to stand protected from light for 2 min. No reddish-brown colour develops.

Sulfates (*2.4.13*)

Maximum 150 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Thiosulfates

To 10 mL of solution S add 0.1 mL of *starch solution R* and 0.1 mL of *0.005 M iodine*. A reddish-brown colour is produced.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.00 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 1.300 g in *water R* and dilute to 100.0 mL with the same solvent. To 20.0 mL of the solution add 40 mL of *hydrochloric acid R* and titrate with *0.05 M potassium iodate* until the colour changes from red to yellow. Add 5 mL of *chloroform R* and continue the titration, shaking vigorously, until the chloroform layer is decolorised.

1 mL of *0.05 M potassium iodate* is equivalent to 14.99 mg of NaI.

STORAGE

Protected from light.

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Sodium Iodide Injection

General Notices

DEFINITION

Sodium Iodide Injection is a sterile solution of Sodium Iodide in Water for Injections. It contains not more than 0.1% w/v of Sodium Thiosulfate or other suitable reducing agent.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sodium iodide, NaI

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. Yields the reactions characteristic of *sodium salts*, Appendix VI.

B. Yields the reactions characteristic of *iodides*, Appendix VI.

ASSAY

Dilute a volume containing 0.3 g of Sodium Iodide to 10 mL with *water*, and add 10 mL of a mixture of 0.05 mL of a 1% w/v solution of *iodine* in *ethanol* (*96%*) and 100 mL of *iodide-free starch solution*. Titrate with *0.1M silver nitrate VS* until only a pale yellow colour remains. Each mL of *0.1M silver nitrate VS* is equivalent to 14.99 mg of NaI.

STORAGE

Sodium Iodide Injection should be kept free from contact with metals.

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Sodium Lactate Infusion

General Notices

Sodium Lactate Injection; Sodium Lactate Intravenous Infusion

DEFINITION

Sodium Lactate Infusion is a sterile solution containing 1.85% w/v of sodium lactate in Water for Injections. It is prepared from Sodium Lactate Solution. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sodium lactate, $C_3H_5NaO_3$

1.75 to 1.95% w/v.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. When warmed with *potassium permanganate*, acetaldehyde is evolved.

B. The residue on evaporation, when moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, imparts a yellow colour to the flame.

C. Carry out reaction C characteristic of *calcium salts*, Appendix VI. No white precipitate is produced.

TESTS

Acidity or alkalinity

pH, 5.0 to 7.0, Appendix V L.

Bacterial endotoxins

The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute 1 volume of the infusion to 5 volumes with the mobile phase.

(2) 0.30% w/v of *lithium lactate BPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

10 volumes of a 2% v/v solution of *octylamine* in *acetonitrile*, the pH of the final mixture being adjusted to 7.0 with a 10% v/v solution of *orthophosphoric acid* and 90 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_3H_5NaO_3$ in the infusion using the declared equivalent content of $C_3H_5NaO_3$ in *lithium lactate BPCRS*.

LABELLING

The label states (1) that solutions containing visible solid particles should not be used; (2) that the Infusion is one-sixth molar and contains, in one litre, approximately 167 millimoles of sodium ions and of bicarbonate ions (as lactate).

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Sodium Lactate Solution

General Notices

(Ph. Eur. monograph 1151)

Action and use

Systemic alkalinising agent.

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DEFINITION

Solution of a mixture of the enantiomers of sodium (2*RS*)-2-hydroxypropanoate in approximately equal proportions.

Content

Minimum declared content 50 per cent *m/m* of sodium (2*RS*)-2-hydroxypropanoate ($C_3H_5NaO_3$; M_r 112.1); 96.0 per cent to 104.0 per cent of the content of sodium lactate stated on the label.

CHARACTERS

Appearance

Clear, colourless, slightly syrupy liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. To 0.1 mL add 10 mL of *water R*. 5 mL of the solution gives the reaction of lactates (2.3.1).

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dilute a quantity of the substance to be examined corresponding to 40.0 g of sodium lactate to 200 mL with *distilled water R*.

Appearance of solution

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

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pH (*2.2.3*)

6.5 to 9.0 for the substance to be examined.

Reducing sugars and sucrose

To 5 mL of the substance to be examined add 0.2 mL of *copper sulfate solution R* and 2 mL of *dilute sodium hydroxide solution R*. The solution is clear and blue and remains so on boiling. Add to the hot solution 4 mL of *hydrochloric acid R*. Boil for 1 min. Add 6 mL of *strong sodium hydroxide solution R* and heat to boiling again. The solution is clear and blue.

Methanol

Gas chromatography (*2.4.24*).

Limit:

— *methanol*: maximum 50 ppm, calculated with reference to sodium lactate, if intended for use in the manufacture of parenteral preparations, dialysis, haemodialysis or haemofiltration solutions.

Chlorides (*2.4.4*)

Maximum 50 ppm calculated with reference to sodium lactate.

Dilute 5 mL of solution S to 15 mL with *water R*.

Oxalates and phosphates

To 1 mL of the substance to be examined add 15 mL of *ethanol (96 per cent) R* and 2 mL of *calcium chloride solution R*. Heat at 75 °C for 5 min. Any opalescence in the solution is not more intense than that of a standard prepared at the same time and in the same manner using a mixture of 1 mL of the substance to be examined, 15 mL of *ethanol (96 per cent) R* and 2 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm calculated with reference to sodium lactate.

To 7.5 mL of solution S, add 1.9 mL of *hydrochloric acid R1* and dilute to 15 mL with *distilled water R*. The solution complies with the test for sulfates without addition of 0.5 mL of *acetic acid R*. Acidify the standard solution with 0.05 mL of *hydrochloric acid R1* instead of 0.5 mL of *acetic acid R*.

Aluminium

Maximum 0.1 ppm, if intended for use in the manufacture of parenteral preparations, dialysis, haemodialysis or haemofiltration solutions.

Atomic absorption spectrometry (*2.2.23, Method I*). For the preparation of the solutions, use equipment that is aluminium-free or that will not release aluminium under the conditions of use (glass, polyethylene, etc).

Modifier solution Dissolve 100.0 g of *ammonium nitrate R* in a mixture of 4 mL of *nitric acid R* and 50 mL of *water R* and dilute to 200 mL with *water R*.

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Blank solution Dilute 2.0 mL of the modifier solution to 25.0 mL with *water R*.

Test solution To 5.0 g add 2.0 mL of the modifier solution and dilute to 25.0 mL with *water R*.

Reference solutions Prepare the reference solutions immediately before use (0.010 ppm to 0.050 ppm of aluminium) using *aluminium standard solution (200 ppm Al) R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Graphite furnace.

Carrier gas *argon R*.

Conditions The device is equipped with a non-specific absorption correction system. Heat the oven to 120 °C for as many seconds as there are microlitres of solution introduced into the apparatus, then heat at 1000 °C for 30 s and finally at 2700 °C for 6 s.

Iron (*2.4.9*)

Maximum 10 ppm calculated with reference to sodium lactate.

Dilute 5 mL of solution S to 10 mL with *water R*.

ASSAY

Dissolve a quantity of the substance to be examined corresponding to 75.0 mg of sodium lactate in a mixture of 10 mL of *glacial acetic acid R* and 20 mL of *acetic anhydride R*. Allow to stand for 15 min. Add 1 mL of *naphtholbenzein solution R* and titrate with *0.1 M perchloric acid*.

1 mL of *0.1 M perchloric acid* is equivalent to 11.21 mg of $C_3H_5NaO_3$.

LABELLING

The label states:

— where applicable, that the substance is suitable for use in the manufacture of dialysis, haemodialysis and haemofiltration solutions;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations;

— the declared content of sodium lactate.

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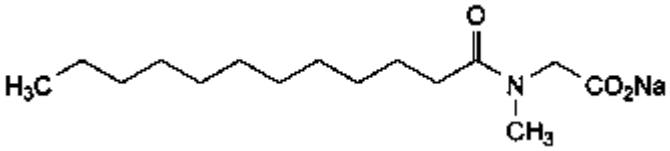
Sodium Lauroylsarcosinate for External Use

General Notices

(Ph. Eur. monograph 2542)



$C_{15}H_{28}NNaO_3$ 293.4 *137-16-6*

Action and use

Surfactant.

Ph Eur

DEFINITION

Mixture of sodium *N*-acyl-*N*-methylglycinates, mainly consisting of sodium *N*-lauroyl-*N*-methylglycinate (sodium [dodecanoyl(methyl)amino]acetate).

A suitable chelating agent (e.g. edetic acid (EDTA)) may be added.

PRODUCTION

Sodium lauroylsarcosinate is typically obtained using the reaction of lauroyl chloride with sodium sarcosinate (sodium *N*-methylglycinate) under aqueous alkaline conditions.

The production method is validated to ensure a limit of maximum 0.1 per cent of free sodium sarcosinate.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water giving a clear or slightly turbid solution, sparingly soluble in ethanol 96 per cent.

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About 145 °C.

IDENTIFICATION

A. Dissolve 0.1 g in 10 mL of *water R* and shake. Copious foam is formed.

B. Examine the chromatograms obtained in the test for composition of fatty acids.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Place 0.5 g in a silica crucible and ignite in a muffle furnace at 600 ± 25 °C for 1 h. Allow to cool to room temperature and dissolve the residue in 10 mL of *water R*. 0.5 mL of the solution obtained gives reaction (b) of sodium (*2.3.1*). Rub the inside of the tube to initiate the precipitation.

TESTS

pH (*2.2.3*)

7.5 to 8.5.

Dissolve 3.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Composition of fatty acids

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution (a) To 2.5 g in a 150 mL round-bottomed flask add 30.0 mL of *boron trifluoride-methanol solution R*, fit a reflux condenser and boil for 20 min. Add 120 mL of hot *water R* so that the upper layer is brought into the neck of the flask in order to recover the methyl esters. Dissolve 0.50 g of the methyl esters in 10.0 mL of *heptane R*.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *heptane R*.

Reference solution (a) Prepare 0.50 g of the mixture of calibrating substances with the composition described in Table 2542.-1, dissolve in *heptane R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *heptane R*. Dilute 1.0 mL of this solution to 10.0 mL with *heptane R*.

Reference solution (c) To 0.5 g of *sodium lauroylsarcosinate CRS* in a 25 mL round-bottomed flask, add 6.0 mL of *boron trifluoride-methanol solution R*, fit a reflux condenser and boil for 20 min. Add 20.0 mL of hot *water R* so that the upper layer is brought into the neck of the flask in order to recover the methyl esters. Dissolve 0.25 g of the methyl esters in 50.0 mL of *heptane R*.

Table 2542.-1. – *Mixture of calibrating substances*

Mixture of the following substances	Composition (per cent *m/m*)
Methyl caproate R	10

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Mixture of the following substances	Composition (per cent *m/m*)
Methyl caprylate R	10
Methyl decanoate R	20
Methyl laurate R	20
Methyl myristate R	40

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Split ratio 1:5.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3	100
	3 - 13	100 → 200
	13 - 19	200 → 230
	19 - 29	230
	29 - 31	230 → 250
	31 - 40	250
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peaks due to methyl caprylate, methyl decanoate, methyl laurate and methyl myristate.

System suitability:

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— *resolution*: minimum 4.0 between the peaks due to methyl caprylate and methyl decanoate in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 20 for the peak due to methyl laurate in the chromatogram obtained with reference solution (b).

Disregard any peak eluting after the peak due to methyl myristate, as well as any peak with an area less than 0.05 per cent of the total area of the peaks used for quantification.

Composition of the fatty-acid fraction of the substance Test solution (a):

— *capric acid*: maximum 0.5 per cent;

— *lauric acid*: minimum 98.0 per cent;

— *myristic acid*: maximum 1.5 per cent.

Sodium laurate

Proceed as described in the test for composition of fatty acids with the following modifications.

Internal standard *undecanoic acid R*.

Test solution To 2.5 g in a 150 mL round-bottomed flask add 0.100 g of the internal standard. Add 30.0 mL of *boron trifluoride-methanol solution R*, fit a reflux condenser and boil for 20 min. Add 120 mL of hot *water R* so that the upper layer is brought into the neck of the flask in order to recover the methyl esters. Dissolve 0.50 g of the methyl esters in 10.0 mL of *heptane R*.

Calculate the percentage content of sodium laurate using the following expression:

$$\frac{A_1 \times m_2 \times 1.110 \times 100}{A_2 \times m_1}$$

A_1	=	area of the peak due to methyl laurate in the chromatogram obtained with the test solution;
A_2	=	area of the peak due to methyl undecanoate in the chromatogram obtained with the test solution;
m_1	=	mass of the substance to be examined in the test solution, in grams;
m_2	=	mass of the internal standard in the test solution, in grams;
1.110	=	ratio of the molecular mass of sodium laurate to that of lauric acid (222/200).

Limit:

— *sodium laurate*: maximum 5.0 per cent.

Sodium chloride

Maximum 0.5 per cent.

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Dissolve 0.500 g in 50 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*. Add 10 mL of *nitric acid R* and titrate with *0.005 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

Calculate the percentage content of sodium chloride using the following expression:

$$\frac{M \times V \times 58.44}{m \times 10}$$

M	=	molarity of the silver nitrate solution, in moles per litre;
V	=	volume of *0.005 M silver nitrate* used, in mL;
m	=	mass of the substance to be examined, in grams.

Sodium sulfate

Maximum 1.5 per cent.

Test solution In a 150 mL borosilicate-glass beaker, dissolve 0.3 g in 20 mL of *deionised distilled water R*. Add 0.3 mL of *naphtharson solution R1*, 1.0 mL of *perchloric acid R* and 70.0 mL of *2-propanol R*.

Degas the solution obtained under vacuum for 30 s or using an ultrasonic bath for 2 min, then titrate with 0.005 M barium perchlorate.

Determine the end-point using a suitable autotitrator equipped with a photometric sensor at 523 nm and at 25 °C. Adjust the stirrer speed to avoid the formation of bubbles.

1 mL of 0.005 M barium perchlorate is equivalent to 0.7102 mg of Na_2SO_4.

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Sodium Lauryl Sulfate[1]

General Notices

Sodium Dodecyl Sulfate

Sodium Lauryl Sulphate

(Sodium Laurilsulfate, Ph. Eur. monograph 0098)

Sodium dodecyl sulfate *151-21-3*

Action and use

Anionic emulsifying agent.

Ph Eur

DEFINITION

Mixture of sodium alkyl sulfates consisting mainly of sodium dodecyl sulfate ($C_{12}H_{25}NaO_4S$; M_r 288.4).

Content

— *sodium alkyl sulfates*: minimum 85.0 per cent, expressed as $C_{12}H_{25}NaO_4S$.

♦ CHARACTERS

Appearance

White or pale yellow, powder or crystals.

Solubility

Freely soluble in water giving an opalescent solution, partly soluble in ethanol (96 per cent).♦

IDENTIFICATION

First identification: A, B, C.

◊ *Second identification: B, C, D.*◊

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sodium laurilsulfate CRS*.

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B. Place 2.5 g in a silica or platinum crucible and add 2 mL of a 500 g/L solution of *sulfuric acid R*. Heat on a water-bath, then cautiously raise the temperature progressively over an open flame. Ignite, preferably in a muffle furnace, at 600 ± 25 °C. Continue heating until all black particles have disappeared. Cool, add a few drops of a 100 g/L solution of *sulfuric acid R*, and heat and ignite as above. Add a few drops of *ammonium carbonate solution R1*, evaporate to dryness, and ignite as above. Cool, dissolve the residue in 50 mL of *water R* and mix. To 2 mL of this solution add 4 mL of *potassium pyroantimonate solution R1*. If necessary, rub the inside of the test-tube with a glass rod. A white, crystalline precipitate is formed.

C. Prepare a 100 g/L solution. After acidification with *hydrochloric acid R* and boiling for 20 min, no precipitate is formed. Add a 120 g/L solution of *barium chloride R*; a white precipitate is produced.

◊ D. Dissolve 0.1 g in 10 mL of *water R* and shake. A copious foam is formed.◊

TESTS

Alkalinity

Dissolve 1.0 g in 100 mL of *carbon dioxide-free water R* and add 0.1 mL of *phenol red solution R*. Not more than 0.5 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Non-esterified alcohols

Maximum 4.0 per cent.

Dissolve 10.0 g in 100 mL of *water R*, add 100 mL of *ethanol (96 per cent) R* and shake the solution with 3 quantities, each of 50 mL, of *light petroleum R*, adding *sodium chloride R*, if necessary, to promote separation of the 2 layers. Wash the combined organic layers with 3 quantities, each of 50 mL, of *water R*, dry over *anhydrous sodium sulfate R*, filter and evaporate on a water-bath until the solvent has evaporated. Heat the residue at 105 °C for 30 min and cool. The residue weighs a maximum of 0.4 g.

Sodium chloride and sodium sulfate

Maximum 8.0 per cent for the total percentage content.

Sodium chloride Dissolve 5.00 g in 50 mL of *water R*, add *dilute nitric acid R* dropwise, if necessary, until the solution is neutral, and add 5.0 mL of a 5.84 g/L solution of *sodium chloride R*. Titrate with *0.1 M silver nitrate*, while stirring vigorously to disperse the silver chloride, using 0.1 mL of a 2 g/L solution of *sodium fluoresceinate R* as indicator, to the first appearance of turbidity with solution colour change from yellow-green to orange through yellow. Perform a blank determination.

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Sodium sulfate Dissolve 1.00 g in 10 mL of *water R*, add 100 mL of *ethanol (96 per cent) R* and heat at a temperature just below the boiling point for 2 h. Filter while hot through a glass or porcelain filter with a porosity of 4-10 µm and wash with 100 mL of boiling *ethanol (96 per cent) R*. Dissolve the precipitate by washing with 150 mL of *water R*, collecting the washings in a beaker. Add 10 mL of *dilute hydrochloric acid R*, heat to boiling, add 25 mL of a 120 g/L solution of *barium chloride R* and allow to stand overnight. Collect the precipitate by filtration (maximum pore size 16 µm) and wash with *water R* until the last washing shows no opalescence with *0.1 M silver nitrate*. Dry the precipitate, ignite to constant mass at 500-600 °C by raising the temperature gradually, and weigh as barium sulfate.

1 mg of barium sulfate is equivalent to 0.609 mg of Na_2SO_4.

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ASSAY

Dissolve 1.15 g in *water R*, warming if necessary, and dilute to 1000.0 mL with the same solvent. To 20.0 mL of the solution add 15 mL of *methylene chloride R* and 10 mL of *dimidium bromide-sulfan blue mixed solution R* and mix. Titrate with *0.004 M benzethonium chloride*, shaking vigorously and allowing the layers to separate before each addition, until the pink colour of the methylene chloride layer is completely discharged and a greyish-blue colour is obtained.

1 mL of *0.004 M benzethonium chloride* is equivalent to 1.154 mg of sodium alkyl sulfates, expressed as $C_{12}H_{25}NaO_4S$.

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Sodium Metabisulfite

General Notices

Sodium Metabisulphite

Sodium Pyrosulphite

(Ph. Eur. monograph 0849)

$Na_2S_2O_5$ 190.1 *7681-57-4*

Action and use

Antioxidant.

Ph Eur

DEFINITION

Sodium metabisulfite also called sodium disulfite.

Content

95.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. pH (see Tests).

B. To 0.4 mL of *iodinated potassium iodide solution R* add 8 mL of *distilled water R* and 1 mL of solution S diluted 1 to 10 in *distilled water R*. The solution is colourless and gives reaction (a) of sulfates (*2.3.1*).

C. Solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

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Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

3.5 to 5.0 for solution S.

Thiosulfates

To 5 mL of solution S add 5 mL of *dilute hydrochloric acid R*. The solution remains clear (*2.2.1*) for at least 15 min.

Iron (*2.4.9*)

Maximum 20 ppm, determined on solution S.

ASSAY

Dissolve 0.200 g in 50.0 mL of *0.05 M iodine* and add 5 mL of *dilute hydrochloric acid R*. Titrate the excess of iodine with *0.1 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator.

1 mL of *0.05 M iodine* is equivalent to 4.753 mg of $Na_2S_2O_5$.

STORAGE

Protected from light.

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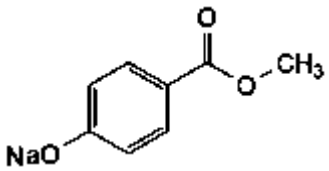
Sodium Methyl Hydroxybenzoate

General Notices

Sodium Methylparaben

(Sodium Methyl Parahydroxybenzoate, Ph. Eur. monograph 1262)



$C_8H_7NaO_3$ 174.1 *5026-62-0*

Action and use

Antimicrobial preservative.

Ph Eur

DEFINITION

Sodium 4-(methoxycarbonyl)phenolate.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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A. Dissolve 0.5 g in 50 mL of *water R*. Immediately add 5 mL of *hydrochloric acid R1*. Filter and wash the precipitate with *water R*. Dry *in vacuo* at 80 °C for 2 h. The precipitate melts (*2.2.14*) at 125 °C to 128 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Precipitate obtained in identification test A.

Comparison *methyl parahydroxybenzoate CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution (a) Dissolve 0.10 g of the substance to be examined in 10 mL of *water R*. Immediately add 2 mL of *hydrochloric acid R* and shake with 50 mL of *1,1-dimethylethyl methyl ether R*. Evaporate the upper layer to dryness and take up the residue with 10 mL of *acetone R*.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *acetone R*.

Reference solution (a) Dissolve 10 mg of *methyl parahydroxybenzoate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *ethyl parahydroxybenzoate CRS* in 1 mL of test solution (a) and dilute to 10 mL with *acetone R*.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R* (1:30:70 *V/V/V*).

Application 5 µL of test solution (b) and reference solutions (a) and (b).

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To 1 mL of solution S (see Tests) add 1 mL of *water R*. The solution gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

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Solution S examined immediately after preparation is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

pH (2.2.3)

Dilute 1 mL of solution S to 100 mL with carbon dioxide-free water R. The pH of the solution is 9.5 to 10.5.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of 4-hydroxybenzoic acid R (impurity A) and 5 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50.0 mg of methyl parahydroxybenzoate CRS in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase 6.8 g/L solution of potassium dihydrogen phosphate R, methanol R (35:65 *V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 5 times the retention time of methyl parahydroxybenzoate.

Relative retention With reference to methyl parahydroxybenzoate (retention time = about 2.3 min): impurity A = about 0.6.

System suitability Reference solution (a):

— resolution: minimum 2.0 between the peaks due to impurity A and methyl parahydroxybenzoate.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

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— *impurity A*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Chlorides (2.4.4)

Maximum 350 ppm.

To 10 mL of solution S, add 30 mL of *water R* and 1 mL of *nitric acid R* and dilute to 50 mL with *water R*. Shake and filter. Dilute 10 mL of the filtrate to 15 mL with *water R*. Prepare the standard using 14 mL of *chloride standard solution (5 ppm Cl) R* to which 1 mL of *water R* has been added.

Sulfates (2.4.13)

Maximum 300 ppm.

To 25 mL of solution S, add 5 mL of *distilled water R* and 10 mL of *hydrochloric acid R* and dilute to 50 mL with *distilled water R*. Shake and filter. Dilute 10 mL of the filtrate to 15 mL with *distilled water R*.

Water (2.5.12)

Maximum 5.0 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_8H_7NaO_3$ using the declared content of *methyl parahydroxybenzoate CRS* and multiplying by a correction factor of 1.145.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A.*

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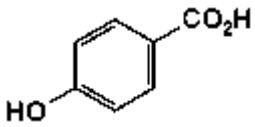
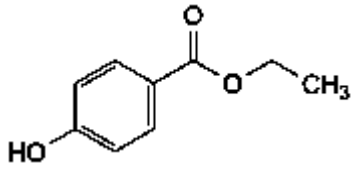
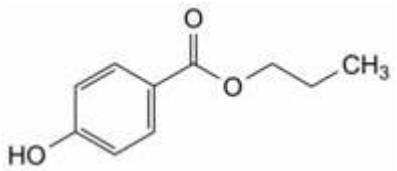
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D.*



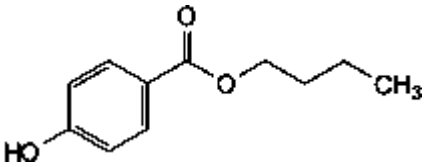
A. 4-hydroxybenzoic acid,



B. ethyl 4-hydroxybenzoate (ethyl parahydroxybenzoate),



C. propyl 4-hydroxybenzoate (propyl parahydroxybenzoate),



D. butyl 4-hydroxybenzoate (butyl parahydroxybenzoate).

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Sodium Molybdate Dihydrate

General Notices

(Ph. Eur. monograph 1565)

$MoNa_2O_4,2H_2O$ 241.9 *10102-40-6*

Ph Eur

DEFINITION

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals.

Solubility

Freely soluble in water.

IDENTIFICATION

A. Loss on drying (see Tests).

B. Dissolve 0.2 g in 5 mL of a mixture of equal volumes of *nitric acid R* and *water R* and add 0.1 g of *ammonium chloride R*. Add 0.3 mL of *disodium hydrogen phosphate solution R* and heat slowly at 50-60 °C. A yellow precipitate is formed.

C. Dissolve 0.15 g in 2 mL of *water R*. The solution gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Chlorides

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Maximum 50 ppm.

To 10 mL of a mixture of equal volumes of *nitric acid R* and *water R* add 10 mL of solution S with shaking. Add 1 mL of *0.1 M silver nitrate*. Any opalescence in the solution is not more intense after 5 min than that of a standard solution prepared at the same time in the same manner with 10 mL of *chloride standard solution (5 ppm Cl) R*.

Phosphates

Maximum 200 ppm.

Dissolve 2.0 g by heating in 13 mL of *water R*. In the still-hot solution, dissolve 8.0 g of *ammonium nitrate R1*. Add this solution to 27 mL of a mixture of equal volumes of *nitric acid R* and *water R*. Any yellow colour or opalescence in the solution is not more intense within 3 h than that in a standard solution prepared at the same time in the same manner as follows: dissolve 1.0 g in 12 mL of *water R* and add 1 mL of *phosphate standard solution (200 ppm PO_4) R*.

Ammonium (*2.4.1, Method B*)

Maximum 10 ppm, determined on 0.10 g.

Prepare the standard using 1 mL of *ammonium standard solution (1 ppm NH_4) R*.

Loss on drying (*2.2.32*)

14.0 per cent to 16.0 per cent, determined on 1.000 g by drying in an oven at 140 °C for 3 h.

ASSAY

Dissolve 0.100 g in 30 mL of *water R*, add 0.5 g of *hexamethylenetetramine R* and 0.1 mL of a 250 g/L solution of *nitric acid R*. Heat to 60 °C. Titrate with *0.05 M lead nitrate* using *4-(2-pyridylazo)resorcinol monosodium salt R* as indicator.

1 mL of *0.05 M lead nitrate* is equivalent to 10.30 mg of $MoNa_2O_4$.

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Sodium Nitrite

General Notices

(Ph. Eur. monograph 1996)

$NaNO_2$ 69.0 *7632-00-0*

Action and use

Used in treatment of cyanide poisoning.

Ph Eur

DEFINITION

Content

98.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

Colourless crystals or mass or yellowish rods, hygroscopic.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dilute 1 mL of solution S1 (see Tests) to 25 mL with *water R*. To 0.1 mL of the solution add 1 mL of *sulfanilic acid solution R1*. Allow to stand for 2-3 min. Add 1 mL of *β-naphthol solution R* and 1 mL of *dilute sodium hydroxide solution R*. An intense red colour develops.

B. To 1 mL of the solution prepared for identification test A add 3 mL of a 20 g/L solution of *phenazone R* and 0.4 mL of *dilute sulfuric acid R*. An intense green colour develops.

C. To 0.15 mL of solution S1, add 0.35 mL of *water R*. The solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Solution S1

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Solution S2

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Dissolve 3 g in *distilled water R*. Cautiously add 10 mL of *nitric acid R* and evaporate to dryness. Dissolve the residue in 10 mL of *distilled water R*, neutralise with *dilute sodium hydroxide solution R* and dilute to 30 mL with *distilled water R*.

Appearance of solution

Solution S1 is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S1, add 0.05 mL of *phenol red solution R*. Add 0.1 mL of *0.01 M sodium hydroxide*. The solution is red. Add 0.3 mL of *0.01 M hydrochloric acid*. The solution is yellow.

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dilute 10 mL of solution S2 to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 7.5 mL of solution S2 to 15 mL with *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo*.

ASSAY

Dissolve 0.400 g in 100.0 mL of *water R*. Introduce 20.0 mL of the solution, while stirring continuously and keeping the tip of the pipette below the surface of the liquid, into a conical flask containing 30.0 mL of *0.1 M cerium sulfate*. Immediately stopper the flask and allow to stand for 2 min. Add 10 mL of a 200 g/L solution of *potassium iodide R* and 2 mL of *starch solution R*.

While stirring continuously, titrate with *0.1 M sodium thiosulfate* until the blue colour disappears. Carry out a blank titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 3.45 mg of $NaNO_2$.

STORAGE

In an airtight container.

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Sodium Nitroprusside

General Notices

(Ph. Eur. monograph 0565)

$Na_2[Fe(CN)_5(NO)],2H_2O$ 298.0 *13755-38-9*

Action and use

Vasodilator.

Preparation

Sodium Nitroprusside Infusion

Ph Eur

DEFINITION

Sodium pentacyanonitrosylferrate (III) dihydrate.

Content

99.0 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance

Reddish-brown powder or crystals.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution Dissolve 0.700 g in *water R* and dilute to 100.0 mL with the same solvent. Examine the solution immediately after preparation.

Spectral range 350-600 nm.

Absorption maximum At 395 nm.

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Shoulder At about 510 nm.

Absorption minimum At 370 nm.

Specific absorbance at the absorption maximum 0.65 to 0.80.

B. Dissolve about 20 mg in 2 mL of *water R* and add 0.1 mL of *sodium sulfide solution R*. A deep violet-red colour is produced.

C. Dissolve 50 mg in 1 mL of *water R* and acidify the solution by the addition of *hydrochloric acid R*. Place a drop of the solution in an oxidising flame. A persistent yellow colour is produced.

TESTS

Insoluble matter

Maximum 100 ppm.

Dissolve 10 g without heating in 50 mL of *water R*. Allow to stand for 30 min and filter through a sintered-glass filter (16) (*2.1.2*). Wash the filter with cold *water R* until the filtrate is colourless. Dry the residue on the filter at 105 °C. The residue weighs a maximum of 1 mg.

Chlorides (*2.4.4*)

Maximum 200 ppm.

In a metallic crucible (nickel) mix 1.0 g with 8 mL of a 200 g/L solution of *sodium hydroxide R*. Heat slowly and evaporate carefully to dryness over a small flame, then heat to a dull red colour for 30 min. Allow to cool and transfer the solid residue with 3 quantities, each of 8 mL, of *dilute sulfuric acid R*. Filter the sulfuric acid extracts on a filter paper and collect the filtrates. Render the filtrate acid to *blue litmus paper R* by adding, if necessary, a few drops of *dilute sulfuric acid R*. Wash the crucible and the filter paper with 3 quantities, each of 10 mL, of *water R*, add the washings to the main sulfuric acid solution and dilute to 60 mL with *water R*. Mix.

Ferricyanides

Maximum 200 ppm.

Dissolve 1.25 g in *acetate buffer solution pH 4.6 R* and dilute to 50.0 mL with the same buffer solution. Use three 50 mL volumetric flasks (*A, B, C*). To flask *B* add 1.0 mL of *ferricyanide standard solution (50 ppm $Fe(CN)_6$) R*. To flasks *A* and *B* add 1 mL of a 5 g/L solution of *ferrous ammonium sulfate R*. To the 3 flasks add 10.0 mL of the solution of the substance to be examined. Dilute the contents of each flask to 50.0 mL with *water R*. Allow to stand for 30 min. The absorbance (*2.2.25*) of the solution in flask *A* measured at 720 nm using the solution in flask *C* as the compensation liquid is not greater than the absorbance of the solution in flask *B* measured at 720 nm using the solution in flask *A* as the compensation liquid.

Ferrocyanides

Maximum 200 ppm.

Dissolve 4.0 g in *water R* and dilute to 100.0 mL with the same solvent. Use three 50 mL volumetric flasks (*A*, *B*, *C*). To flask *B* add 2.0 mL of *ferrocyanide standard solution (100 ppm $Fe(CN)_6$) R*. To flasks *A* and *B* add 1 mL of *ferric chloride solution R2*. To the 3 flasks add

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25.0 mL of the solution of the substance to be examined. Dilute the contents of each flask to 50.0 mL with *water R*. Allow to stand for 30 min. The absorbance (*2.2.25*) of the solution in flask *A* measured at 695 nm using the solution in flask *C* as the compensation liquid is not greater than the absorbance of the solution in flask *B* measured at 695 nm using the solution in flask *A* as the compensation liquid.

Sulfates

Maximum 100 ppm.

Test solution Dissolve 3.6 g in 120 mL of *distilled water R*, add with mixing 4 mL of *sulfate standard solution (10 ppm SO_4) R* and 20 mL of a 250 g/L solution of *cupric chloride R* and dilute to 150.0 mL with *distilled water R*. Allow to stand for 16 h and filter or centrifuge until a clear light-blue solution is obtained.

Reference solution To 40 mL of *sulfate standard solution (10 ppm SO_4) R* add 80 mL of *distilled water R* and 12-13 mL of a 250 g/L solution of *cupric chloride R*. Dilute to 150.0 mL with *distilled water R*. The volume of cupric chloride solution added is such that the colour of the final solution matches that of the test solution.

Allow the solutions to stand. Filter both solutions, discarding the first 25 mL of filtrate. To 100 mL of each filtrate, add 0.5 mL of *acetic acid R*. Mix and add 2 mL of a 250 g/L solution of *barium chloride R* and mix again. The test solution is not more opalescent than the reference solution.

Water (*2.5.12*)

9.0 per cent to 15.0 per cent, determined on 0.250 g.

ASSAY

Dissolve 0.250 g in 100 mL of *water R* and add 0.1 mL of *dilute sulfuric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 13.10 mg of $Na_2[Fe(CN)_5(NO)]$.

STORAGE

Protected from light.

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Sodium Nitroprusside Infusion

General Notices

Sodium Nitroprusside Intravenous Infusion

DEFINITION

Sodium Nitroprusside Infusion is a sterile solution containing Sodium Nitroprusside in Glucose Infusion containing 50 g of Glucose per litre. It is prepared by dissolving Sodium Nitroprusside for Injection in the requisite amount of Glucose Infusion (50 g per litre) and diluting the resulting solution with 250 to 500 times its volume of Glucose Infusion (50 g per litre).

The infusion complies with the requirements stated under Parenteral Preparations.

STORAGE

Sodium Nitroprusside Infusion should be used immediately after preparation.

SODIUM NITROPRUSSIDE FOR INJECTION

DEFINITION

Sodium Nitroprusside for Injection is a sterile material obtained from a solution of Sodium Nitroprusside by freeze drying. It is supplied in a sealed container and may contain excipients.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of sodium nitroprusside

The equivalent of 90.0 to 110.0% of the stated amount of sodium nitroprusside dihydrate, $Na_2Fe(CN)_5NO,2H_2O$.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 350 to 600 nm of a 1.6% w/v solution exhibits a maximum only at 395 nm. The *absorbance* at 395 nm is about 1.1.

B. Dissolve 20 mg in 2 mL of *water* and add 0.1 mL of *sodium sulfide solution*. A deep purple colour is produced.

C. Yields the reactions characteristic of *sodium salts*, Appendix VI.

Uniformity of content

Sealed containers containing the equivalent of 50 mg or less of sodium nitroprusside dihydrate comply with the requirements stated under Parenteral Preparations, Powders for Injections or Infusions. Use the individual results obtained in the Assay.

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) Dissolve the contents of a sealed container in 5 mL of *water* and dilute the resulting solution with *water* to produce a solution containing the equivalent of 0.15% w/v of sodium nitroprusside dihydrate.

(2) 0.15% w/v of *sodium nitroprusside BPCRS* in *water*.

(3) 0.015% w/v of *sodium nitroprusside BPCRS* and 0.015% w/v of *potassium hexacyanoferrate*(III) in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *phenyl silica gel for chromatography* (10 µm) (µBondapak phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

6 volumes of *methanol* and 9 volumes of a solution containing 0.34% w/v of *tetrabutylammonium hydrogen sulfate* and 0.284% w/v of *anhydrous disodium hydrogen orthophosphate* adjusted to pH 6.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to ferricyanide and nitroprusside is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $Na_2Fe(CN)_5NO,2H_2O$ in the sealed container using the declared content of $Na_2Fe(CN)_5NO,2H_2O$ in *sodium nitroprusside BPCRS*.

Repeat the procedure with a further nine sealed containers and calculate the average content of $Na_2Fe(CN)_5NO,2H_2O$ from the individual results thus obtained.

LABELLING

The label states (1) the content of Sodium Nitroprusside in terms of the equivalent of sodium nitroprusside dihydrate contained in it; (2) that the contents of the sealed container should be dissolved in, and immediately diluted with, the stated volume of Glucose Infusion (50 g per litre); (3) that Sodium Nitroprusside Infusion must be used immediately after preparation; (4) that highly coloured solutions must not be used; (5) that the diluted solution must be protected from light during infusion.

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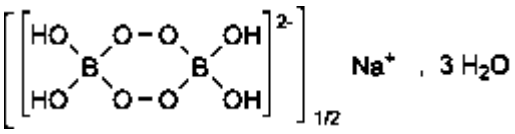
Sodium Perborate

General Notices

(Hydrated Sodium Perborate, Ph. Eur. monograph 1997)



$NaBO_3,4H_2O$ or $NaBO_2,H_2O_2,3H_2O$ 153.9

Action and use

Antiseptic.

Ph Eur

DEFINITION

Content

96.0 per cent to 103.0 per cent.

CHARACTERS

Appearance

Colourless, prismatic crystals or white or almost white powder, stable in the crystalline form.

Solubility

Sparingly soluble in water, with slow decomposition. It dissolves in dilute mineral acids.

IDENTIFICATION

A. Dissolve 20 mg in a mixture of 1 mL of *dilute sulfuric acid R* and 1 mL of *water R*. Add 1 mL of *potassium iodide solution R*. A reddish-brown colour appears.

B. The mixture obtained by treating about 100 mg with 0.1 mL of *sulfuric acid R* and 5 mL of *methanol R* burns with a greenish flame when ignited.

C. It gives reaction (a) of sodium (*2.3.1*).

TESTS

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Chlorides (*2.4.4*)

Maximum 330 ppm.

Dissolve 0.15 g in 15 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 1.2 per cent.

Dissolve 0.13 g in 150 mL of *distilled water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

Dissolve 2.5 g in 10 mL of *dilute hydrochloric acid R* with heating, evaporate to dryness, with stirring, and dissolve the residue in 25 mL of hot *water R*. Dilute 5 mL of the obtained solution to 10 mL with *water R*.

ASSAY

Dissolve 0.300 g in 50.0 mL of *water R*. Dilute 10.0 mL of the solution to 50 mL with *water R* and add 10 mL of *dilute sulfuric acid R*. Titrate with *0.02 M potassium permanganate*.

1 mL of *0.02 M potassium permanganate* is equivalent to 7.693 mg of NaH_8BO_7.

STORAGE

In an airtight container.

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Sodium Pertechnetate (^{99m}Tc) Injection (accelerator-produced)

General Notices

(Ph. Eur. monograph 2891)

Ph Eur

DEFINITION

Sterile solution containing technetium-99m in the form of pertechnetate ion prepared by proton irradiation of highly enriched molybdenum-100, made isotonic by the addition of sodium chloride.

Technetium-99m 90 per cent to 110 per cent of the declared technetium-99m radioactivity at the date and time stated on the label.

CHARACTERS

Appearance

Clear, colourless solution.

Half-life and nature of radiation of technetium-99m

See general chapter *5.7*. *Table of physical characteristics of radionuclides*.

IDENTIFICATION

A. Gamma-ray spectrometry.

Result The most prominent gamma photons of technetium-99m have an energy of 0.141 MeV.

B. Examine the chromatogram obtained in the test for radiochemical purity (see Tests).

Result The retardation factor of the principal peak in the radiochromatogram obtained with the test solution is about 0.7.

TESTS

pH (*2.2.4*)

4.0 to 8.0.

Aluminium

Maximum 5 ppm.

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Determine the content of aluminium using an *aluminium test strip R*, *aluminium standard solution (5 ppm Al) R* and following the instructions given by the test strip manufacturer.

Sterility

It complies with the test for sterility prescribed in the monograph *Radiopharmaceutical preparations (0125)*. The preparation may be released for use before completion of the test.

RADIONUCLIDIC PURITY

The preparation may be released for use before completion of the test for long-lived radionuclidic impurities.

Short-lived impurities

Gamma-ray spectrometry.

Take a volume of the preparation to be examined equivalent to 40–100 MBq and record the gamma and X-ray spectrum using a high purity germanium detector with a 6 mm thick lead shield interposed between the sample and the detector.

Limits:

— *Impurity A*: maximum 0.005 per cent of the total radioactivity.

Identification of impurity A The most prominent gamma photons have energies of 0.181 MeV and 0.740 MeV; use the most prominent gamma line at 0.740 MeV for the radioactivity calculation; molybdenum-99 has a half-life of 65.94 h.

— *Impurity B*: maximum 0.005 per cent of the total radioactivity.

Identification of impurity B The most prominent gamma photons have energies of 0.460 MeV, 0.569 MeV, 0.778 MeV and 1.091 MeV; use the gamma line at 0.569 MeV for the radioactivity calculation; niobium-96 has a half-life of 23.35 h.

— *Impurity C*: maximum 0.005 per cent of the total radioactivity.

Identification of impurity C The most prominent gamma photons have an energy of 0.658 MeV; use this gamma line for the radioactivity calculation; niobium-97 has a half-life of 72.1 min.

— *Impurity D*: maximum 0.01 per cent of the total radioactivity.

Identification of impurity D The most prominent gamma photons have an energy of 0.392 MeV; use this gamma line for the radioactivity calculation; technetium-93m has a half-life of 43.5 min.

— *Impurity E*: maximum 0.04 per cent of the total radioactivity.

Identification of impurity E The most prominent gamma photons have energies of 1.363 MeV and 1.520 MeV; use the gamma line at 1.363 MeV for the radioactivity calculation; technetium-93 has a half-life of 2.75 h.

— *Impurity F*: maximum 0.02 per cent of the total radioactivity.

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Identification of impurity F The most prominent gamma photons have energies of 0.871 MeV and 1.869 MeV; use the gamma line at 1.869 MeV for the radioactivity calculation; technetium-94m has a half-life of 52 min.

— *Impurity G*: maximum 0.04 per cent of the total radioactivity.

Identification of impurity G The most prominent gamma photons have energies of 0.703 MeV, 0.850 MeV and 0.871 MeV; use the gamma line at 0.703 MeV for the radioactivity calculation; technetium-94 has a half-life of 4.883 h.

— *Impurity H*: maximum 0.07 per cent of the total radioactivity.

Identification of impurity H The most prominent gamma photons have an energy of 0.766 MeV; use this gamma line for the radioactivity calculation; technetium-95 has a half-life of 20.0 h.

— *Impurity I*: maximum 0.07 per cent of the total radioactivity.

Identification of impurity I The most prominent gamma photons have energies of 0.778 MeV, 0.813 MeV and 0.850 MeV; use the gamma line at 0.813 MeV for the radioactivity calculation; technetium-96 has a half-life of 4.28 days.

Long-lived impurities

Gamma-ray spectrometry.

Retain the sample used for determining short-lived impurities for a sufficient time (> 132 h) allowing for detection of radionuclidic impurities without lead shielding. Record its gamma and X-ray spectrum using a high purity germanium detector.

Limits:

— *Impurity J*: maximum 0.005 per cent of the total radioactivity.

Identification of impurity J The most prominent gamma photons have energies of 0.204 MeV, 0.582 MeV and 0.835 MeV; use the gamma line at 0.204 MeV for the radioactivity calculation; technetium-95m has a half-life of 61 days.

— *Impurity K*: maximum 0.01 per cent of the total radioactivity.

Identification of impurity K The most prominent gamma photons have an energy of 0.097 MeV; use this gamma line for the radioactivity calculation; technetium-97m has a half-life of 91.0 days.

— *Other gamma-ray emitting impurities*: maximum 0.02 per cent of the total radioactivity.

Examine the gamma-ray spectrum of the shielded and that of the decayed sample for the presence of other radionuclidic impurities. Identify and quantify these impurities.

NOTE: impurities A and I may also be identified and quantified in the decayed sample.

RADIOCHEMICAL PURITY

[^{99m}Tc]Pertechnetate ion

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Ascending paper chromatography (2.2.26).

Test solution Dilute the preparation to be examined with *water R* to a suitable radioactivity concentration.

Paper *paper for chromatography R*.

Mobile phase A 9 g/L solution of *sodium chloride R* in *water R*.

Application 1-2 µL.

Development Over a path of 7 cm.

Drying In air.

Detection Suitable detector to determine the distribution of radioactivity.

Retardation factors [^{99m}Tc]pertechnetate ion = about 0.7; impurity L = about 0.

Limit:

— *[^{99m}Tc]pertechnetate ion*: minimum 95 per cent of the total radioactivity due to technetium-99m.

RADIOACTIVITY

Determine the radioactivity using a calibrated instrument.

IMPURITIES

A. molybdenum-99,
B. niobium-96,
C. niobium-97,
D. technetium-93m,
E. technetium-93,
F. technetium-94m,
G. technetium-94,
H. technetium-95,
I. technetium-96,
J. technetium-95m,
K. technetium-97m,
L. technetium-99m in colloidal form.

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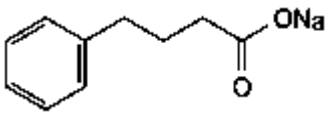
Sodium Phenylbutyrate

General Notices

(Ph. Eur. monograph 2183)



$C_{10}H_{11}NaO_2$ 186.2 *1716-12-7*

Action and use

Glutamine conjugate; treatment of hyperammonaemia.

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DEFINITION

Sodium 4-phenylbutanoate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sodium phenylbutyrate CRS*.

B. Dissolve 0.15 g in 2 mL of *water R*. The solution gives reaction (a) of sodium (*2.3.1*).

TESTS

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pH (*2.2.3*)

6.5 to 7.5.

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Impurity C

Gas chromatography (*2.2.28*).

Silylation solution To 2 mL of *N,O-bis(trimethylsilyl)trifluoroacetamide R* add 0.04 mL of *chlorotrimethylsilane R* and mix.

Test solution Dissolve 50.0 mg of the substance to be examined in 3 mL of *water R* and add 0.5 mL of *hydrochloric acid R*. Extract with 2 quantities, each of 5 mL, of *methylene chloride R*. Evaporate the combined methylene chloride extracts to dryness in a vial with a screw cap and add 0.5 mL of the silylation solution. Seal the vial and heat at 70 ± 5 °C for 20 min.

Reference solution (a) Dissolve 5.0 mg of *sodium phenylbutyrate impurity C CRS* in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *methylene chloride R*. Place 1.0 mL of this solution in a vial with a screw cap, evaporate to dryness and add 0.5 mL of the silylation solution. Seal the vial and heat at 70 ± 5 °C for 20 min.

Reference solution (c) Dissolve 10 mg of the substance to be examined in 25 mL of *water R*. To 3 mL of this solution add 0.1 mL of *hydrochloric acid R*. Extract with 2 quantities, each of 5 mL, of *methylene chloride R*. Combine the methylene chloride extracts in a vial with a screw cap and add 2 mL of reference solution (a). Evaporate to dryness and add 0.5 mL of the silylation solution. Seal the vial and heat at 70 ± 5 °C for 20 min.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 1.0 µm).

Carrier gas *helium for chromatography R*.

Flow rate 0.9 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	50
	5 - 27	50 → 270

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	Time (min)	Temperature (°C)
	27 - 32	270
Injection port		270
Detector		270

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to phenylbutyrate (retention time = about 20 min): impurity C = about 0.98.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurity C and phenylbutyrate.

Limit:

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.20 g of the substance to be examined in 10 mL of *methanol R* and dilute to 50.0 mL with *water R*.

Reference solution (a) Dissolve 4.0 mg of *α-tetralone R* (impurity B) in 10 mL of *methanol R* and dilute to 200.0 mL with the same solvent.

Reference solution (b) Dissolve 0.20 g of the substance to be examined in 10 mL of *methanol R*, add 1 mL of reference solution (a) and dilute to 50 mL with *water R*.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 50.0 mL with *water R*.

Reference solution (d) Dissolve 5.0 mg of *3-benzoylpropionic acid R* (impurity A) in 2.5 mL of *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R*, *methanol R*, *water R* (1:49:50 *V/V/V*).

Flow rate 1.3 mL/min.

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Detection Spectrophotometer at 245 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time Twice the retention time of phenylbutyrate.

Relative retention With reference to phenylbutyrate (retention time = about 17 min): impurity A = about 0.3; impurity B = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 6 between the peaks due to impurity B and phenylbutyrate.

Limits:

— *impurity A*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.01 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *disregard limit of impurities other than B*: 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.03 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 2.00 g.

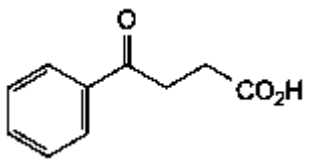
ASSAY

Disperse 0.150 g in 50 mL of *anhydrous acetic acid R*. The opalescence of the solution disappears during the titration. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 18.62 mg of $C_{10}H_{11}NaO_2$.

IMPURITIES

Specified impurities *A, B, C.*



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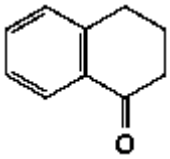
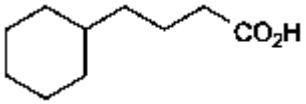
A. 4-oxo-4-phenylbutanoic acid (3-benzoylpropionic acid),



B. 3,4-dihydronaphthalen-1(2*H*)-one (α-tetralone),



C. 4-cyclohexylbutanoic acid.

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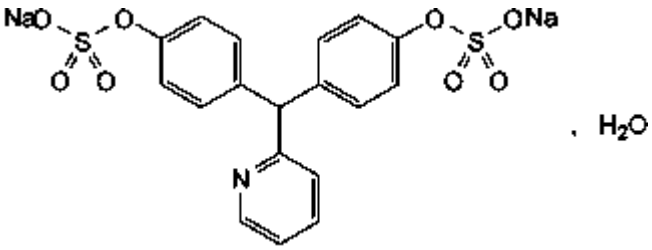
Sodium Picosulfate

General Notices

(Ph. Eur. monograph 1031)



$C_{18}H_{13}NNa_2O_8S_2,H_2O$ 499.4

Action and use

Stimulant laxative.

Preparations

Compound Sodium Picosulfate Powder for Oral Solution

Sodium Picosulfate Oral Solution Drops

Sodium Picosulfate Oral Solution

Ph Eur

DEFINITION

4,4′-[(Pyridin-2-yl)methylene]diphenyl bis(sodium sulfate) monohydrate.

Content

98.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sodium picosulfate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 20 mg of *sodium picosulfate CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *water R*, *methanol R*, *ethyl acetate R* (2.5:12.5:25:60 *V/V/V/V*).

Application 5 µL.

Development Over 1/2 of the plate.

Drying In a current of warm air for 15 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 5 mL of solution S (see Tests) add 1 mL of *dilute hydrochloric acid R* and heat to boiling. Add 1 mL of *barium chloride solution R1*. A white precipitate is formed.

D. Solution S gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution GY_7 (2.2.2, *Method II*).

Acidity or alkalinity

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To 10 mL of solution S add 0.05 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.25 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *picosulfate for system suitability CRS* (containing impurities A and B) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R1* (5 µm);

— *temperature*: 40 °C.

Mobile phase Dissolve 2.3 g of *disodium hydrogen phosphate dihydrate R* in 800 mL of *water for chromatography R*, add 0.2 g of *cetyltrimethylammonium bromide R*, adjust to pH 7.5 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*; mix 550 mL of this solution and 450 mL of *acetonitrile R* (if necessary vary the buffer/acetonitrile proportion in 10 mL increments in order to fulfil the resolution requirement).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 263 nm.

Injection 40 µL.

Run time Twice the retention time of picosulfate.

Identification of impurities Use the chromatogram supplied with *picosulfate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to picosulfate (retention time = about 7.4 min): impurity B = about 0.5; impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurities B and A.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity B = 0.5;

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— *impurities A, B*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Water (2.5.12)

3.0 per cent to 5.0 per cent, determined on 0.500 g.

ASSAY

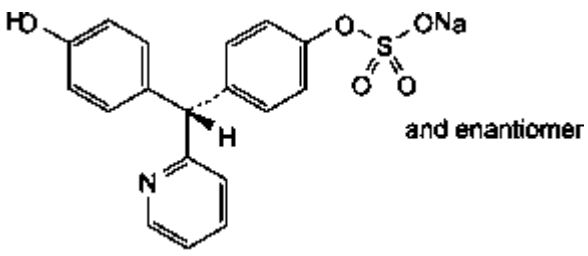
Dissolve 0.400 g in 80 mL of *methanol R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 48.14 mg of $C_{18}H_{13}NNa_2O_8S_2$.

IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



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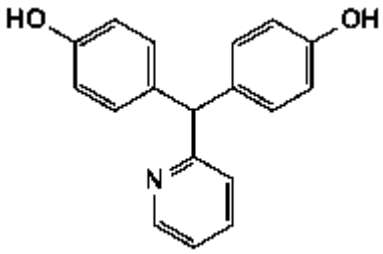
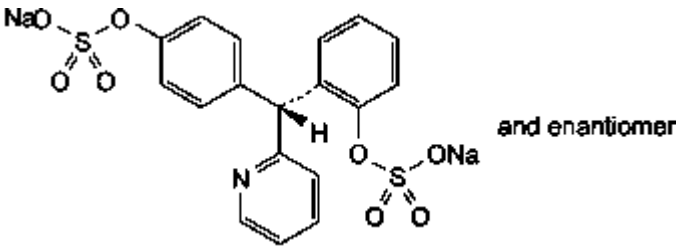
A. 4-[(*RS*)-(4-hydroxyphenyl)(pyridin-2-yl)methyl]phenyl sodium sulfate,



B. 4,4′-[(pyridin-2-yl)methylene]diphenol,



and enantiomer

C. 2-[(*RS*)-(pyridin-2-yl)[4-(sulfonatooxy)phenyl]methyl]phenyl disodium sulfate.

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Sodium Picosulfate Oral Drops

General Notices

Action and use

Stimulant laxative.

DEFINITION

Sodium Picosulfate Oral Drops are a solution of Sodium Picosulfate in a suitable vehicle in a suitable device fitted with an appropriate measuring system.

The oral drops complies with the requirements stated under Oral Liquids and with the following requirements.

Content of sodium picosulfate, $C_{18}H_{13}NNa_2O_8S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

(1) Dilute, if necessary, a volume of the oral drops with sufficient *methanol* to produce a solution containing 0.1% w/v of Sodium Picosulfate.

(2) 0.1% w/v of *sodium picosulfate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*. Spray with a 20% w/v solution of *hydrochloric acid* in *methanol* and heat at 110° for 10 minutes. Spray the hot plate with a freshly prepared solution containing 5% w/v of *iron(III) chloride* and 0.1% w/v of *potassium hexacyanoferrate(III)* and examine the wet plate in daylight.

MOBILE PHASE

2.5 volumes of *anhydrous formic acid*, 12.5 volumes of *water*, 25 volumes of *methanol* and 60 volumes of *ethyl acetate*.

CONFIRMATION

Under ultraviolet light (254 nm) The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

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After spraying The principal spot in the chromatogram obtained with solution (1) is similar in position, size and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Impurity A

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, a volume of the oral drops with sufficient *water* to produce a solution containing 0.005% w/v of Sodium Picosulfate.

(2) 0.0001% w/v of *sodium picosulfate BPCRS* in *water*.

(3) Dissolve 10 mg of *sodium picosulfate BPCRS* in 2 mL of 0.1M *hydrochloric acid*, bring rapidly to the boil and heat for 1 minute. Cool in ice-water, add 2 mL of 0.1M *sodium hydroxide* and dilute to 10 mL with the mobile phase. Dilute 1 volume to 25 volumes with the mobile phase (generation of impurity A).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 µm) (YMC Basic is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

380 volumes of *acetonitrile* and 620 volumes of a buffer solution containing 3.0 g *disodium hydrogen orthophosphate* and 0.5 g *cetyltrimethylammonium bromide* in 1000 mL of *water*, adjusting the final pH to 5.0 with orthophosphic acid.

When the chromatograms are recorded under the prescribed conditions the retention time relative to sodium picosulfate (retention time about 26 minutes) is impurity A, about 0.2.

SYSTEM SUITABILITY

The test is not valid unless, the chromatogram obtained with solution (3), closely resembles the appropriate reference chromatogram supplied with *sodium picosulfate BPCRS*.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, a volume of the oral drops with sufficient *water* to produce a solution containing 0.005% w/v of Sodium Picosulfate.

(2) 0.005% w/v of *sodium picosulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under the test for Impurity A may be used.

DETERMINATION OF CONTENT

Calculate the content of sodium picosulfate, $C_{18}H_{13}NNa_2O_8S_2$, in the oral drops from the chromatograms obtained and using the declared content of $C_{18}H_{13}NNa_2O_8S_2$ in *sodium picosulfate BPCRS*.

STORAGE

Sodium Picosulfate Oral Drops should be kept in an airtight container and protected from light.

IMPURITIES

The impurity limited by the requirements of this monograph is:

A. 4-[(*RS*)-(4-Hydroxyphenyl)(pyridin-2-yl)methyl]phenyl sodium sulfate.

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Sodium Picosulfate Oral Solution

General Notices

Sodium Picosulfate Elixir

Action and use

Stimulant laxative.

DEFINITION

Sodium Picosulfate Oral Solution is a solution of Sodium Picosulfate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of Sodium Picosulfate, $C_{18}H_{13}NNa_2O_8S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute, if necessary, a volume of the oral solution with sufficient *methanol* to produce a solution containing 0.1% w/v of Sodium Picosulfate.

(2) 0.1% w/v of *sodium picosulfate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}. (Merck HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry the plate in a current of hot air for 15 minutes and examine under *ultraviolet light (254 nm)*. Spray with a 20% w/v solution of *hydrochloric acid* in *methanol* and heat at 110° for 10 minutes. Spray the hot plate with a freshly prepared solution containing 5% w/v of *iron(III) chloride* and 0.1% w/v of *potassium hexacyanoferrate(III)* and examine the wet plate in daylight.

MOBILE PHASE

2.5 volumes of *anhydrous formic acid*, 12.5 volumes of *water*, 25 volumes of *methanol* and 60 volumes of *ethyl acetate*.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds to the principal spot in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to sodium picosulfate in the chromatogram obtained with solution (2).

TESTS

Impurity A

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, a volume of the oral solution with sufficient *water* to produce a solution containing 0.005% w/v of Sodium Picosulfate.
(2) 0.0001% w/v of *sodium picosulfate BPCRS* in *water*.
(3) Dissolve 10 mg of *sodium picosulfate BPCRS* in 2 mL of 0.1M *hydrochloric acid*, bring rapidly to the boil and heat for 1 minute. Cool in ice-water, add 2 mL of 0.1M *sodium hydroxide* and dilute to 10 mL with the mobile phase. Dilute 2 volumes to 50 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 µm) (YMC Basic is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 263 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

380 volumes of *acetonitrile* and 620 volumes of a buffer solution containing 3.0 g of *disodium hydrogen orthophosphate* and 0.5 g of *cetyltrimethylammonium bromide* in 1000 mL of *water*, adjusting the pH to 5.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to sodium picosulfate (retention time about 26 minutes) is impurity A, about 0.2.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the appropriate reference chromatogram supplied with *sodium picosulfate BPCRS*.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Dilute, if necessary, a volume of the oral solution with sufficient *water* to produce a solution containing 0.005% w/v of Sodium Picosulfate.

(2) 0.005% w/v of *sodium picosulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{13}NNa_2O_8S_2$ in the oral solution using the declared content of $C_{18}H_{13}NNa_2O_8S_2$ in *sodium picosulfate BPCRS*.

STORAGE

Sodium Picosulfate Oral Solution should be protected from light.

IMPURITIES

The impurity limited by this monograph is:

A. 4-[(pyridin-2-yl)(4-hydroxyphenyl)methyl]phenyl sodium sulfate.

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Sodium Polystyrene Sulfonate

General Notices

Sodium Polystyrene Sulphonate

(Ph. Eur. monograph 1909)

Action and use

Used in the treatment of hyperkalaemia.

Ph Eur

DEFINITION

Polystyrene sulfonate resin prepared in the sodium form.

Exchange capacity 2.8 mmol to 3.4 mmol of potassium per gram (dried substance).

Content

9.4 per cent to 11.0 per cent of Na (dried substance).

CHARACTERS

Appearance

Almost white or light brown powder.

Solubility

Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs using finely ground substance.

Comparison *Ph. Eur. reference spectrum of sodium polystyrene sulfonate*.

B. Suspend 0.1 g in *water R*, add 2 mL of a 150 g/L solution of *potassium carbonate R*, and heat to boiling. Allow to cool and filter. To the filtrate add 4 mL of *potassium pyroantimonate solution R* and heat to boiling. Allow to cool in iced water and if necessary rub the inside of the test-tube with a glass rod. A dense white precipitate is formed.

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TESTS

Styrene

Liquid chromatography (2.2.29).

Test solution Shake 10.0 g of the substance to be examined with 10 mL of acetone R for 30 min, centrifuge and use the supernatant.

Reference solution Dissolve 10 mg of styrene R in acetone R and dilute to 100 mL with the same solvent. Dilute 1 mL of this solution to 100 mL with acetone R.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase acetonitrile R, water R (1:1 *V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Limit:

— styrene: not more than the area of the principal peak in the chromatogram obtained with the reference solution (1 ppm).

Calcium

Maximum 0.10 per cent.

Atomic emission spectrometry (2.2.22, Method I).

Test solution To 1.10 g add 5 mL of hydrochloric acid R, heat to boiling, cool and add 10 mL of water R. Filter, wash the filter and residue with water R and dilute the filtrate and washing to 25.0 mL with water R.

Reference solutions Prepare the reference solutions using calcium standard solution (400 ppm Ca) R, diluted as necessary with water R.

Wavelength 422.7 nm.

Potassium

Maximum 0.10 per cent.

Atomic emission spectrometry (2.2.22, Method I).

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Test solution To 1.10 g add 5 mL of *hydrochloric acid R*, heat to boiling, cool and add 10 mL of *water R*. Filter, wash the filter and residue with *water R* and dilute the filtrate and washings to 25.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *potassium standard solution (100 ppm K) R*, diluted as necessary with *water R*.

Wavelength 766.5 nm.

Loss on drying (*2.2.32*)

Maximum 7.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Microbial contamination (*2.6.13*)

Bile-tolerant gram-negative bacteria: acceptance criterion less than 10^2 CFU/g.

ASSAY

Sodium

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution In a platinum crucible moisten 0.90 g with a few drops of *sulfuric acid R*, ignite very gently and allow to cool. Moisten with a few drops of *sulfuric acid R* again, ignite at 800 ± 50 °C until a carbon-free ash is obtained and allow to cool.

Add 20 mL of *water R* to the crucible, warm gently on a water-bath until dissolution, cool, transfer quantitatively to a 100 mL graduated flask and dilute to 100.0 mL with *water R*. Dilute 5 mL of this solution to 1000.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluted as necessary with *water R*.

Wavelength 589 nm.

Exchange capacity

Atomic emission spectrometry (*2.2.22, Method I*).

Solution A 9.533 g/L solution of *potassium chloride R*.

Test solution To 1.6 g of the substance to be examined in a dry 250 mL ground-glass-stoppered flask add 100 mL of solution A, stopper and shake for 15 min. Filter, discard the first 20 mL of the filtrate and dilute 4 mL of the filtrate to 1000 mL with *water R*.

Reference solutions Prepare the reference solutions by diluting 0, 1, 2, 3 and 4 mL of solution A respectively and 4, 3, 2, 1 and 0 mL of a 7.63 g/L solution of *sodium chloride R* to 1000 mL with *water R*.

Wavelength 766.5 nm.

Prepare a calibration curve using the reference solutions and calculate the potassium exchange capacity of the substance to be examined in millimoles per gram taking the concentration of potassium in solution A as 128 mmoles of K per litre.

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STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A.*

A. styrene.

Ph Eur

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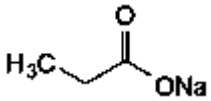
Sodium Propionate

General Notices

(Ph. Eur. monograph 2041)



$C_3H_5NaO_2$ 96.1 *137-40-6*

Action and use

Antifungal.

Ph Eur

DEFINITION

Sodium propanoate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Colourless crystals or, white or almost white powder, slightly hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of sodium propionate*.

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B. Dissolve 0.1 g in a mixture of 2 mL of *copper sulfate solution R* and 2 mL of *methylene chloride R*. Shake vigorously and allow to stand. Both the upper and the lower layer show a blue colour.

C. To 5 mL of solution S (see Tests) add 2 mL of *0.1 M silver nitrate*. A white precipitate is formed.

D. Solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 10 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

7.8 to 9.2.

Dilute 1 mL of solution S to 5 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.250 g of the substance to be examined in *water R* and dilute to 100 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of the substance to be examined and 10 mg of *sodium acetate R* in *water R* and dilute to 100 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dilute 1 mL of *phosphoric acid R* to 1000 mL with *water for chromatography R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to sodium acetate and sodium propionate.

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Limits:

— *any impurity*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total*: not more than half the area of the principal peak in the chromatrogram obtained with reference solution (b) (0.5 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Readily oxidisable substances

In a ground-glass-stoppered conical flask introduce 10 g of the substance to be examined. Add 100 mL of *water R* and stir to dissolve. Add 25 mL of *sodium hypobromite solution R* and 10 mL of a 200 g/L solution of *sodium acetate R*, stopper the flask and allow to stand for 15 min. Add 10 mL of *potassium iodide solution R* and 20 mL of *hydrochloric acid R* while cooling. Titrate with *0.1 M sodium thiosulfate*, adding 2 mL of *starch solution R* towards the end of the titration. Carry out a blank titration. The difference between the volumes used in the 2 titrations is not greater than 2.2 mL.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by heating in an oven at 105 °C for 3 h.

ASSAY

Dissolve 80.0 mg in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 9.61 mg of $C_3H_5NaO_2$.

STORAGE

In an airtight container.

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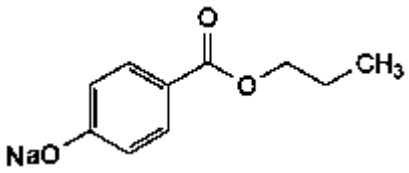
Sodium Propyl Hydroxybenzoate

General Notices

Sodium Propylparaben

(Sodium Propyl Parahydroxybenzoate, Ph. Eur. monograph 1263)



$C_{10}H_{11}NaO_3$ 202.2 *35285-69-9*

Action and use

Antimicrobial preservative.

Ph Eur

DEFINITION

Sodium 4-(propoxycarbonyl)phenolate.

Content

94.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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A. Dissolve 0.5 g in 50 mL of *water R*. Immediately add 5 mL of *hydrochloric acid R1*. Filter and wash the precipitate with *water R*. Dry *in vacuo* at 80 °C for 2 h. The precipitate melts (*2.2.14*) at 96 °C to 99 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Precipitate obtained in identification test A.

Comparison *propyl parahydroxybenzoate CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution (a) Dissolve 0.10 g of the substance to be examined in 10 mL of *water R*. Immediately add 2 mL of *hydrochloric acid R* and shake with 50 mL of *1,1-dimethylethyl methyl ether R*. Evaporate the upper layer to dryness and take up the residue with 10 mL of *acetone R*.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *acetone R*.

Reference solution (a) Dissolve 10 mg of *propyl parahydroxybenzoate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *ethyl parahydroxybenzoate CRS* in 1 mL of test solution (a) and dilute to 10 mL with *acetone R*.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R* (1:30:70 *V/V/V*).

Application 5 µL of test solution (b) and reference solutions (a) and (b).

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To 1 mL of solution S (see Tests) add 1 mL of *water R*. The solution gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* prepared from *distilled water R*, and dilute to 50 mL with the same solvent.

Appearance of solution

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Solution S, examined immediately after preparation, is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

pH (2.2.3)

9.5 to 10.5.

Dilute 1 mL of solution S to 100 mL with carbon dioxide-free water R.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of ethyl parahydroxybenzoate CRS (impurity C), 5 mg of 4-hydroxybenzoic acid R (impurity A) and 5 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50.0 mg of propyl parahydroxybenzoate CRS in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase 6.8 g/L solution of potassium dihydrogen phosphate R, methanol R (35:65 *V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 2.5 times the retention time of propyl parahydroxybenzoate.

Relative retention With reference to propyl parahydroxybenzoate (retention time = about 4.5 min): impurity A = about 0.3; impurity C = about 0.7.

System suitability Reference solution (a):

— resolution: minimum 5.0 between the peaks due to impurity C and propyl parahydroxybenzoate.

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Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

— *impurity A*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (c) (4.0 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Chlorides (2.4.4)

Maximum 350 ppm.

To 10 mL of solution S, add 1 mL of *nitric acid R* and 30 mL of *water R* and dilute to 50 mL with *water R*. Shake and filter. Dilute 10 mL of the filtrate to 15 mL with *water R*. Prepare the standard using 14 mL of *chloride standard solution (5 ppm Cl) R* to which 1 mL of *water R* has been added.

Sulfates (2.4.13)

Maximum 300 ppm.

To 25 mL of solution S, add 5 mL of *distilled water R* and 10 mL of *hydrochloric acid R* and dilute to 50 mL with *distilled water R*. Shake and filter. Dilute 10 mL of the filtrate to 15 mL with *distilled water R*.

Water (2.5.12)

Maximum 5.0 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{10}H_{11}NaO_3$ from the declared content of *propyl parahydroxybenzoate CRS*, multiplied by a correction factor of 1.122.

STORAGE

In an airtight container.

IMPURITIES

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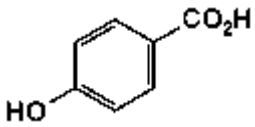
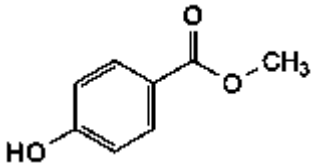
Specified impurities A.

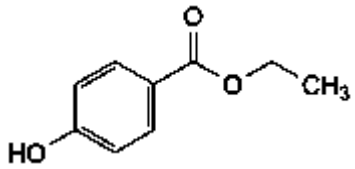
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D.



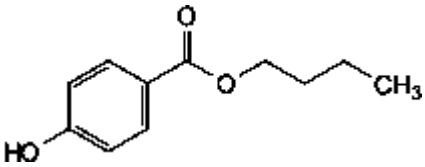
A. 4-hydroxybenzoic acid,



B. methyl 4-hydroxybenzoate (methyl parahydroxybenzoate),



C. ethyl 4-hydroxybenzoate (ethyl parahydroxybenzoate),



D. butyl 4-hydroxybenzoate (butyl parahydroxybenzoate).

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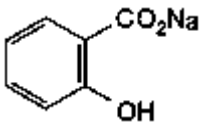
Sodium Salicylate

General Notices

(Ph. Eur. monograph 0413)



$C_7H_5NaO_3$ 160.1 *54-21-7*

Action and use

Anti-inflammatory; analgesic.

Ph Eur

DEFINITION

Sodium 2-hydroxybenzenecarboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or small, colourless crystals or shiny flakes.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sodium salicylate CRS*.

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B. Solution S (see Tests) gives the reactions of salicylates (2.3.1).

C. It gives reaction (b) of sodium (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Acidity

To 20 mL of solution S add 0.1 mL of *phenol red solution R*. The solution is yellow. Not more than 2.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to violet-red.

Chlorides (2.4.4)

Maximum 200 ppm.

To 5 mL of solution S add 5 mL of *water R* and 10 mL of *dilute nitric acid R* and filter. Dilute 10 mL of the filtrate to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 600 ppm.

Dilute 2.5 mL of solution S to 15 mL with *distilled water R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.00 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.130 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 16.01 mg of $C_7H_5NaO_3$.

STORAGE

In an airtight container, protected from light.

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Sodium Selenite

General Notices

(Ph. Eur. monograph 2740)

Na_2SeO_3 172.9 *10102-18-8*

Action and use

Used in treatment of selenium deficiency.

Ph Eur

DEFINITION

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline deliquescent powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 50 mg in 5 mL of a mixture of equal volumes of *dilute hydrochloric acid R* and *water R* and heat to boiling. Add 50 mg of *ascorbic acid R*; a red precipitate is formed which may become black.

B. Dissolve 50 mg in a mixture of 1 mL of *dilute hydrochloric acid R* and 5 mL of *water R*. Add 1 mL of *barium chloride solution R1*; the solution remains clear.

C. It gives reaction (a) of sodium (*2.3.1*).

D. It complies with the limits of the assay.

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

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Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

9.8 to 10.8 for solution S.

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dissolve 1.0 g in 5 mL of *water R*, add 9 mL of *nitric acid R* and dilute to 15 mL with *water R*.

Sulfates and selenates (*2.4.13*)

Maximum 300 ppm (determined as sulfates).

Dissolve 0.5 g in 10 mL of *distilled water R*, add 0.5 mL of *hydrochloric acid R1* and dilute to 15 mL with *distilled water R*.

Iron

Maximum 50 ppm.

To 2 mL of solution S add 2 mL of a 200 g/L solution of *sulfosalicylic acid R* and 5 mL of *concentrated ammonia R*, and dilute to 10 mL with *water R*. The solution is not more intensely coloured than a reference solution prepared at the same time and in the same manner using 1 mL of *iron standard solution (10 ppm Fe) R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 130 °C for 2 h.

ASSAY

Dissolve 80.0 mg in 50 mL of *water R*. Add 1.0 mL of *anhydrous formic acid R*, 25.0 mL of *0.1 M sodium thiosulfate* and 0.5 g of *potassium iodide R*. Titrate immediately with *0.05 M iodine* using *starch solution R* as indicator. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 4.323 mg of Na_2SeO_3.

STORAGE

In an airtight container.

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Sodium Selenite Pentahydrate

General Notices

(Ph. Eur. monograph 1677)

$Na_2SeO_3,5H_2O$ 263.0 *26970-82-1*

Action and use

Used in treatment of selenium deficiency.

Ph Eur

DEFINITION

Content

98.5 per cent to 101.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 50 mg in 5 mL of a mixture of equal volumes of *dilute hydrochloric acid R* and *water R* and heat to boiling. Add 50 mg of *ascorbic acid R*; a red precipitate is formed which may become black.

B. Dissolve 50 mg in a mixture of 1 mL of *dilute hydrochloric acid R* and 5 mL of *water R*. Add 1 mL of *barium chloride solution R1*; the solution remains clear.

C. It gives reaction (a) of sodium (*2.3.1*).

D. It complies with the limits of the assay.

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

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Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

9.8 to 10.8 for solution S.

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dissolve 1.0 g in 5 mL of *water R*, add 9 mL of *nitric acid R* and dilute to 15 mL with *water R*.

Sulfates and selenates (*2.4.13*)

Maximum 300 ppm (determined as sulfates).

Dissolve 0.5 g in 10 mL of *distilled water R*, add 0.5 mL of *hydrochloric acid R1* and dilute to 15 mL with *distilled water R*.

Iron

Maximum 50 ppm.

To 2 mL of solution S add 2 mL of a 200 g/L solution of *sulfosalicylic acid R*, 5 mL of *concentrated ammonia R* and dilute to 10 mL with *water R*. The solution is not more intensely coloured than a reference solution prepared at the same time and in the same manner using 1 mL of *iron standard solution (10 ppm Fe) R*.

ASSAY

Dissolve 0.120 g in 50 mL of *water R*. Add 1.0 mL of *anhydrous formic acid R*, 25.0 mL of *0.1 M sodium thiosulfate* and 0.5 g of *potassium iodide R*. Titrate immediately with *0.05 M iodine* using *starch solution R* as indicator. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 6.575 mg of $Na_2SeO_3,5H_2O$.

STORAGE

In an airtight container.

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Sodium Starch Glycolate (Type A)[1]

General Notices

(Ph. Eur. monograph 0983)

Action and use

Excipient.

Ph Eur

DEFINITION

Sodium salt of a cross-linked partly *O*-carboxymethylated starch.

Content

2.8 per cent to 4.2 per cent of Na (A_r 22.99) (substance washed with ethanol (80 per cent *V/V*) and dried).

♦ CHARACTERS

Appearance

White or almost white, fine, free-flowing powder, very hygroscopic.

Solubility

Practically insoluble in methylene chloride. It gives a translucent suspension in water.♦

IDENTIFICATION

◊ A. pH (see Tests).

B. Prepare with shaking and without heating a mixture of 4.0 g of the substance to be examined and 20 mL of *carbon dioxide-free water R*. The mixture has the appearance of a gel. Add 100 mL of *carbon dioxide-free water R* and shake. A suspension forms that settles after standing.◊

C. To an acidified solution, add *iodinated potassium iodide solution R1*. The solution becomes blue or violet.

D. Solution S2 (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S1

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Centrifuge the suspension obtained in identification test B at 2500 *g* for 10 min. Collect carefully the supernatant.

Solution S2

Place 2.5 g in a silica or platinum crucible and add 2 mL of a 500 g/L solution of *sulfuric acid R*. Heat on a water-bath, then cautiously over a naked flame, raising the temperature progressively, then incinerate in a muffle furnace at 600 ± 25 °C. Continue heating until all black particles have disappeared. Allow to cool, add a few drops of *dilute sulfuric acid R*, heat and incinerate as above. Allow to cool, add a few drops of *ammonium carbonate solution R*, evaporate to dryness and incinerate cautiously. Allow to cool and dissolve the residue in 50 mL of *water R*.

◊ Appearance of solution S1

Solution S1 is clear (*2.2.1*) and colourless (*2.2.2, Method II*).◊

pH (*2.2.3*)

5.5 to 7.5.

Disperse 1.0 g in 30 mL of *carbon dioxide-free water R*.

Sodium glycolate

Maximum 2.0 per cent. *Carry out the test protected from light*.

Test solution Place 0.20 g in a beaker. Add 5 mL of *acetic acid R* and 5 mL of *water R*. Stir until dissolution is complete (about 10 min). Add 50 mL of *acetone R* and 1 g of *sodium chloride R*. Filter through a fast filter paper impregnated with *acetone R*, rinse the beaker and filter with *acetone R*. Combine the filtrate and washings and dilute to 100.0 mL with *acetone R*. Allow to stand for 24 h without shaking. Use the clear supernatant.

Reference solution Dissolve 0.310 g of *glycolic acid R*, previously dried in a desiccator (*2.2.32*) at room temperature overnight, in *water R* and dilute to 500.0 mL with the same solvent. To 5.0 mL of this solution add 5 mL of *acetic acid R* and allow to stand for about 30 min. Add 50 mL of *acetone R* and 1 g of *sodium chloride R*. Filter through a fast filter paper impregnated with *acetone R*, rinse the beaker and filter with *acetone R*. Combine the filtrate and washings and dilute to 100.0 mL with *acetone R*. Allow to stand for 24 h without shaking. Use the clear supernatant.

Heat 2.0 mL of the test solution on a water-bath for 20 min. Cool to room temperature and add 20.0 mL of *2,7-dihydroxynaphthalene solution R*. Shake and heat on a water-bath for 20 min. Cool under running water, transfer to a volumetric flask and dilute to 25.0 mL with *sulfuric acid R*, maintaining the flask under running water. Within 10 min, measure the absorbance at 540 nm (*2.2.25*) using *water R* as the compensation liquid. The absorbance of the solution prepared with the test solution is not greater than that of a solution prepared at the same time and in the same manner with 2.0 mL of the reference solution.

Sodium chloride

Maximum 7.0 per cent.

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Place 0.500 g in a beaker and suspend in 100 mL of *water R*. Add 1 mL of *nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*), using a silver-based indicator electrode and a double-junction reference electrode containing a 100 g/L solution of *potassium nitrate R* in the outer jacket and a standard filling solution in the inner jacket.

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Iron (*2.4.9*)

Maximum 20 ppm, determined on 10 mL of solution S2.

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 1.5 h.

Microbial contamination

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

ASSAY

Shake about 1 g with 20 mL of *ethanol (80 per cent V/V) R*, stir for 10 min and filter. Repeat the operation until chloride has been completely extracted and verify the absence of chloride using *silver nitrate solution R2*. Dry the residue at 105 °C to constant mass. To 0.700 g of the dried residue, add 80 mL of *glacial acetic acid R* and heat under a reflux condenser for 2 h. Cool the solution to room temperature. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 2.299 mg of Na.

♦ STORAGE

In an airtight container, protected from light.♦

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sodium starch glycolate (type A) used as disintegrant in tablets.

Settling volume

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Introduce 70 mL of *water R* in a flask, add 1.0 g of the substance to be examined (dried substance) and stir with a glass rod so that no lumps remain. Transfer the suspension to a 100 mL graduated cylinder, rinse the walls of the flask with *water R* and dilute to 100 mL with the same solvent. Stir again until the substance is evenly distributed. Allow to stand for 4 h. The volume of the sediment is typically less than 45 mL.

Degree of substitution

Place 1.000 g (dried substance) in a 500 mL conical flask, add 300 mL of a 100 g/L solution of *sodium chloride R* and 25.0 mL of *0.1 M sodium hydroxide*, stopper the flask and allow to stand for 5 min, shaking occasionally. Add 0.05 mL of *m-cresol purple solution R* and about 15 mL of *0.1 M hydrochloric acid* from a burette. Insert the stopper and shake. If the solution is violet, add *0.1 M hydrochloric acid* in 1 mL portions until the solution becomes yellow, shaking after each addition. Titrate with *0.1 M sodium hydroxide* until the colour turns to violet. Calculate the number of milliequivalents (*M*) of base required to neutralise the equivalent of 1 g of dried substance.

Calculate the degree of acid carboxymethyl substitution (*A*) using the following expression:

$$A = \frac{1150_M}{(7102 - 412_{M-80C})}$$

C = sulfated ash as a percentage, determined as follows.

Introduce 1.3 g of the substance to be examined in a flask and add 20 mL of *ethanol (80 per cent V/V) R*. Shake for 10 min and filter on a sintered-glass filter (*2.1.2*). Repeat this operation 4 times. Add to the residue 10 mL of *ethanol (96 per cent) R* and filter. Collect the residue and place it in an oven at 105 °C for 4 h. Place the dried residue in a mortar and crush. Determine the sulfated ash content (*C*) (*2.4.14*) on 1.000 g of the powder obtained.

Calculate the degree of sodium carboxymethyl substitution (*S*) using the following expression:

$$S = \frac{(162 + 58_A)_C}{(7102 - 80_C)}$$

The degree of substitution is the sum of *A* and *S*.

Particle-size distribution (*2.9.31* or *2.9.38*

).◊

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Sodium Starch Glycolate (Type B)[1]

General Notices

(Ph. Eur. monograph 0984)

Action and use

Excipient.

Ph Eur

DEFINITION

Sodium salt of a cross-linked partly *O*-carboxymethylated starch.

Content

2.0 per cent to 3.4 per cent of Na (A_r 22.99) (substance washed with ethanol (80 per cent *V/V*) and dried).

♦ CHARACTERS

Appearance

White or almost white, fine, free-flowing powder, very hygroscopic.

Solubility

Practically insoluble in methylene chloride. It gives a translucent suspension in water.♦

IDENTIFICATION

◊ A. pH (see Tests).

B. Prepare with shaking and without heating a mixture of 4.0 g of the substance to be examined and 20 mL of *carbon dioxide-free water R*. The mixture has the appearance of a gel. Add 100 mL of *carbon dioxide-free water R* and shake. A suspension forms that settles after standing.◊

C. To an acidified solution, add *iodinated potassium iodide solution R1*. The solution becomes blue or violet.

D. Solution S2 (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S1

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Centrifuge the suspension obtained in identification test B at 2500 *g* for 10 min. Collect carefully the supernatant.

Solution S2

Place 2.5 g in a silica or platinum crucible and add 2 mL of a 500 g/L solution of *sulfuric acid R*. Heat on a water-bath, then cautiously over a naked flame, raising the temperature progressively, and then incinerate in a muffle furnace at 600 ± 25 °C. Continue heating until all black particles have disappeared. Allow to cool, add a few drops of *dilute sulfuric acid R* and heat and incinerate as above. Allow to cool, add a few drops of *ammonium carbonate solution R*, evaporate to dryness and incinerate cautiously. Allow to cool and dissolve the residue in 50 mL of *water R*.

◊ Appearance of solution S1

Solution S1 is clear (*2.2.1*) and colourless (*2.2.2, Method II*).◊

pH (*2.2.3*)

3.0 to 5.0.

Disperse 1.0 g in 30 mL of *carbon dioxide-free water R*.

Sodium glycolate

Maximum 2.0 per cent. *Carry out the test protected from light*.

Test solution Place 0.20 g in a beaker. Add 5 mL of *acetic acid R* and 5 mL of *water R*. Stir until dissolution is complete (about 10 min). Add 50 mL of *acetone R* and 1 g of *sodium chloride R*. Filter through a fast filter paper impregnated with *acetone R*, rinse the beaker and filter with *acetone R*. Combine the filtrate and washings and dilute to 100.0 mL with *acetone R*. Allow to stand for 24 h without shaking. Use the clear supernatant.

Reference solution Dissolve 0.310 g of *glycolic acid R*, previously dried in a desiccator (*2.2.32*) at room temperature overnight, in *water R* and dilute to 500.0 mL with the same solvent. To 5.0 mL of this solution add 5 mL of *acetic acid R* and allow to stand for about 30 min. Add 50 mL of *acetone R* and 1 g of *sodium chloride R*. Filter through a fast filter paper impregnated with *acetone R*, rinse the beaker and filter with *acetone R*. Combine the filtrate and washings and dilute to 100.0 mL with *acetone R*. Allow to stand for 24 h without shaking. Use the clear supernatant.

Heat 2.0 mL of the test solution on a water-bath for 20 min. Cool to room temperature and add 20.0 mL of *2,7-dihydroxynaphthalene solution R*. Shake and heat on a water-bath for 20 min. Cool under running water, transfer quantitatively to a volumetric flask and dilute to 25.0 mL with *sulfuric acid R*, maintaining the flasks under running water. Within 10 min, measure the absorbance at 540 nm (*2.2.25*) using *water R* as the compensation liquid. The absorbance of the solution prepared with the test solution is not greater than that of a solution prepared at the same time and in the same manner with 2.0 mL of the reference solution.

Sodium chloride

Maximum 7.0 per cent.

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Place 0.500 g in a beaker and suspend in 100 mL of *water R*. Add 1 mL of *nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*), using a silver-based indicator electrode and a double-junction reference electrode containing a 100 g/L solution of *potassium nitrate R* in the outerjacket and a standard filling solution in the inner jacket.

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Iron (*2.4.9*)

Maximum 20 ppm, determined on 10 mL of solution S2.

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 1.5 h.

Microbial contamination

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

ASSAY

Shake about 1 g with 20 mL of *ethanol (80 per cent V/V) R*, stir for 10 min and filter. Repeat the operation until chloride has been completely extracted and verify the absence of chloride using *silver nitrate solution R2*. Dry the residue at 105 °C to constant mass. To 0.700 g of the dried residue, add 80 mL of *glacial acetic acid R* and heat under a reflux condenser for 2 h. Cool the solution to room temperature. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 2.299 mg of Na.

♦ STORAGE

In an airtight container, protected from light.♦

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sodium starch glycolate (type B) used as disintegrant in tablets.

Settling volume

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Introduce 70 mL of *water R* in a flask, add 1.0 g of the substance to be examined (dried substance) and stir with a glass rod so that no lumps remain. Transfer the suspension to a 100 mL graduated cylinder, rinse the walls of the flask with *water R* and dilute to 100 mL with the same solvent. Stir again until the substance is evenly distributed. Allow to stand for 4 h. The volume of the sediment is typically less than 45 mL.

Degree of substitution

Place 1.000 g (dried substance) in a 500 mL conical flask, add 300 mL of a 100 g/L solution of *sodium chloride R* and 25.0 mL of *0.1 M sodium hydroxide*, stopper the flask and allow to stand for 5 min, shaking occasionally. Add 0.05 mL of *m-cresol purple solution R* and about 15 mL of *0.1 M hydrochloric acid* from a burette. Insert the stopper and shake. If the solution is violet, add *0.1 M hydrochloric acid* in 1 mL portions until the solution becomes yellow, shaking after each addition. Titrate with *0.1 M sodium hydroxide* until the colour turns to violet. Calculate the number of milliequivalents (*M*) of base required to neutralise the equivalent of 1 g of dried substance.

Calculate the degree of acid carboxymethyl substitution (*A*) using the following expression:

$$A = \frac{1150M}{(7102 - 412M - 80C)}$$

C = sulfated ash as a percentage, determined as follows.

Introduce 1.3 g of the substance to be examined in a flask and add 20 mL of *ethanol (80 per cent V/V) R*. Shake for 10 min and filter on a sintered-glass filter (*2.1.2*). Repeat this operation 4 times. Add to the residue 10 mL of *ethanol (96 per cent) R* and filter. Collect the residue and place it in an oven at 105 °C for 4 h. Place the dried residue in a mortar and crush. Determine the sulfated ash content (*C*) (*2.4.14*) on 1.000 g of the powder obtained.

Calculate the degree of sodium carboxymethyl substitution (*S*) using the following expression:

$$S = \frac{(162 + 58A)C}{(7102 - 80C)}$$

The degree of substitution is the sum of *A* and *S*.

Particle-size distribution (*2.9.31* or *2.9.38*

).◊

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Sodium Starch Glycolate (Type C)[1]

General Notices

(Ph. Eur. monograph 1566)

Action and use

Excipient.

Ph Eur

DEFINITION

Sodium salt of a partly *O*-carboxymethylated starch, cross-linked by physical dehydration.

Content

2.8 per cent to 5.0 per cent of Na (A_r 22.99) (substance washed with ethanol (80 per cent *V/V*) and dried).

CHARACTERS

Appearance

White or almost white, fine, free-flowing powder, very hygroscopic.

Microscopic examination: it is seen to consist of granules, irregularly shaped, ovoid or pear-shaped, 30-100 µm in size, or rounded, 10-35 µm in size; compound granules consisting of 2-4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations; between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water.

Solubility

Soluble in water, practically insoluble in methylene chloride. It gives a translucent gel-like product in water.

IDENTIFICATION

A. pH (see Tests).

B. Prepare with shaking and without heating a mixture of 4.0 g of the substance to be examined and 20 mL of *carbon dioxide-free water R*. The mixture has the appearance of a gel. Add 100 mL of *carbon dioxide-free water R* and shake: the gel remains stable (difference from types A and B). Keep the gel for the tests for appearance of gel and pH.

C. To 5 mL of the gel obtained in identification test B add 0.05 mL of *iodine solution R1*. A dark blue colour is produced.

D. Solution S (see Tests) gives reaction (a) of sodium (*2.3.1*).

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TESTS

Solution S

Place 2.5 g in a silica or platinum crucible and add 2 mL of a 500 g/L solution of *sulfuric acid R*. Heat on a water-bath, then cautiously over a naked flame, raising the temperature progressively, and then incinerate in a muffle furnace at 600 ± 25 °C. Continue heating until all black particles have disappeared. Allow to cool, add a few drops of *sulfuric acid R*, heat and incinerate as above. Allow to cool, add a few drops of *ammonium carbonate solution R*, evaporate to dryness and incinerate cautiously. Allow to cool and dissolve the residue in 50 mL of *water R*.

Appearance of gel

The gel obtained in identification test B is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.5 to 7.5 for the gel obtained in identification test B.

Sodium glycolate

Maximum 2.0 per cent. *Carry out the test protected from light.*

Test solution Place 0.20 g in a beaker. Add 5 mL of *acetic acid R* and 5 mL of *water R*. Stir until dissolution is complete (about 10 min). Add 50 mL of *acetone R* and 1 g of *sodium chloride R*. Filter through a fast filter paper impregnated with *acetone R*, rinse the beaker and filter with *acetone R*. Combine the filtrate and washings and dilute to 100.0 mL with *acetone R*. Allow to stand for 24 h without shaking. Use the clear supernatant.

Reference solution Dissolve 0.310 g of *glycolic acid R*, previously dried in a desiccator (*2.2.32*), in *water R* and dilute to 500.0 mL with the same solvent. To 5.0 mL of this solution, add 5 mL of *acetic acid R* and allow to stand for about 30 min. Add 50 mL of *acetone R* and 1 g of *sodium chloride R* and dilute to 100.0 mL with *acetone R*.

Heat 2.0 mL of the test solution on a water-bath for 20 min. Cool to room temperature and add 20.0 mL of *2,7-dihydroxynaphthalene solution R*. Shake and heat on a water-bath for 20 min. Cool under running water, transfer to a volumetric flask and dilute to 25.0 mL with *sulfuric acid R*, maintaining the flask under running water. Within 10 min, measure the absorbance (*2.2.25*) at 540 nm using *water R* as the compensation liquid. The absorbance of the solution prepared with the test solution is not greater than that of a solution prepared at the same time and in the same manner with 2.0 mL of the reference solution.

Sodium chloride

Maximum 1 per cent.

Shake 1.00 g with 20 mL of *ethanol (80 per cent V/V) R* for 10 min and filter. Repeat the operation 4 times. Dry the residue to constant mass at 100 °C and set aside for the assay. Combine the filtrates. Evaporate to dryness, take up the residue with *water R* and dilute to 25.0 mL with the same solvent. To 10.0 mL of the solution add 30 mL of *water R* and 5 mL of *dilute nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*), using a silver-based indicator electrode and a double-junction reference electrode containing a 100 g/L solution of *potassium nitrate R* in the outer jacket and a standard filling solution in the inner jacket.

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1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Iron (*2.4.9*)

Maximum 20 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 7.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Microbial contamination

It complies with the test for *Escherichia coli* and *Salmonella* (*2.6.13*).

ASSAY

To 0.500 g of the dried and crushed residue obtained in the test for sodium chloride add 80 mL of *anhydrous acetic acid R* and heat under a reflux condenser for 2 h. Cool the solution to room temperature. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank test.

1 mL of *0.1 M perchloric acid* is equivalent to 2.299 mg of Na.

STORAGE

In an airtight container, protected from light.

Ph Eur

1 In contrast to sodium starch glycolate type A and type B, this monograph has NOT undergone pharmacopoeial harmonisation.

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Sodium Stearate

General Notices

(Ph. Eur. monograph 2058)

Action and use

Excipient.

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DEFINITION

Mixture of sodium salts of different fatty acids consisting mainly of stearic (octadecanoic) acid [$C_{17}H_{35}COONa$; M_r 306.5] and palmitic (hexadecanoic) acid [$C_{15}H_{31}COONa$; M_r 278.4].

Content

— *sodium* (Na; A_r 22.99): 7.4 per cent to 8.5 per cent (dried substance);

— *stearic acid in the fatty acid fraction*: minimum 40 per cent;

— *sum of stearic acid and palmitic acid in the fatty acid fraction*: minimum 90 per cent.

CHARACTERS

Appearance

White or yellowish, fine powder, greasy to the touch.

Solubility

Slightly soluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: C, D.

Second identification: A, B, D.

A. Freezing point (2.2.18): minimum 53 °C for the residue obtained in the preparation of solution S (see Tests).

B. Acid value (2.5.1): 195 to 210, determined on 0.200 g of the residue obtained in the preparation of solution S dissolved in 25 mL of the prescribed mixture of solvents.

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C. Examine the chromatograms obtained in the assay of stearic acid and palmitic acid.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time and size to the 2 principal peaks in the chromatogram obtained with the reference solution.

D. Solution S gives reaction (b) of sodium (*2.3.1*).

TESTS

Solution S

To 10.0 g add 100 mL of *peroxide-free ether R* and 80 mL of *acetic acid R*. Boil under a reflux condenser until dissolution is complete. Allow to cool. In a separating funnel, separate the aqueous layer and shake the ether layer with 2 quantities, each of 8 mL, of *acetic acid R*. Combine the aqueous layers, wash with 30 mL of *peroxide-free ether R* and dilute to 100 mL with *distilled water R* (solution S). Evaporate the ether layers to dryness on a water-bath and dry the residue at 100-105 °C. Keep the residue for identification tests A and B.

Acidity or alkalinity

Suspend 2.0 g in 50 mL of previously neutralised *ethanol (96 per cent) R*. Heat under reflux to dissolve and add 3 drops of *phenolphthalein solution R*; the solution is colourless. Not less than 0.60 mL and not more than 0.85 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*)

Maximum 0.2 per cent.

Dilute 0.25 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.3 per cent.

Dilute 0.5 mL of solution S to 15 mL with *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent.

In a weighing glass introduce 1.0 g of previously washed *sand R*, dry at 105 °C and weigh. Add 0.500 g of the substance to be examined and 10 mL of *ethanol (96 per cent) R*. Evaporate at 80 °C and dry the residue at 105 °C for 4 h.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

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Absence of *Salmonella* (2.6.13).

ASSAY

Sodium

Dissolve 0.250 g with gentle heating in a mixture of 5 mL of *acetic anhydride R* and 20 mL of *anhydrous acetic acid R*. Cool and add 20 mL of *dioxan R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 2.299 mg of Na.

Stearic acid and palmitic acid

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution In a conical flask fitted with a reflux condenser, dissolve 0.10 g of the substance to be examined in 5 mL of *boron trifluoride-methanol solution R*. Boil under a reflux condenser for 10 min. Add 4 mL of *heptane R* through the condenser and boil again under a reflux condenser for 10 min. Allow to cool. Add 20 mL of *saturated sodium chloride solution R*. Shake and allow the layers to separate. Remove about 2 mL of the organic layer and dry over 0.2 g of *anhydrous sodium sulfate R*. Dilute 1.0 mL of the solution to 100.0 mL with *heptane R*.

Reference solution Prepare the reference solution in the same manner as the test solution using 50 mg of *palmitic acid CRS* and 50 mg of *stearic acid CRS* instead of the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.4 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	70
	2 - 36	70 → 240
	36 - 41	240
Injection port		220
Detector		260

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Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to methyl stearate (retention time = about 40 min): methyl palmitate = about 0.88.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to methyl palmitate and methyl stearate.

STORAGE

In an airtight container, protected from light.

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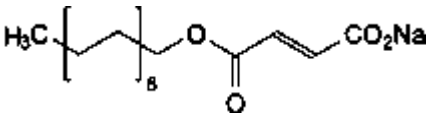
Sodium Stearyl Fumarate

General Notices

(Ph. Eur. monograph 1567)



$C_{22}H_{39}NaO_4$ 390.5 *4070-80-8*

Ph Eur

DEFINITION

Sodium octadecyl (*E*)-butenedioate.

Content

99.0 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, fine powder with agglomerates of flat, circular particles.

Solubility

Practically insoluble in water, slightly soluble in methanol, practically insoluble in acetone and in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *sodium stearyl fumarate CRS*.

TESTS

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

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Silylation solution n. To 2 mL of *N,O-bis(trimethylsilyl)trifluoroacetamide R* add 0.02 mL of *chlorotrimethylsilane R* and mix.

Test solution Introduce 15.0 mg of the substance to be examined in a vial with a screw cap and add 1 mL of the silylation solution. Seal the vial and heat at about 70 °C for 1 h. After the reaction a precipitate remains in the vial; filter the solution through a nylon filter (pore size 0.45 µm).

Reference solution Introduce 1.0 mg of *sodium stearyl maleate CRS* and 1.0 mg of *sodium stearyl fumarate CRS* into a vial with a screw cap and add 1 mL of the silylation solution. Seal the vial and heat at about 70 °C for 1 h.

Column:

— *material*: fused silica;

— *size*: *l* = 15 m, Ø = 0.53 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.15 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2 mL/min.

Split ratio 1:25.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	180
	1 - 21	180 → 320
	21 - 26	320
Injection port		250
Detector		320

Detection Flame ionisation.

Injection 2 µL.

Relative retention With reference to stearyl trimethylsilyl fumarate (retention time = about 9 min): stearyl alcohol = 0.30; stearyl trimethylsilyl ether = 0.35; palmityl trimethylsilyl fumarate = 0.80; heptadecyl trimethylsilyl fumarate = 0.85; stearyl trimethylsilyl maleate = 0.90; nonadecyl trimethylsilyl fumarate = 1.05; eicos-11-enyl trimethylsilyl fumarate = 1.15; distearyl fumarate = 2.25.

System suitability:

— *resolution*: minimum 1.5 between the peaks in the chromatogram obtained with the reference solution.

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Limits:

— *any impurity*: maximum 0.5 per cent;

— *total*: maximum 5.0 per cent.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.250 g.

ASSAY

Dissolve 0.250 g, accurately weighed, in 10 mL of *methylene chloride R* and add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 39.05 mg of $C_{22}H_{39}NaO_4$.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sodium stearyl fumarate used as a lubricant in tablets and capsules.

Particle-size distribution (*2.9.31*)

Specific surface area (*2.9.26, Method I*)

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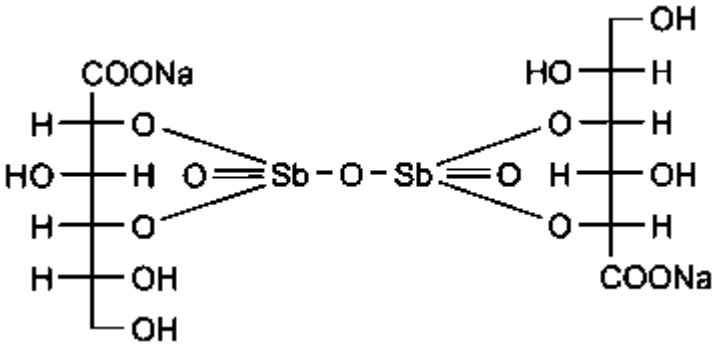
Sodium Stibogluconate

General Notices



16037-91-5

Action and use

Pentavalent antimony compound; antiprotozoal.

Preparation

Sodium Stibogluconate Injection

DEFINITION

Sodium Stibogluconate is mainly the disodium salt of μ-oxy-bis[gluconato(3-)-O^2, O^3,O^4-hydroxoantimony]. It contains not less than 30.0% and not more than 34.0% of antimony(V), calculated with reference to the dried and methanol-free substance.

PRODUCTION

The method of manufacture is such as to ensure consistently controlled reaction stoichiometry in order to yield sodium stibogluconate that is satisfactory with regard to intrinsic toxicity.

CHARACTERISTICS

A colourless, mostly amorphous powder.

Very soluble in *water*; practically insoluble in *ethanol (96%)* and in *ether*.

IDENTIFICATION

A. A solution is dextrorotatory.

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B. Pass *hydrogen sulfide* into a 5% w/v solution for several minutes. An orange precipitate is produced.

C. When heated it chars, without melting, leaving a residue which yields the reactions characteristic of *antimony compounds* and the reactions characteristic of *sodium salts*, Appendix VI.

TESTS

Stability and acidity of solution

Heat a solution containing the equivalent of 10% w/v of antimony(V) in an autoclave at 115.5° and at a pressure of 70 kPa for 30 minutes. The resulting solution is colourless or almost colourless and has a pH of 5.0 to 5.6, Appendix V L.

Antimony(III)

Dissolve 2 g in 30 mL of *water*, add 15 mL of *hydrochloric acid* and titrate with *0.00833M potassium bromate VS* using *methyl orange solution* as indicator. Not more than 1.3 mL of *0.00833M potassium bromate VS* is required.

Chloride

Dissolve 2.5 g in 50 mL of *water* and add 2 mL of 2M *nitric acid* and 75 mL of *acetate buffer pH 5.0*. Titrate with *0.1M silver nitrate VS* determining the end point potentiometrically. Not more than 3.0 mL of *0.1M silver nitrate VS* is required.

Methanol

Not more than 2.0% w/w when determined by the following method. Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) add 1 mL of a 1.0% v/v solution of *methanol* to 5 mL of a 0.2% v/v solution of *absolute ethanol* (internal standard). For solution (2) add 5 mL of *water* to 0.5 g of the substance being examined and mix with the aid of ultrasound until solution is complete. For solution (3) add 5 mL of a 0.2% v/v solution of the internal standard to 0.5 g of the substance being examined and mix with the aid of ultrasound until solution is complete.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with porous polymer beads (80 to 100 mesh) (Porapak Q and Chromosorb 101 are suitable) and maintained at 130°.

Calculate the percentage w/w of methanol taking 0.792 g as its weight per mL at 20°.

Loss on drying

When dried to constant weight at 130° at a pressure not exceeding 0.7 kPa, loses not more than 15.0% of its weight. Use 1 g.

ASSAY

Dissolve 0.16 g in 30 mL of *hydrochloric acid*, add 70 mL of *orthophosphoric acid* and stir carefully until completely mixed. Titrate with 0.05M *ammonium iron(II) sulfate VS* prepared using *sulfuric acid (1%)* and determining the end point potentiometrically using a platinum electrode and a silver-silver chloride reference electrode. Each mL of 0.05M *ammonium iron(II) sulfate VS* is equivalent to 3.044 mg of antimony(V).

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Sodium Stibogluconate Injection

General Notices

Action and use

Pentavalent antimony compound; antiprotozoal.

DEFINITION

Sodium Stibogluconate Injection is a sterile solution of Sodium Stibogluconate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of pentavalent antimony, Sb(V)

9.5 to 10.5% w/v.

CHARACTERISTICS

A colourless or faintly straw-coloured solution.

IDENTIFICATION

A. It is dextrorotatory.

B. Dilute 2 mL to 10 mL with *water* and pass *hydrogen sulfide* through the solution; no immediate precipitate is produced. Continue to pass *hydrogen sulfide* through the solution for several minutes; an orange precipitate is produced.

C. The residue after evaporation to dryness and incineration yields the reactions characteristic of *antimony compounds* and the reactions characteristic of *sodium salts*, Appendix VI.

Acidity

pH, 5.0 to 5.6, Appendix V L.

ASSAY

To 0.5 mL add 30 mL of *hydrochloric acid*, mix, add 70 mL of *orthophosphoric acid* and stir carefully until completely mixed. Titrate with *0.05 M ammonium iron(II) sulfate VS* prepared with *water* containing, in each litre, 20 mL of *sulfuric acid* (*50%*), determining the end point potentiometrically using a platinum electrode and a silver-silver chloride reference electrode. Each mL of *0.05M ammonium iron(II) sulfate VS* is equivalent to 3.044 mg of Sb(V).

STORAGE

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Sodium Stibogluconate Injection should be protected from light.

LABELLING

The strength is stated in terms of the equivalent amount of pentavalent antimony per mL.

Sodium Stibogluconate Injection contains, in 6 mL, the equivalent of 600 mg of pentavalent antimony or 2 g of Sodium Stibogluconate.

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Sodium Sulfate

General Notices

Glauber's Salt

(Sodium Sulfate Decahydrate, Ph. Eur. monograph 0100)

$Na_2SO_4,10H_2O$ 322.2 *7727-73-3*

Action and use

Laxative.

Ph Eur

DEFINITION

Disodium sulfate decahydrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless, transparent crystals.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent). It partly dissolves in its own water of crystallisation at about 33 °C.

IDENTIFICATION

A. It gives reaction (a) of sulfates (*2.3.1*).

B. It gives reaction (a) of sodium (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

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Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Calcium (*2.4.3*)

Maximum 200 ppm, if intended for use in the manufacture of parenteral preparations.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 40 ppm, if intended for use in the manufacture of parenteral preparations.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium

Maximum 100 ppm, if intended for use in the manufacture of parenteral preparations.

To 10 mL of solution S add 1 mL of *glycerol (85 per cent) R*, 0.15 mL of *titan yellow solution R*, 0.25 mL of *ammonium oxalate solution R* and 5 mL of *dilute sodium hydroxide solution R* and shake. Any pink colour in the test solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 5 mL of *magnesium standard solution (10 ppm Mg) R* and 5 mL of *water R*.

Loss on drying (*2.2.32*)

52.0 per cent to 57.0 per cent, determined on 1.000 g by drying at 30 °C for 1 h, then at 130 °C.

ASSAY

Pack 20 g of *strongly acidic ion-exchange resin R* into a glass column, at least 20 cm long and 20 mm in internal diameter, and cover it with *water R*. After 5 min, wash the resin with *water R* until the pH of the eluate is about 6 to 7 using a *pH indicator strip R*. Keep the resin covered with *water R*. Dissolve 1.100 g of the substance to be examined in 10 mL of *water R* in a beaker. Load the solution onto the column and pass through the resin at a flow rate of about 4 mL/min until the resin is just covered with the solution. Using about 200 mL of *water R*, rinse the beaker and pass the rinsings through the column at the same flow rate. Check that the pH of the last eluate is about 6 to 7 using a *pH indicator strip R*.

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Titrate the eluate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 71.00 mg of Na_2SO_4.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Sodium Sulfite

General Notices

Anhydrous Sodium Sulfite

Anhydrous Sodium Sulphite

(Ph. Eur. monograph 0775)

Na_2SO_3 126.0 *7757-83-7*

Action and use

Antioxidant.

Ph Eur

DEFINITION

Content

95.0 per cent to 100.5 per cent of Na_2SO_3.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly alkaline (*2.2.4*).

B. To 5 mL of solution S add 0.5 mL of *0.05 M iodine*. The solution is colourless and gives reaction (a) of sulfates (*2.3.1*).

C. Solution S gives reaction (a) of sodium (*2.3.1*).

D. It complies with the limits of the assay.

TESTS

Solution S

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Dissolve 2.5 g in *water R* and dilute to 50 mL with the same solvent.

Solution S1

To 5.0 g add 12.5 mL of *water R*. Shake until mostly dissolved, carefully and progressively add 7.5 mL of *hydrochloric acid R* and heat to boiling. Cool and dilute to 50.0 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method I*).

Thiosulfates

Maximum 0.1 per cent.

To 2.00 g add 100 mL of *water R*. Shake, add 10 mL of *formaldehyde solution R* and 10 mL of *acetic acid R* and allow to stand for 5 min. Add 0.5 mL of *starch solution R* and titrate with *0.05 M iodine*. Carry out a blank titration. The difference between the volumes used in the titrations is not more than 0.15 mL.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S1.

Zinc

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 2.0 mL of solution S1 to 10.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *zinc standard solution (100 ppm Zn) R*, diluting with *water R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame.

ASSAY

Introduce 0.250 g into a 500 mL conical flask containing 50.0 mL of *0.05 M iodine*. Shake until completely dissolved. Add 1 mL of *starch solution R* and titrate the excess of iodine with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.05 M iodine* is equivalent to 6.30 mg of Na_2SO_3.

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Sodium Sulfite Heptahydrate

General Notices

Sodium Sulphite Heptahydrate

(Ph. Eur. monograph 0776)

$Na_2SO_3,7H_2O$ 252.1 *10102-15-5*

Action and use

Antioxidant.

Ph Eur

DEFINITION

Content

48.0 per cent to 52.5 per cent of Na_2SO_3.

CHARACTERS

Appearance

Colourless crystals.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly alkaline (*2.2.4*).

B. To 5 mL of solution S add 0.5 mL of *0.05 M iodine*. The solution is colourless and gives reaction (a) of sulfates (*2.3.1*).

C. Solution S gives reaction (a) of sodium (*2.3.1*).

D. It complies with the limits of the assay.

TESTS

Solution S

Dissolve 5 g in *water R* and dilute to 50 mL with the same solvent.

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Solution S1

To 10.0 g add 12.5 mL of *water R*. Shake until mostly dissolved, carefully and progressively add 7.5 mL of *hydrochloric acid R* and heat to boiling. Cool and dilute to 50.0 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method I*).

Thiosulfates

Maximum 0.05 per cent.

To 4.00 g add 100 mL of *water R*. Shake to dissolve, then add 10 mL of *formaldehyde solution R* and 10 mL of *acetic acid R*. Allow to stand for 5 min, add 0.5 mL of *starch solution R* and titrate with *0.05 M iodine*. Carry out a blank titration. The difference between the volumes used in the titrations is not more than 0.15 mL.

Iron (*2.4.9*)

Maximum 5 ppm, determined on solution S1.

Zinc

Maximum 12 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 2.0 mL of solution S1 to 10.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *zinc standard solution (100 ppm Zn) R*, diluting with *water R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame.

ASSAY

Introduce 0.500 g into a 500 mL conical flask containing 50.0 mL of *0.05 M iodine*. Shake until completely dissolved. Add 1 mL of *starch solution R* and titrate the excess of iodine with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.05 M iodine* is equivalent to 6.30 mg of Na_2SO_3.

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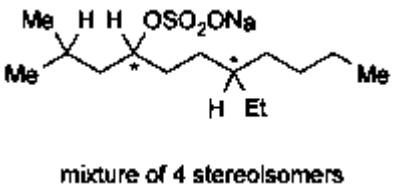
Sodium Tetradecyl Sulfate Concentrate

General Notices

Sodium Tetradecyl Sulphate Concentrate



mixture of 4 stereoisomers

$C_{14}H_{29}NaO_4S$ 316.4 *139-88-8*

Action and use

Sclerosant.

Preparation

Sodium Tetradecyl Sulfate Injection

DEFINITION

Sodium Tetradecyl Sulfate Concentrate is an aqueous gel containing sodium *all-rac*-4-ethyl-1-isobutyloctyl sulfate. It contains not less than 46.0% w/w and not more than 52.0% w/w of $C_{14}H_{29}NaO_4S$.

CHARACTERISTICS

A clear, colourless gel.

IDENTIFICATION

A. Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) boil 0.2 g under a reflux condenser with 20 mL of 2M *hydrochloric acid* for 15 minutes, allow to cool, add 20 mL of *ethanol (96%)* and extract the mixture with two 10 mL quantities of *n-pentane*. Wash the combined pentane extracts with 20 mL of *water* and dry over *anhydrous sodium sulfate*. Solution (2) contains 0.35% w/v of *decan-1-ol* and 0.7% w/v of *dodecan-1-ol* in *n-pentane*.
The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (80 to 100 mesh) coated with 3% w/w of polyethylene glycol (Carbowax 20M is suitable) and maintained at 120°.

The retention time of the principal peak in the chromatogram obtained with solution (1) is less than the retention time of the peak due to dodecan-1-ol and more than that of the peak due to decan-1-ol in the chromatogram obtained with solution (2).

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B. Mix 0.1 mL of a 2% w/v solution with 0.1 mL of a 0.1% w/v solution of *methylene blue* and 2 mL of 1M *sulfuric acid*, add 2 mL of *chloroform* and shake. The chloroform layer is intensely blue.

C. Mix 20 mg with 10 mL of *ethanol (96%)* and heat to boiling on a water bath, shaking frequently. Filter immediately and evaporate the ethanol. Dissolve the residue in 8 mL of *water*, add 3 mL of 2M *hydrochloric acid*, evaporate the solution to half its volume and cool. Filter to remove the congealed fatty alcohols and add 1 mL of 0.25M *barium chloride* to the filtrate. A white, crystalline precipitate is produced.

D. Yields reaction B characteristic of *sodium salts*, Appendix VI.

TESTS

Alkalinity

Dissolve 1 g in 100 mL of *water* and add 0.1 mL of *methyl red solution*; the solution is yellow. Not more than 0.5 mL of *0.1M hydrochloric acid VS* is required to change the colour of the solution.

Non-ionic impurities

Not more than 3.0% w/w, with respect to the nominal content of Sodium Tetradecyl Sulfate, when determined by the method for *gas chromatography*, Appendix III B, using the following solutions. Dissolve 75 mg of *dodecan-1-ol* (internal standard) in sufficient n-*hexane* to produce 100 mL (solution A). For solution (1) extract 1 g of the concentrate being examined with 10 mL of solution A followed by two 10 mL quantities of n-*hexane*. Pass 10 mL of the combined extracts at a rate of about 1.5 mL per minute through a column, 1 cm in diameter, packed with 5 g of *basic aluminium oxide* and pre-washed with 25 mL of n-*hexane*. Elute with 20 mL of a mixture of equal volumes of n-*hexane* and *ether*, evaporate to dryness using a rotary evaporator and dissolve the residue in 2 mL of n-*hexane*. Prepare solution (2) in the same manner but using 10 mL of n-*hexane* in place of 10 mL of solution A.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (80 to 100 mesh) coated with 3% w/w of polyethylene glycol (Carbowax 20M is suitable) and maintained at 120°.

Allow the chromatography to proceed for the retention time of the peak due to the internal standard.

In the chromatogram obtained with solution (1) the sum of the areas of any *secondary peaks* is not greater than twice the area of the peak due to the internal standard.

Chloride

Dissolve 33 mg in sufficient *water* to produce 100 mL. 15 mL of the resulting solution complies with the *limit test for chlorides*, Appendix VII (1%).

Sulfated ash

10.3 to 13.3%, Appendix IX A.

ASSAY

Dissolve 2.4 g in sufficient *water* to produce 1000 mL. To 20 mL add 15 mL of *chloroform* and 10 mL of *dimidium bromide-sulfan blue mixed solution* and titrate with *0.004M benzethonium chloride VS*, shaking vigorously and allowing the layers to separate after each addition, until

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the pink colour of the chloroform layer is completely discharged and a greyish blue colour is produced. Each mL of *0.004M benzethonium chloride VS* is equivalent to 1.266 mg of $C_{14}H_{29}NaO_4S$.

STORAGE

Sodium Tetradecyl Sulfate Concentrate should be protected from light.

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Sodium Tetradecyl Sulfate Injection

General Notices

Sodium Tetradecyl Sulphate Injection

DEFINITION

Sodium Tetradecyl Sulfate Injection is a sterile solution of Sodium Tetradecyl Sulfate Concentrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sodium tetradecyl sulfate, $C_{14}H_{29}NaO_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) boil a volume of the injection containing 0.1 g of sodium tetradecyl sulfate under a reflux condenser with 20 mL of 2M *hydrochloric acid* for 15 minutes, allow to cool, add 20 mL of *ethanol* (*96%*) and extract the mixture with two 10-mL quantities of n-*pentane*. Wash the combined pentane extracts with 20 mL of *water* and dry over *anhydrous sodium sulfate*. Solution (2) contains 0.35% w/v of *decan-1-ol* and 0.7% w/v of *dodecan-1-ol* in n-*pentane*.
The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (80 to 100 mesh) coated with 3% w/w of *polyethylene glycol* (Carbowax 20M is suitable) and maintained at 120°.

The retention time of the principal peak in the chromatogram obtained with solution (1) is less than the retention time of the peak due to dodecan-1-ol and more than that of the peak due to decan-1-ol in the chromatogram obtained with solution (2). A peak due to benzyl alcohol with a retention time less than that of the peak due to decan-1-ol may also be seen.

B. Mix 0.1 mL with 0.1 mL of a 0.1% w/v solution of *methylene blue* and 2 mL of 1M *sulfuric acid*, add 2 mL of *chloroform* and shake. The chloroform layer is intensely blue.
C. Dilute 0.5 mL with 10 mL of *ethanol* (*96%*) and heat to boiling on a water bath, shaking frequently. Filter immediately and evaporate the ethanol. Dissolve the residue in 8 mL of *water*, add 3 mL of 2M *hydrochloric acid*, evaporate the solution to half its volume and cool. Filter to remove the congealed fatty alcohols and add 1 mL of 0.25M *barium chloride* to the filtrate. A white crystalline precipitate is produced.

Alkalinity

pH, 7.5 to 7.9, Appendix V L.

ASSAY

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Dilute a volume containing 0.12 g of sodium tetradecyl sulfate to 100 mL with *water*. To 20 mL add 15 mL of *chloroform* and 10 mL of *dimidium bromide-sulfan blue mixed solution* and titrate with *0.004M benzethonium chloride VS*, shaking vigorously and allowing the layers to separate after each addition, until the pink colour of the chloroform layer is completely discharged and a greyish blue colour is produced. Each mL of *0.004M benzethonium chloride VS* is equivalent to 1.266 mg of $C_{14}H_{29}NaO_4S$.

STORAGE

Sodium Tetradecyl Sulfate Injection should be protected from light.

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Sodium Thiosulfate

General Notices

Sodium Thiosulphate

(Ph. Eur. monograph 0414)

$Na_2S_2O_3,5H_2O$ 248.2 *10102-17-7*

Action and use

Used in treatment of cyanide poisoning.

Preparation

Sodium Thiosulfate Injection

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DEFINITION

Content

99.0 per cent to 101.0 per cent of $Na_2S_2O_3,5H_2O$.

CHARACTERS

Appearance

Transparent, colourless crystals, efflorescent in dry air.

Solubility

Very soluble in water, practically insoluble in ethanol 96 per cent. It dissolves in its water of crystallisation at about 49 °C.

IDENTIFICATION

A. It decolourises *iodinated potassium iodide solution R*.

B. To 0.5 mL of solution S (see Tests) add 0.5 mL of *water R* and 2 mL of *silver nitrate solution R2*. A white precipitate is formed which rapidly becomes yellowish and then black.

C. To 2.5 mL of solution S add 2.5 mL of *water R* and 1 mL of *hydrochloric acid R*. A precipitate of sulfur is formed and gas is evolved which gives a blue colour to *starch iodate paper R*.

D. 1 mL of solution S gives reaction (a) of sodium (*2.3.1*).

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TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

The freshly prepared solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 10.0 g in 50 mL of *distilled water R*, add 1 mL of *0.1 M sodium hydroxide* and dilute to 100 mL with the same solvent.

pH (*2.2.3*)

6.0 to 8.4 for the freshly prepared solution S.

Sulfates and sulfites (*2.4.13*)

Maximum 0.2 per cent.

Dilute 2.5 mL of freshly prepared solution S to 10 mL with *distilled water R*. To 3 mL of this solution first add 2 mL of *iodinated potassium iodide solution R* and continue the addition dropwise until a very faint persistent yellow colour appears. Dilute to 15 mL with *distilled water R*.

Sulfides

To 10 mL of solution S add 0.05 mL of a freshly prepared 50 g/L solution of *sodium nitroprusside R*. The solution does not become violet.

ASSAY

Dissolve 0.500 g in 20 mL of *water R* and titrate with *0.05 M iodine*, using 1 mL of *starch solution R*, added towards the end of the titration, as indicator.

1 mL of *0.05 M iodine* is equivalent to 24.82 mg of $Na_2S_2O_3,5H_2O$.

STORAGE

In an airtight container.

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Sodium Thiosulfate Injection

General Notices

Sodium Thiosulphate Injection

DEFINITION

Sodium Thiosulfate Injection is a sterile solution of Sodium Thiosulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sodium thiosulfate, $Na_2S_2O_3,5H_2O$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. Yields the reactions characteristic of *sodium salts*, Appendix VI.

B. To 1 mL add *iodinated potassium iodide solution*, the reagent is initially decolourised, until a very faint persistent yellow colour appears. The mixture does not yield reaction A characteristic of sulfates, Appendix VI.

C. To 5 mL add 1 mL of *hydrochloric acid*. A white precipitate which quickly changes to yellow is formed, and a gas is evolved which turns *starch iodate paper* blue.

TESTS

Acidity or alkalinity

pH, 7.0 to 9.0, Appendix V L.

ASSAY

Dilute a volume containing 0.5 g of Sodium Thiosulfate to about 20 mL with *water* and titrate with *0.05M iodine VS* using 1 mL of *starch solution*, added towards the end of the titration, as indicator. Each mL of *0.05M iodine VS* is equivalent to 24.82 mg of $Na_2S_2O_3,5H_2O$.

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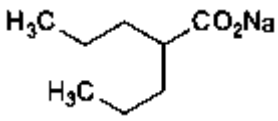
Sodium Valproate

General Notices

(Ph. Eur. monograph 0678)



$C_8H_{15}NaO_2$ 166.2 *1069-66-5*

Action and use

Antiepileptic.

Preparations

Sodium Valproate Gastro-resistant Tablets

Sodium Valproate Oral Solution

Sodium Valproate Tablets

Sodium Valproate Prolonged-release Capsules

Sodium Valproate Prolonged-release Tablets

Ph Eur

DEFINITION

Sodium 2-propylpentanoate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline, hygroscopic powder.

Solubility

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Very soluble in water, freely soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sodium valproate CRS*.

If the spectra obtained in the solid state show differences, record new spectra using discs prepared by placing 50 µL of a 100 g/L solution in *methanol R* on a disc of *potassium bromide R* and evaporating the solvent *in vacuo*. Examine immediately.

B. 2 mL of solution S (see Tests) gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 1.25 g in 20 mL of *distilled water R* in a separating funnel, add 5 mL of *dilute nitric acid R* and shake. Allow the mixture to stand for 12 h. Use the aqueous lower layer.

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 2.0 g in *water R* and dilute to 10 mL with the same solvent.

Acidity or alkalinity

Dissolve 1.0 g in 10 mL of *water R*. Add 0.1 mL of *phenolphthalein solution R*. Not more than 0.75 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 0.500 g of the substance to be examined in 10 mL of *water R*. Add 5 mL of *dilute sulfuric acid R* and shake with 3 quantities, each of 20 mL, of *heptane R*. Dilute the combined upper layers to 100.0 mL with *heptane R*.

Reference solution (a) Dissolve 5 mg of *valproic acid for system suitability CRS* (containing impurity K) in 1.0 mL of *heptane R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *heptane R*.

Column:

— *material*: wide-bore fused silica;

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— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *macrogol 20 000 2-nitroterephthalate R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 8 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	80
	5 - 15	80 → 150
	15 - 28.3	150 → 190
	28.3 - 30	190
Injection port		220
Detector		220

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to valproic acid (retention time = about 17 min): impurity K = about 0.97.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity K and valproic acid.

Limits:

— *impurity K*: not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.03 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

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To 5 mL of solution S add 10 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.150 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.62 mg of $C_8H_{15}NaO_2$.

STORAGE

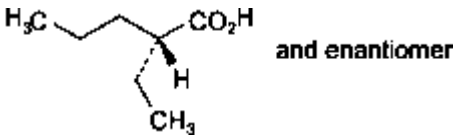
In an airtight container.

IMPURITIES

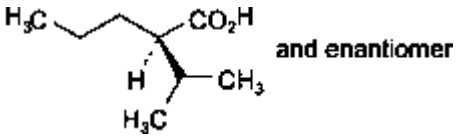
Specified impurities K.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, F, G, I, J, L.

A. pentanoic acid (valeric acid),



B. (2*RS*)-2-ethylpentanoic acid,



C. (2*RS*)-2-(1-methylethyl)pentanoic acid,

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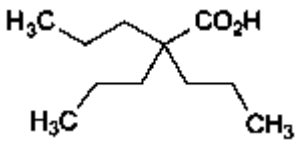
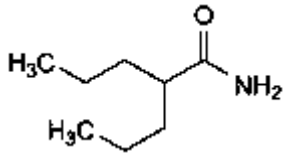
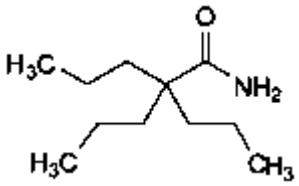


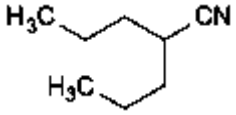
D. 2,2-dipropylpentanoic acid,



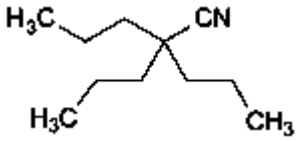
F. 2-propylpentanamide,



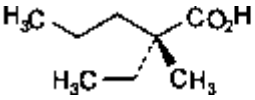
G. 2,2-dipropylpentanamide,



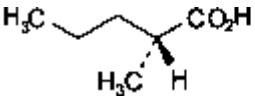
I. 2-propylpentanenitrile,



J. 2,2-dipropylpentanenitrile,



K. (2*RS*)-2-ethyl-2-methylpentanoic acid,



L. (2*RS*)-2-methylpentanoic acid.

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Sodium Valproate Gastro-resistant Tablets

General Notices

Gastro-resistant Sodium Valproate Tablets

Sodium Valproate Gastro-resistant Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.

Action and use

Antiepileptic.

DEFINITION

Sodium Valproate Gastro-resistant Tablets contain Sodium Valproate. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sodium valproate, $C_8H_{15}NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 10 mL of *water* and centrifuge. Acidify 5 mL of the supernatant liquid with 2M *sulfuric acid*, shake with 25 mL of *dichloromethane* and wash the dichloromethane layer with 5 mL of *water*. Dry by shaking with *anhydrous sodium sulfate*, filter and evaporate the dichloromethane to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of valproic acid (*RS 431*).

B. Shake a quantity of the powdered tablets containing 0.25 g of Sodium Valproate with 3 mL of *water* and centrifuge. To 2 mL of the supernatant liquid add 0.5 mL of a 10% w/v solution of *cobalt(II) nitrate*. A purple precipitate is produced which is soluble in *dichloromethane*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

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(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 2 hours, withdraw a 20-mL sample of the medium and filter.

(2) 0.001% w/v of *sodium valproate BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

45 volumes of a 0.32% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid* and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of sodium valproate, $C_8H_{15}NaO_2$, in the medium using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

LIMITS

The amount of sodium valproate released is not more than 5% of the stated amount.

Final stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Replace the *0.1M hydrochloric acid* in the vessel with 900 mL of *phosphate buffer pH 6.8*, previously held at 37°, as the medium.

PROCEDURE

(1) After 60 minutes, withdraw a 20-mL sample of the medium and filter. Use the filtrate diluted, if necessary, to give a solution expected to contain 0.002% w/v of Sodium Valproate.

(2) 0.02% w/v solution of *sodium valproate BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of sodium valproate, $C_8H_{15}NaO_2$, in the medium using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

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LIMITS

The amount of sodium valproate released after the final stage is not less than 70% of the stated amount.

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) 0.005% w/v of *octanoic acid* in *dichloromethane* (internal standard solution).

(2) Disperse a quantity of the powdered tablets containing 1 g of Sodium Valproate with 20 mL of 0.1M *sodium hydroxide*, and mix with the aid of ultrasound for 30 minutes. Centrifuge the solution and transfer 10 mL of the supernatant into a separating funnel. Mix the resulting solution with 1 mL of 2M *sulfuric acid* and add 10 mL of solution (1). Extract the mixture with three 20-mL quantities of *dichloromethane* and combine the organic layers. Dry by shaking with *anhydrous sodium sulfate*, and filter (a GF/A filter is suitable). Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 10 mL with *dichloromethane*.

(3) Dilute 1 volume of solution (2) to 100 volumes with solution (1). Dilute 1 volume of the resulting solution to 10 volumes with solution 1.

(4) 5% w/v of *valproic acid for system suitability EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 0.5-µm layer of *macrogol 20,000 2-nitroterephthalate* (DB-FFAP is suitable).

(b) Use *helium* as the carrier gas at 8 mL per minute.

(c) Use the temperature gradient conditions as described below.

(d) Use an injection temperature of 220°.

(e) Use a flame ionisation detector at 220°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature (°C)	Comment
0-5	80	isothermal
5-15	80→150	linear gradient
15-28.3	150→190	linear gradient
28.3-30	190	isothermal
30-35	190→250	linear gradient
35-45	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to valproic acid (retention time, about 15 minutes) are: impurity K, about 0.97; octanoic acid, about 1.12.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity K and valproic acid is at least 2.0.

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LIMITS

Using the chromatogram obtained with solution (3), calculate the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard (*R*).

In the chromatogram obtained with solution (2):

the ratio of the area of the peak due to impurity K to the area of the peak due to the internal standard is not greater than 2*R* (0.2%);

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than *R* (0.1%);

the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than 4*R* (0.4%).

Disregard any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not greater than half of *R* (0.05%) and any peak eluting after 30 minutes.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

Solution A: Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 6.8 with 0.2M *sodium hydroxide*.

(1) Weigh and powder 20 tablets. Shake with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 50 mL of *acetonitrile R1*. Add 100 mL of solution A and mix further with the aid of ultrasound. Dilute the solution to 200 mL and filter (a 0.2-µm nylon syringe filter is suitable). Dilute 1 volume of this solution to 5 volumes with solution A.
(2) Mix with the aid of ultrasound 50 mg of *sodium valproate BPCRS* with 5 mL of *acetonitrile R1*. Add 10 mL of solution A and mix further with the aid of ultrasound. Dilute the resulting solution to 100 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile R1* and 50 volumes of a solution prepared by dissolving 1.56 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 2.3 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}NaO_2$ in the tablets using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

IMPURITIES

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Sodium Valproate Oral Solution

General Notices

Sodium Valproate Oral Solutions from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.

Action and use

Antiepileptic.

DEFINITION

Sodium Valproate Oral Solution is a solution of Sodium Valproate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of sodium valproate, $C_8H_{15}NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the oral solution containing 0.25 g of Sodium Valproate with two 25-mL quantities of *dichloromethane* and discard the dichloromethane extracts. Add 10 mL of a saturated solution of *sodium chloride* and 10 mL of 2M *hydrochloric acid*, mix and shake with 25 mL of *dichloromethane*. Wash the dichloromethane layer with 5 mL of *water*, shake with *anhydrous sodium sulfate*, filter and evaporate to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of valproic acid *(RS 431)*.

B. Shake a quantity of the oral solution containing 0.25 g of Sodium Valproate with 3 mL of *water*. To 2 mL of the resulting solution add 0.5 mL of a 10% w/v solution of *cobalt(II) nitrate*. A purple precipitate is produced which is soluble in *dichloromethane*.

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) 0.005% w/v of *octanoic acid* in *dichloromethane* (internal standard solution).

(2) Shake a quantity of the oral solution containing 0.5 g of Sodium Valproate with 80 mL of *water* and acidify with 1 mL of 2M *sulfuric acid*. Mix the solution and add 10 mL of solution (1). Extract the mixture with three 20-mL quantities of *dichloromethane* and combine the organic layers. Dry by shaking with *anhydrous sodium sulfate*, and filter (a GF/A filter is suitable). Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 10 mL with *dichloromethane*.

(3) Dilute 1 volume of solution (2) to 100 volumes with solution (1). Dilute 1 volume of the resulting solution to 10 volumes with solution (1).

(4) 5% w/v of *valproic acid for system suitability EPCRS* in *dichloromethane*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 0.5-µm layer of *macrogol 20,000 2-nitroterephthalate* (DB-FFAP is suitable).

(b) Use *helium* as the carrier gas at 8 mL per minute.

(c) Use the temperature gradient conditions as described below.

(d) Use an injection temperature of 220°.

(e) Use a flame ionisation detector at 220°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature (°C)	Comment
0-5	80	isothermal
5-15	80→150	linear gradient
15-28.3	150→190	linear gradient
28.3-30	190	isothermal
30-35	190→250	linear gradient
35-45	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to valproic acid (retention time, about 15 minutes) are: impurity K, about 0.97; octanoic acid, about 1.12.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity K and valproic acid is at least 2.0;

LIMITS

Using the chromatogram obtained with solution (3), calculate the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard (*R*).

In the chromatogram obtained with solution (2):

the ratio of the area of the peak due to impurity K to the area of the peak due to the internal standard is not greater than 2*R* (0.2%);

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than *R* (0.1%);

the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than 4*R* (0.4%).

Disregard any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not greater than half of *R* (0.05%) and any peak eluting after 30 minutes.

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions.

(1) Add 1 mL of a 10% v/v solution of *orthophosphoric acid* to a weighed quantity of the oral solution containing 0.16 g of Sodium Valproate and dilute to 50 mL with the mobile phase.

(2) Dissolve 0.16 g of *sodium valproate BPCRS* in 15 mL of the mobile phase, add 1 mL of a 10% v/v solution of *orthophosphoric acid*, mix and dilute to 50 mL with the mobile phase.

(3) 0.002% w/v of *propyl 4-hydroxybenzoate* in solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of 0.05M *potassium dihydrogen orthophosphate* and 65 volumes of *methanol R1*, the pH of the final mixture being adjusted to 5.0 with a 10% v/v solution of *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_8H_{15}NaO_2$, weight in volume, from the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sodium Valproate.

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Sodium Valproate Prolonged-release Capsules

General Notices

Prolonged-release Sodium Valproate Capsules

Sodium Valproate Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Antiepileptic.

DEFINITION

Sodium Valproate Prolonged-release Capsules contain Sodium Valproate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Sodium Valproate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of sodium valproate, $C_8H_{15}NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered contents of the capsules containing 0.5 g of Sodium Valproate with 10 mL of *water* and centrifuge. Acidify 5 mL of the supernatant liquid with 2M *sulfuric acid*, shake with 25 mL of *dichloromethane* and wash the dichloromethane layer with 5 mL of *water*. Dry by shaking with *anhydrous sodium sulfate*, filter and evaporate the dichloromethane. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of valproic acid (*RS 431*).

B. Shake a quantity of the powdered capsule contents containing 0.25 g of Sodium Valproate with 3 mL of *water* and centrifuge. To 2 mL of the supernatant liquid add 0.5 mL of a 10% w/v solution of *cobalt(II) nitrate*. A purple precipitate is produced which is soluble in *dichloromethane*.

TESTS

Related substances

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Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) 0.005% w/v of *octanoic acid* in *dichloromethane* (internal standard solution).

(2) Disperse a quantity of the powdered contents of the capsules containing 1 g of Sodium Valproate with 20 mL of 0.1M *sodium hydroxide*, and mix with the aid of ultrasound for 30 minutes. Centrifuge the solution and transfer 10 mL of the supernatant into a separating funnel. Mix the resulting solution with 1 mL of 2M *sulfuric acid* and add 5 mL of solution (1). Extract the mixture with three 20-mL quantities of *dichloromethane* and combine the organic layers. Dry by shaking with *anhydrous sodium sulfate*, and filter (a GF/A filter is suitable). Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 10 mL with *dichloromethane*.

(3) Dilute 1 volume of solution (2) to 100 volumes with solution (1). Dilute 1 volume of the resulting solution to 10 volumes with solution (1).

(4) 5% w/v of *valproic acid for system suitability EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 0.5-µm layer of *macrogol 20,000 2-nitroterephthalate* (DB-FFAP is suitable).

(b) Use *helium* as the carrier gas at 8 mL per minute.

(c) Use the temperature gradient conditions as described below.

(d) Use an injection temperature of 220°.

(e) Use a flame ionisation detector at 220°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature (°C)	Comment
0-5	80	isothermal
5-15	80→150	linear gradient
15-28.3	150→190	linear gradient
28.3-30	190	isothermal
30-35	190→250	linear gradient
35-45	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to valproic acid (retention time, about 15 minutes) are: impurity K, about 0.97; octanoic acid, about 1.12.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity K and valproic acid is at least 2.0.

LIMITS

Using the chromatogram obtained with solution (3), calculate the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard (*R*).

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In the chromatogram obtained with solution (2):

the ratio of the area of the peak due to impurity K to the area of the peak due to the internal standard is not greater than 2*R* (0.2%);

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than *R* (0.1%);

the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than 4*R* (0.4%).

Disregard any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not greater than half of *R* (0.05%) and any peak eluting after 30 minutes.

ASSAY

Weigh and mix the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

Solution A: Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 6.8 with 0.2M *sodium hydroxide*.

(1) Shake with the aid of ultrasound a quantity of the powdered capsule contents containing 0.5 g of Sodium Valproate with 50 mL of *acetonitrile R1*. Add 100 mL of solution A and mix further with the aid of ultrasound. Dilute the solution to 200 mL and filter (a 0.2-µm nylon syringe filter is suitable). Dilute 1 volume of this solution to 5 volumes with solution A.
(2) Mix with the aid of ultrasound 50 mg of *sodium valproate BPCRS* with 5 mL of *acetonitrile R1*. Add 10 mL of solution A and mix further with the aid of ultrasound. Dilute the resulting solution to 100 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile R1* and 50 volumes of a solution prepared by dissolving 1.56 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 2.3 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of sodium valproate is about 8 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}NaO_2$ in the capsules using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sodium Valproate.

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Sodium Valproate Prolonged-release Tablets

General Notices

Prolonged-release Sodium Valproate Tablets

Sodium Valproate Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Antiepileptic.

DEFINITION

Sodium Valproate Prolonged-release Tablets contain Sodium Valproate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Sodium Valproate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sodium valproate, $C_8H_{15}NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 10 mL of *water* and centrifuge. Acidify 5 mL of the supernatant liquid with 2M *sulfuric acid*, shake with 25 mL of *dichloromethane* and wash the dichloromethane layer with 5 mL of *water*. Dry by shaking with *anhydrous sodium sulfate*, filter and evaporate the dichloromethane. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of valproic acid (*RS 431*).

B. Shake a quantity of the powdered tablets containing 0.25 g of Sodium Valproate with 3 mL of *water* and centrifuge. To 2 mL of the supernatant liquid add 0.5 mL of a 10% w/v solution of *cobalt(II) nitrate*. A purple precipitate is produced which is soluble in *dichloromethane*.

TESTS

Related substances

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Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) 0.005% w/v of *octanoic acid* in *dichloromethane* (internal standard solution).

(2) Disperse a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 25 mL of 0.1M *sodium hydroxide*, and mix with the aid of ultrasound for 30 minutes. Centrifuge the solution and transfer 12.5 mL of the supernatant into a separating funnel. Mix the resulting solution with 1.25 mL of 2M *sulfuric acid* and add 5 mL of solution (1). Extract the mixture with three 10-mL quantities of *dichloromethane* and combine the organic layers. Dry by shaking with *anhydrous sodium sulfate*, and filter (a GF/A filter is suitable). Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 5 mL with *dichloromethane*.

(3) Dilute 1 volume of solution (2) to 100 volumes with solution (1). Dilute 1 volume of the resulting solution to 10 volumes with solution (1).

(4) 5% w/v of *valproic acid for system suitability EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 0.5-µm layer of *macrogol 20,000 2-nitroterephthalate* (DB-FFAP is suitable).

(b) Use *helium* as the carrier gas at 8 mL per minute.

(c) Use the temperature gradient conditions as described below.

(d) Use an injection temperature of 220°.

(e) Use a flame ionisation detector at 220°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:10

Time (Minutes)	Temperature (°C)	Comment
0-5	80	isothermal
5-15	80→150	linear gradient
15-28.3	150→190	linear gradient
28.3-30	190	isothermal
30-35	190→250	linear gradient
35-45	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to valproic acid (retention time, about 15 minutes) are: impurity K, about 0.97; octanoic acid, about 1.12.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity K and valproic acid is at least 2.0.

LIMITS

Using the chromatogram obtained with solution (3), calculate the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard (*R*).

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In the chromatogram obtained with solution (2):

the ratio of the area of the peak due to impurity K to the area of the peak due to the internal standard is not greater than 2*R* (0.2%);

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than *R* (0.1%);

the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than 4*R* (0.4%).

Disregard any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not greater than half of *R* (0.05%) and any peak eluting after 30 minutes.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

Solution A: Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 6.8 with 0.2M *sodium hydroxide*.

(1) Weigh and powder 20 tablets. Shake with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 50 mL of *acetonitrile R1*. Add 100 mL of solution A and mix further with the aid of ultrasound. Dilute the solution to 200 mL and filter (a 0.2-µm nylon syringe filter is suitable). Dilute 1 volume of this solution to 5 volumes with solution A.
(2) Mix with the aid of ultrasound 50 mg of *sodium valproate BPCRS* with 5 mL of *acetonitrile R1*. Add 10 mL of solution A and mix further with the aid of ultrasound. Dilute the resulting solution to 100 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile R1* and 50 volumes of a solution prepared by dissolving 1.56 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 2.3 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of sodium valproate is about 8 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}NaO_2$ in the tablets using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sodium Valproate.

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Sodium Valproate Tablets

General Notices

Sodium Valproate Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.

Action and use

Antiepileptic.

DEFINITION

Sodium Valproate Tablets contain Sodium Valproate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sodium valproate, $C_8H_{15}NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 10 mL of *water* and centrifuge. Acidify 5 mL of the supernatant liquid with 2M *sulfuric acid*, shake with 25 mL of *dichloromethane* and wash the dichloromethane layer with 5 mL of *water*. Dry by shaking with *anhydrous sodium sulfate*, filter and evaporate the dichloromethane. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of valproic acid (*RS 431*).

B. Shake a quantity of the powdered tablets containing 0.25 g of Sodium Valproate with 3 mL of *water* and centrifuge. To 2 mL of the supernatant liquid add 0.5 mL of a 10% w/v solution of *cobalt(II) nitrate*. A purple precipitate is produced which is soluble in *dichloromethane*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtrate diluted, if necessary, to give a solution expected to contain 0.01% w/v of Sodium Valproate.

(2) 0.01% w/v of *sodium valproate BPCRS* in *phosphate buffer pH 6.8*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile R1* and 50 volumes of a solution prepared by dissolving 1.56 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 2.3 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of sodium valproate, $C_8H_{15}NaO_2$, in the medium from the chromatograms obtained and using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

LIMITS

The amount of sodium valproate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) 0.005% w/v of *octanoic acid* in *dichloromethane* (internal standard solution).

(2) Disperse a quantity of the powdered tablets containing 1 g of Sodium Valproate with 20 mL of 0.1M *sodium hydroxide*, and mix with the aid of ultrasound for 30 minutes. Centrifuge the solution and transfer 10 mL of the supernatant into a separating funnel. Mix the resulting solution with 1 mL of 2M *sulfuric acid* and add 10 mL of solution (1). Extract the mixture with three 20-mL quantities of *dichloromethane* and combine the organic layers. Dry by shaking with *anhydrous sodium sulfate*, and filter (a GF/A filter is suitable). Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 10 mL with *dichloromethane*.

(3) Dilute 1 volume of solution (2) to 100 volumes with solution (1). Dilute 1 volume of the resulting solution to 10 volumes with solution (1).

(4) 5% w/v of *valproic acid for system suitability EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 0.5-µm layer of *macrogol 20,000 2-nitroterephthalate* (DB-FFAP is suitable).

(b) Use *helium* as the carrier gas at 8 mL per minute.

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(c) Use the temperature gradient conditions as described below.

(d) Use an injection temperature of 220°.

(e) Use a flame ionisation detector at 220°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature (°C)	Comment
0-5	80	isothermal
5-15	80→150	linear gradient
15-28.3	150→190	linear gradient
28.3-30	190	isothermal
30-35	190→250	linear gradient
35-45	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to valproic acid (retention time, about 15 minutes) is: impurity K, about 0.97; octanoic acid, about 1.12.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity K and valproic acid is at least 2.0.

LIMITS

Using the chromatogram obtained with solution (3), calculate the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard (*R*).

In the chromatogram obtained with solution (2):

the ratio of the area of the peak due to impurity K to the area of the peak due to the internal standard is not greater than 2*R* (0.2%);

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than *R* (0.1%);

the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than 4*R* (0.4%).

Disregard any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not greater than half of *R* (0.05%) and any peak eluting after 30 minutes.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

Solution A: Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 6.8 with 0.2M *sodium hydroxide*.

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(1) Weigh and powder 20 tablets. Shake with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 50 mL of *acetonitrile R1*. Add 100 mL of solution A and mix further with the aid of ultrasound. Dilute the solution to 200 mL and filter (a 0.2-µm nylon syringe filter is suitable). Dilute 1 volume of this solution to 5 volumes with solution A.

(2) Mix with the aid of ultrasound 50 mg of *sodium valproate BPCRS* with 5 mL of *acetonitrile R1*. Add 10 mL of solution A and mix further with the aid of ultrasound. Dilute the resulting solution to 100 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

When the chromatograms are recorded under the prescribed conditions the retention time of sodium valproate is about 8 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}NaO_2$ in the tablets using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sodium Valproate.

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Soft Soap

General Notices

Preparation

Soap Spirit

DEFINITION

Soft Soap is soap made by the interaction of potassium hydroxide or sodium hydroxide with a suitable vegetable oil or oils or with fatty acids derived there from. It yields not less than 44.0% of fatty acids. It may be coloured with chlorophyll or not more than 0.015% of a suitable green soap dye.

CHARACTERISTICS

A yellowish white to green or brown, unctuous substance.

Soluble in *water* and in *ethanol (96%)*.

TESTS

Chlorides and other ethanol-insoluble substances

Dissolve 5 g in 100 mL of hot *ethanol (96%)* previously neutralised to *phenolphthalein solution R1*, filter through a dried and tared filter, wash the residue thoroughly with hot neutralised *ethanol (96%)* and dry to constant weight at 105°. The residue weighs not more than 0.15 g.

Free fatty acid or alkali hydroxide

Boil 250 mL of *ethanol (96%)* to remove carbon dioxide, add 0.5 mL of *phenolphthalein solution R1*, allow to cool to 70° and neutralise, if necessary, with *0.1M sodium hydroxide VS* or *0.05M sulfuric acid VS*. To 100 mL of the neutral ethanol add 10 g of the substance being examined and dissolve it as quickly as possible by heating under a reflux condenser. Cool to 70° and, if the solution is not pink, titrate at 70° with *0.1M sodium hydroxide VS*; not more than 0.2 mL is required. If the solution is pink add, in a thin stream, 5 mL of hot *barium chloride solution* previously neutralised to *phenolphthalein solution R1*, mix thoroughly and titrate with *0.1M hydrochloric acid VS* until the pink colour disappears; not more than 1.0 mL is required.

Total free alkali

To 100 mL of the neutral ethanol prepared as described in the test for Free fatty acid or alkali hydroxide add 10 g of the substance being examined and dissolve it as quickly as possible by heating under a reflux condenser. Add immediately 3 mL of *0.5M sulfuric acid VS* and boil under a reflux condenser on a water bath for at least 10 minutes. If the solution is not pink, cool to 70° and titrate with *1M sodium*

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hydroxide VS until a pink colour is produced. The volume of *0.5M sulfuric acid VS* neutralised by the substance being examined is not more than 1.0 mL.

Unsaponifiable matter and unsaponified neutral fat

Dissolve 5 g in 80 mL of a mixture of 50 mL of *ethanol (96%)* and 100 mL of *water*, without heating more than is necessary, and transfer to a separating funnel, washing the vessel with the remaining 70 mL of the mixture. Extract with 100 mL of *ether* while still slightly warm, run off the ethanolic soap layer into a second separating funnel and extract with 50 mL of *ether*. Repeat the extraction with 50 mL of *ether* and pour the three ether extracts into a separating funnel containing 20 mL of *water*. Rotate the separating funnel without violent shaking and, after allowing the liquids to separate, run off the water. Repeat the washing with *water* in the same manner until the separated washings are not more than faintly turbid when acidified. Wash the ether solution twice by shaking vigorously with 20 mL of *0.5M potassium hydroxide*, each washing with alkali being immediately followed by washing with 20 mL of *water*, shaking vigorously each time. Acidify the last alkali washing after separation and, if the liquid becomes turbid, repeat the washing with *0.5M potassium hydroxide* and *water* until the alkali washing remains clear on acidification. Finally wash with successive 20 mL quantities of *water* until the washings do not give a pink colour with *phenolphthalein solution R1*. Transfer the ether solution to a tared flask and remove the ether. When nearly all the ether has evaporated, add 3 mL of *acetone*. With the aid of a gentle current of air remove the solvent completely from the flask, which is preferably almost entirely immersed in boiling *water*, held obliquely and rotated. Repeat the last operation until the weight of the residue is constant. The residue weighs not more than 40 mg.

CHARACTERISTICS OF THE FATTY ACIDS OBTAINED IN THE ASSAY

Acid value

Not more than 205, Appendix X B, when determined on 2 to 3 g of the fatty acids, using *0.5M potassium hydroxide VS* and substituting 2.805 for 5.610 in the formula.

Iodine value

Not less than 83 (*iodine monochloride method*), Appendix X E.

Solidifying point

Not above 31°, Appendix V B, with the following modifications. Where the determination is made at 15° to 20° the 1000 mL beaker and cooling liquid need not be used. Where the room temperature falls outside this range the 1000 mL beaker should contain water maintained at 15° to 20° and the level of this water should not be below the level of the sample in the inner tube.

Transfer about 15 mL of the melted fatty acids to the inner test tube. Before the temperature of the fatty acids drops to a point 10° above their expected solidifying point, begin agitation in a vertical manner at a rate of 100 complete up and down motions per minute, the stirrer moving through a vertical distance of about 38 mm. Continue stirring in this manner until the temperature has remained constant for 30 seconds or has begun to rise within 30 seconds of ceasing to fall. Discontinue stirring immediately and lift the stirrer out of the sample. Observe the rise in temperature; the highest temperature reached after cessation of stirring is the solidifying point of the fatty acids. When reading the thermometer avoid all undue vibration as this will cause the temperature to drop before reaching the maximum.

Resin

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Mix 0.5 mL of the melted fatty acids in a test tube with 2 mL of *acetic anhydride*, warm, shake until clear and cool to 15.5°. Transfer one drop of this solution to a white porcelain tile, place one drop of a cold mixture of equal volumes of *sulfuric acid* and *water* adjacent to it and gently bring the drops together with a glass rod. No transient violet colour is produced.

ASSAY

Dissolve 30 g in 100 mL of *water*, transfer to a separating funnel, acidify with 1M *sulfuric acid* and extract with successive quantities of 50, 40 and 30 mL of *ether*. Mix the ether solutions in a separating funnel and wash with *water* until the washings are free from mineral acid. Transfer the ether solution to a tared flask, remove the ether and dry the residue of fatty acids to constant weight at 80°.

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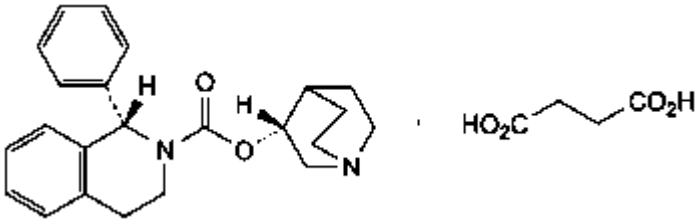
Solifenacin Succinate

General Notices

(Ph. Eur. monograph 2779)



$C_{27}H_{32}N_2O_6$ 480.6 *242478-38-2*

Action and use

Muscarinic M_3 receptor antagonist; anticholinergic.

Preparation

Solifenacin Tablets

Ph Eur

DEFINITION

(3*R*)-1-Azabicyclo[2.2.2]octan-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate hydrogen butanedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or light yellow powder.

Solubility

Very soluble or freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *solifenacin succinate CRS*.

B. Isomeric purity (see Tests).

TESTS

Isomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *solifenacin for system suitability CRS* (containing impurities F, G and H) in 1.0 mL of the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 35 °C.

Mobile phase *diethylamine R*, *anhydrous ethanol R*, *heptane R* (0.1:200:800 *V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 1.5 times the retention time of solifenacin.

Identification of impurities Use the chromatogram supplied with *solifenacin for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities F, G and H.

Relative retention With reference to solifenacin (retention time = about 17 min): impurity F = about 0.7; impurity H = about 0.76; impurity G = about 0.84.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities F and H;

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— *peak-to-valley ratio*: minimum 10, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity H.

Calculation of percentage contents:

— for each impurity, use the concentration of solifenacin succinate in reference solution (b).

Limits:

— *impurities F, G, H*: for each impurity, maximum 0.15 per cent.

Impurity E

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.500 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 5.0 mg of *3-quinuclidinol R* (impurity E) in *methanol R* and dilute to 50.0 mL with the same solvent.

Plate *TLC silica gel plate R* (2-10 µm).

Mobile phase *concentrated ammonia R*, *anhydrous ethanol R*, *toluene R* (6:31:63 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying At 100-105 °C for 1 h.

Detection Expose to iodine vapour for at least 2 h.

Relative retention With reference to solifenacin (R_F = about 0.6): impurity E = about 0.2.

Limit:

— *impurity E*: any spot due to impurity E is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Dissolve 0.6 g of *ammonium phosphate R* in 1 L of *water R*, add 1.0 mL of *diethylamine R* and adjust to pH 11 with *concentrated ammonia R*.

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *1-phenyl-1,2,3,4-tetrahydroisoquinoline R* (impurity A) in the test solution and dilute to 25.0 mL with the test solution.

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Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged polar-embedded octadecylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, solvent mixture (45:55 *V/V*);

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	90	10
0.5 - 10.5	90 → 68	10 → 32
10.5 - 12.5	68	32

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 2.5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to solifenacin (retention time = about 2 min): succinate = about 0.2; impurity A = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity A and solifenacin.

Calculation of percentage contents:

— for each impurity, use the concentration of solifenacin succinate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

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— *reporting threshold*: 0.05 per cent; disregard the peak due to succinate.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

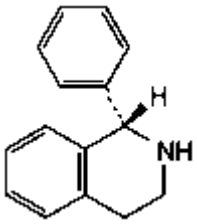
Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 48.06 mg of $C_{27}H_{32}N_2O_6$.

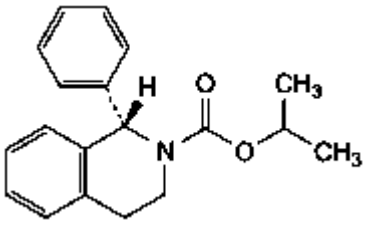
IMPURITIES

Specified impurities *E, F, G, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, I.*



A. (1*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline,



B. propan-2-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate,

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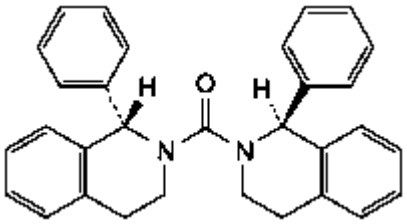
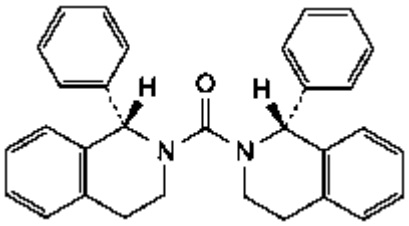
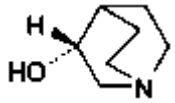


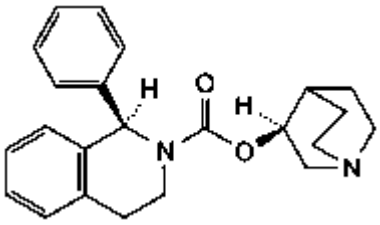
C. bis[(1*S*)-1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]methanone,



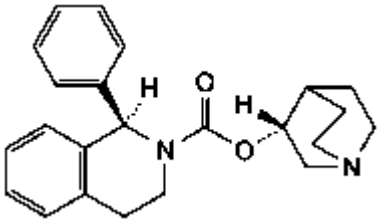
D. [(1*R*)-1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl][(1*S*)-1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]methanone,



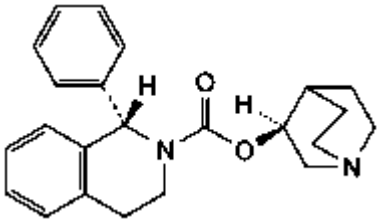
E. (3*R*)-1-azabicyclo[2.2.2]octan-3-ol (3-quinuclidinol),



F. (3*S*)-1-azabicyclo[2.2.2]octan-3-yl (1*R*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate,



G. (3*R*)-1-azabicyclo[2.2.2]octan-3-yl (1*R*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate,



H. (3*S*)-1-azabicyclo[2.2.2]octan-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate,

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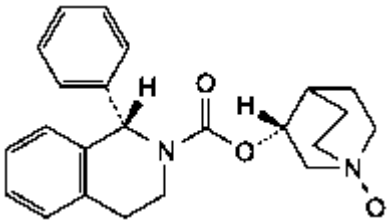

I. (3*R*)-3-[[(1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carbonyl]oxy]-1-azabicyclo[2.2.2]octane 1-oxide (solifenacin *N*-oxide).

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Solifenacin Tablets

General Notices

Action and use

Muscarinic M_3 receptor antagonist; anticholinergic.

DEFINITION

Solifenacin Tablets contain Solifenacin Succinate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of solifenacin succinate, $C_{27}H_{32}N_2O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Disperse an amount of powdered tablets containing 20 mg of Solifenacin Succinate in 30 mL of *water* and filter (a 0.45-µm Nylon filter is suitable). To this solution add 5 mL of 5M *sodium hydroxide*. Extract with three 30-mL quantities of *dichloromethane*, shake the combined extracts with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of solifenacin *(RS 508)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter (a 0.45-µm Nylon filter is suitable). Dilute if necessary, with the dissolution medium to produce a solution expected to contain 0.00055% w/v of Solifenacin Succinate.
(2) 0.00055% w/v of *solifenacin succinate BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanopropyl silica gel for chromatography* (5 µm) (Agilent Zorbax SB-CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Buffer solution Dissolve 3.4 g of *potassium dihydrogen orthophosphate* in 1000 mL *water* and adjust the pH to 3.5 with 85% v/v *orthophosphoric acid*.

40 volumes of buffer solution and 60 volumes of a solution containing 20 volumes of *water*, 40 volumes of *acetonitrile R1* and 40 volumes of *methanol R2*.

When the chromatograms are recorded under the prescribed conditions, the retention time of solifenacin is about 6 minutes.

DETERMINATION OF CONTENT

Calculate the total content of solifenacin succinate, $C_{27}H_{32}N_2O_6$, in the medium from the chromatograms obtained and using the declared content of $C_{27}H_{32}N_2O_6$ in *solifenacin succinate BPCRS*.

LIMITS

The amount of Solifenacin Succinate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared in solution A.

Buffer solution Dissolve 4.11 g *potassium dihydrogen orthophosphate* in 1000 mL *water*, add 1 mL *triethylamine* and adjust the pH to 3.3 with 85% v/v *orthophosphoric acid*.

Solution A Equal volumes of buffer solution and *acetonitrile R1*.

(1) Disperse an amount of powdered tablets containing 38 mg of Solifenacin Succinate in 15 mL of solution A with the aid of ultrasound and occasional shaking. Dilute to 25 mL and filter (a 0.45-µm Nylon filter is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) To 15 mg of *solifenacin succinate BPCRS* add 2.5 mL of solution A and 2.5 mL of *hydrogen peroxide (30%)*, stir and then carefully add 2.5 mL of 50% w/v *sodium metabisulfate* and dilute to 20 mL with solution A (generation of impurity I).

(4) Dilute 1 volume of solution (2) to 5 volumes with solution A.

(5) 0.152% w/v of *solifenacin succinate impurity BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C8 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 15 volumes of *acetonitrile R1*, 15 volumes of *methanol R2* and 70 volumes of buffer solution.

Mobile phase B 30 volumes of buffer solution, 35 volumes of *acetonitrile R1* and 35 volumes of *methanol R2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	90	10	isocratic
5-25	90→30	10→70	linear gradient
25-40	30→10	70→90	linear gradient
40-55	10	90	isocratic
55-60	10→90	90→10	linear gradient
60-65	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to Solifenacin Succinate (retention time about 22 minutes) are: impurity A, about 0.4, impurity 1, about 0.8; impurity I, about 1.1 and impurity B, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to solifenacin succinate and impurity I is at least 2.0;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* is at least 20.

LIMITS

Identify any peak corresponding to impurity A in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (5), and multiply the area of this peak by a correction factor of 1.9.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity I is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks*, excluding impurity I, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Disperse an amount of powdered tablets in sufficient mobile phase to produce a solution containing 0.01% w/v of Solifenacin Succinate and filter (a 0.45-µm Nylon filter is suitable).
(2) 0.01% w/v of *solifenacin succinate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

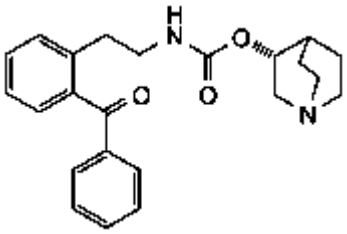
The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of solifenacin succinate, $C_{27}H_{32}N_2O_6$, in the tablets from the chromatograms obtained and using the declared content of $C_{27}H_{32}N_2O_6$ in *solifenacin succinate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and I listed under Solifenacin Succinate and:



1. (+)-(R)-quinuclidin-3-yl [2-(2-benzoylphenyl)ethyl]carbamate

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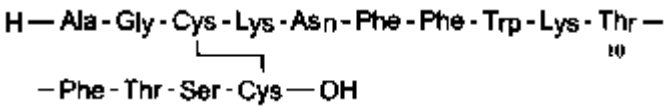
Somatostatin

General Notices

(Ph. Eur. monograph 0949)



$C_{76}H_{104}N_{18}O_{19}S_2$ 1638 *38916-34-6*

Action and use

Growth hormone release inhibiting hormone.

Ph Eur

DEFINITION

S^3,S^{14}-Cyclo(L-alanylglycyl-L-cysteinyl-L-lysyl-L-asparaginyl-L-phenylalanyl-L-phenylalanyl-L-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-cysteine).

Synthetic cyclic tetradecapeptide having the structure of the hypothalamic hormone that inhibits the release of human growth hormone. It contains a variable quantity of acetic acid. It is available in the freeze-dried form.

Content

95.0 per cent to 104.0 per cent (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, amorphous powder.

Solubility

Freely soluble in water and in acetic acid, practically insoluble in methylene chloride.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

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Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. Amino acid analysis (2.2.56). Method 1 for hydrolysis and method 1 for analysis are suitable.

Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids taking 1/8 of the sum of the number of moles of aspartic acid, alanine, lysine, glycine and phenylalanine as equal to 1. The values fall within the following limits: aspartic acid: 0.90 to 1.10; glycine: 0.90 to 1.10; alanine: 0.90 to 1.10; phenylalanine: 2.7 to 3.3; serine: 0.7 to 1.05; threonine: 1.4 to 2.1; half-cystine: 1.4 to 2.1; lysine: 1.8 to 2.2. Not more than traces of other amino acids are present.

TESTS

Specific optical rotation (2.2.7)

-47 to -37 (anhydrous and acetic acid-free substance).

Dissolve 2.0 mg in 1.0 mL of a 1 per cent *V/V* solution of *glacial acetic acid R*.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Prepare the solutions immediately before use.*

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of 1.0 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *somatostatin CRS* in *water R* to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Dissolve the contents of a vial of *somatostatin CRS* in a 1 mg/mL solution of *dithioerythritol R* to obtain a concentration of 1.0 mg/mL. Allow to stand at room temperature for about 1 h. Mix 1 volume of this solution and 1 volume of reference solution (a).

Reference solution (c) Dissolve the contents of a vial of *somatostatin impurity B CRS* in 1.0 mL of *water R*.

Reference solution (d) Dissolve the contents of a vial of *somatostatin impurity F CRS* in 1.0 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *acetonitrile for chromatography R*, *water for chromatography R* (0.1:20:80 *V/V/V*);

— *mobile phase B*: *trifluoroacetic acid R*, *acetonitrile for chromatography R*, *water for chromatography R* (0.1:45:55 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100 → 0	0 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
25 - 30	0 → 100	100 → 0
30 - 32	0 → 100	100 → 0

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 15 µL of the test solution and reference solutions (b), (c) and (d).

Identification of peaks Use the chromatogram obtained with reference solution (b) to identify the peak due to reduced somatostatin; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to somatostatin (retention time = about 12 min): impurities B and F = about 1.03; reduced somatostatin = about 1.09; impurities C and D = about 1.17; impurity E = about 1.22.

System suitability Reference solution (b):

— the ratio of the area of the peak due to reduced somatostatin to the area of the peak due to somatostatin is between 1:9 and 9:1;

— *resolution*: minimum 3.5 between the peaks due to somatostatin and reduced somatostatin;

— *number of theoretical plates*: minimum 15 000, calculated for the peak due to somatostatin;

— *symmetry factor*: maximum 2.7 for the peak due to somatostatin.

Limits:

— *impurity B or F*: maximum 1.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.1 per cent.

Acetic acid (2.5.34)

3.0 per cent to 15.0 per cent.

Test solution Dissolve 7.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A, then dilute to 10.0 mL with the same mixture of mobile phases.

Water (2.5.32)

Maximum 8.0 per cent, determined on 10.0 mg.

Bacterial endotoxins (2.6.14)

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Less than 10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 10 µL of the test solution and reference solution (a).

Calculate the percentage content of somatostatin ($C_{76}H_{104}N_{18}O_{19}S_2$) taking into account the assigned content of $C_{76}H_{104}N_{18}O_{19}S_2$ in *somatostatin CRS*.

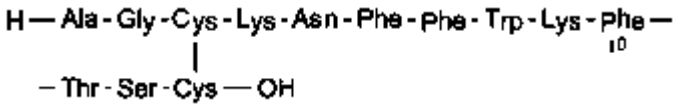
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

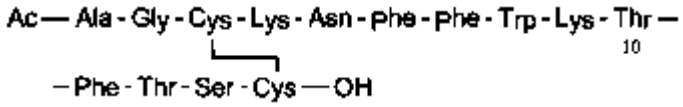
IMPURITIES

Specified impurities *B, F.*

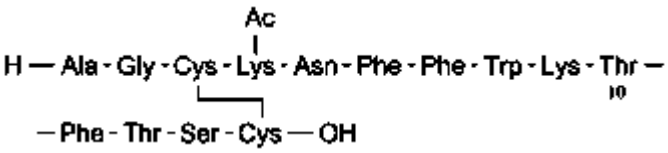
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E.*



B. des-10-threonine-somatostatin (des-Thr^{10}-somatostatin),



C. acetylsomatostatin ([Ac-Ala^1]somatostatin),



D. $N^{6.4}$-acetylsomatostatin ([Lys(Ac)^4]somatostatin),

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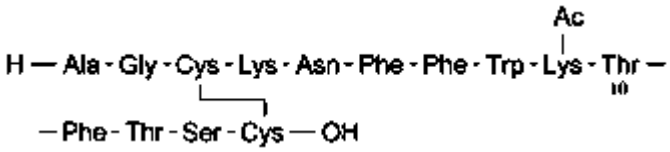
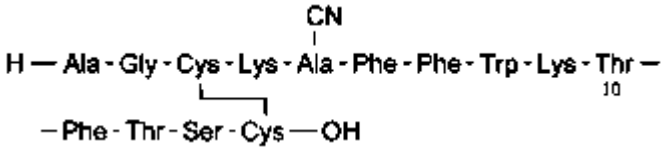


E. $N^{6.9}$-acetylsomatostatin ([Lys(Ac)^{9}]somatostatin),



F. [5-(3-cyanoalanine)]somatostatin ([Ala(CN)^{5}]somatostatin).

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This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Somatropin

General Notices

(Ph. Eur. monograph 0951)

```
FPTIPLSRLF  DNAMLRAHRL  HQLAFDTYQE  FEEAYIPKEQ   40
KYSFLQNPQT  SLCFSESIPT  PSNREETQQK  SNLELLRISL   80
LLIQSWLEPV  QFLRSVFANS  LVYGASDSNV  YDLLKDLEEG  120
IQTLMGRLED  GSPRTGQIFK  QTYSKFDTNS  HNDDALLKNY  160
GLLYCFRKDM  DKVETFLRIV  QCRSVEGSCG  F           191
```

disulfide bridges: 53-165, 182-189

$C_{990}H_{1528}N_{262}O_{300}S_7$ 22 125

Action and use

Growth hormone.

Preparation

Somatropin Injection

Ph Eur

DEFINITION

Protein having the structure (191 amino-acid residues) of the major component of growth hormone produced by the human pituitary.

Content

91.0 per cent to 105.0 per cent (anhydrous substance).

By convention, for the purpose of labelling somatropin preparations, 1 mg of anhydrous somatropin ($C_{990}H_{1528}N_{262}O_{300}S_7$) is equivalent to 3.0 IU of biological activity.

PRODUCTION

Somatropin is produced by a method based on recombinant DNA (rDNA) technology. In the course of product development, it must be demonstrated that the manufacturing process produces a product having a biological activity of not less than 2.5 IU/mg, using a validated

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bioassay based on growth promotion and approved by the competent authority.

Somatropin complies with the following additional requirements.

Host-cell-derived proteins (2.6.34)

The limit is approved by the competent authority.

Host-cell- and vector-derived DNA (2.6.35)

The limit is approved by the competent authority.

CHARACTERS

Appearance

White or almost white powder.

IDENTIFICATION

A. Capillary electrophoresis (2.2.47) as described in the test for charged variants with the following modifications.

Injection Test solution (b); under pressure or vacuum, using the following sequence: sample injection for at least 3 s then CZE buffer injection for 1 s.

Results In the electropherogram obtained, only 1 principal peak, corresponding to somatropin, is detected: no doubling of this peak is observed.

B. Examine the chromatograms obtained in the test for related proteins.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Prepare a solution of the substance to be examined in *0.05 M tris-hydrochloride buffer solution pH 7.5 R* to obtain a solution containing 2.0 mg/mL of somatropin and transfer about 1.0 mL to a tube made from a suitable material such as polypropylene. Prepare a 1 mg/mL solution of *trypsin for peptide mapping R* in *0.05 M tris-hydrochloride buffer solution pH 7.5 R* and add 30 µL to the solution of the substance to be examined. Cap the tube and place in a water-bath at 37 °C for 4 h. Remove from the water-bath and stop the reaction immediately, for example by freezing. If analysed immediately using an automatic injector, maintain at 2-8 °C.

Reference solution Prepare at the same time and in the same manner as for the test solution, but using *somatropin CRS* instead of the substance to be examined.

CHROMATOGRAPHIC SEPARATION Liquid chromatography (2.2.29).

Column:

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— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5-10 µm) with a pore size of 30 nm;

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water for chromatography R*;

— *mobile phase B*: to 100 mL of *water for chromatography R*, add 1 mL of *trifluoroacetic acid R* and dilute to 1000 mL with *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100 → 80	0 → 20
20 - 40	80 → 75	20 → 25
40 - 65	75 → 50	25 → 50
65 - 70	50 → 20	50 → 80

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 100 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of somatropin digest supplied with *somatropin CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

D. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related proteins

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Maintain the solutions at 2-8 °C and use within 24 h.*

Solution A Dilute 5 µL of *strong hydrogen peroxide solution R* to 100 mL with *0.025 M phosphate buffer solution pH 7.0 R*.

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Test solution Prepare a solution of the substance to be examined in an appropriate buffer, for example *0.025 M phosphate buffer solution pH 7.0 R*, to obtain a concentration of 1.6 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 1.6 mg/mL.

Reference solution (b) Dissolve the contents of a vial of *somatropin CRS* in solution A to obtain a concentration of 1.6 mg/mL. Allow to stand for 1-7 days to obtain a sufficient amount of sulfoxide forms.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm) with a pore size of 100 nm;

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: dissolve 82.6 g of *ammonium sulfate R* and 34.5 g of *sodium dihydrogen phosphate monohydrate R* in 2950 mL of *water for chromatography R*; add 25.0 mL of *perchloric acid R* and 2000 mL of *acetonitrile R1*, and dilute to 5000 mL with *water for chromatography R*;

— *mobile phase B*: to 4000 mL of *acetonitrile R1*, add 1000 mL of *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	77 → 72	23 → 28
60 - 61	72 → 77	28 → 23
61 - 72	77	23

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Autosampler Set at 2-8 °C.

Injection 20 µL.

Relative retention With reference to somatropin (retention time = about 40 min): [MetO^{125}]somatropin (double peak) = about 0.40; [β-Asp^{107}]somatropin = about 0.78; [MetO^{14}]somatropin = about 0.91; 130,131-anhydrosomatropin = about 1.27; [seco-130/131]somatropin = about 1.31.

If necessary, adjust the percentage of mobile phase B in the gradient so that the main peak elutes at about 40 min.

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System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to [MetO^{14}]somatropin and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to somatropin.

Limit:

— *total*: maximum 6.0 per cent.

Dimer and related substances of higher molecular mass

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Test solution Prepare a solution of the substance to be examined in *0.025 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 1.0 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Place 1 vial of *somatropin CRS* in an oven at 50 °C for a period sufficient to generate 1-2 per cent of dimer (typically 12-24 h). Dissolve its contents in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 5000 to 150 000.

Mobile phase *2-propanol R*, *0.063 M phosphate buffer solution pH 7.0 R* (3:97 *V/V*); filter and degas.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Relative retention With reference to somatropin monomer (retention time = 12 min to 17 min): related substances of higher molecular mass = about 0.65; somatropin dimer = about 0.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

Limit:

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— *sum of the peaks with retention times less than that of the principal peak*: maximum 4.0 per cent.

Charged variants

Capillary electrophoresis (2.2.47).

Test solution (a) Prepare a solution of the substance to be examined containing 1 mg/mL of somatropin.

Test solution (b) Mix equal volumes of test solution (a) and the reference solution.

Reference solution Dissolve the contents of a vial of somatropin CRS in 0.05 M tris-hydrochloride buffer solution pH 7.5 R and dilute with the same solvent to obtain a concentration of 1 mg/mL.

Capillary:

— *material*: uncoated fused silica;

— *size*: effective length = at least 70 cm, Ø = 50 µm.

Temperature 30 °C.

CZE buffer 13.2 g/L solution of ammonium phosphate R adjusted to pH 6.0 with phosphoric acid R and filtered.

Detection Spectrophotometer at 200 nm.

Set the autosampler to store the samples at 4 °C during analysis.

Preconditioning of the capillary Rinse with 1 M sodium hydroxide for 20 min, with water R for 10 min and with the CZE buffer for 20 min.

Between-run rinsing Rinse with 0.1 M sodium hydroxide for 2 min and with the CZE buffer for 6 min.

NOTE: rinsing times may be adapted according to the length of the capillary and the equipment used.

Injection Test solution (a) and the reference solution; under pressure or vacuum, using the following sequence: sample injection for at least 3 s then CZE buffer injection for 1 s.

The injection time and pressure may be adapted in order to meet the system suitability criteria.

Migration Apply a field strength of 217 V/cm (20 kV for capillaries of 92 cm total length) for 80 min, using the CZE buffer as the electrolyte in both buffer reservoirs.

Relative migration With reference to somatropin: deamidated forms = 1.02 to 1.11.

System suitability Reference solution:

— the electropherogram obtained is similar to the electropherogram of somatropin supplied with somatropin CRS. The peak due to deamidated somatropin, I_4, elutes after and is completely separated from the peak due to somatropin, with a relative migration time (RMT) of at least 1.02. Other commonly observed peaks may include: I_1 (RMT = 0.93 – 0.96), I2 (RMT = 0.96 – 0.98) and I_3 (RMT = 1.01 – 1.03).

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NOTE: peak I_2 corresponds to the cleaved form and peak I_4 corresponds to the deamidated forms, eluting as a doublet.

Limits:

— *deamidated forms*: maximum 5.0 per cent;

— *any other impurity*: for each impurity, maximum 2.0 per cent;

— *total*: maximum 10.0 per cent.

Water (*2.5.32*)

Maximum 10.0 per cent.

Bacterial endotoxins (*2.6.14*)

Less than 5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Size-exclusion chromatography (*2.2.30*) as described in the test for dimer and related substances of higher molecular mass with the following modification.

Injection Test solution and reference solution (a).

Calculate the content of somatropin ($C_{990}H_{1528}N_{262}O_{300}S_7$) from the assigned content of $C_{990}H_{1528}N_{262}O_{300}S_7$ in *somatropin CRS*.

STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

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This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Somatropin Concentrated Solution

General Notices

Somatropin Bulk Solution

(Ph. Eur. monograph 0950)

```
FPTIPLSRLF  DNAMLRAHRL  HQLAFDTYQE  FEEAYIPKEQ   40
KYSFLQNPQT  SLCFSESIPT  PSNREETQQK  SNLELLRISL   80
LLIQSWLEPV  QFLRSVFANS  LVYGASDSNV  YDLLKDLEEG  120
IQTLMGRLED  GSPRTGQIFK  QTYSKFDTNS  HNDDALLKNY  160
GLLYCFRKDM  DKVETFLRIV  QCRSVEGSCG  F           191
```

disulfide bridges: 53-165, 182-189

$C_{990}H_{1528}N_{262}O_{300}S_7$ 22 125

Action and use

Growth hormone.

Preparation

Somatropin Injection

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DEFINITION

Solution containing a protein having the structure (191 amino-acid residues) of the major component of growth hormone produced by the human pituitary. It may contain buffer salts and other excipients.

Content

91.0 per cent to 105.0 per cent of the amount of somatropin stated on the label.

By convention, for the purpose of labelling somatropin preparations, 1 mg of anhydrous somatropin ($C_{990}H_{1528}N_{262}O_{300}S_7$) is equivalent to 3.0 IU of biological activity.

PRODUCTION

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Somatropin concentrated solution is produced by a method based on recombinant DNA (rDNA) technology. In the course of product development, it must be demonstrated that the manufacturing process produces a product having a biological activity of at least 2.5 IU/mg, using a validated bioassay based on growth promotion and approved by the competent authority.

Somatropin concentrated solution complies with the following additional requirements.

Host-cell-derived proteins (2.6.34)

The limit is approved by the competent authority.

Host-cell- and vector-derived DNA (2.6.35)

The limit is approved by the competent authority.

CHARACTERS

Appearance

Clear or slightly turbid, colourless liquid.

IDENTIFICATION

A. Capillary electrophoresis (2.2.47) as described in the test for charged variants with the following modifications.

Injection Test solution (b); under pressure or vacuum, using the following sequence: sample injection for at least 3 s then CZE buffer injection for 1 s.

Results In the electropherogram obtained, only 1 principal peak, corresponding to somatropin, is detected: no doubling of this peak is observed.

B. Examine the chromatograms obtained in the test for related proteins.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Dilute the preparation to be examined with *0.05 M tris-hydrochloride buffer solution pH 7.5 R* so that it contains 2.0 mg/mL of somatropin and transfer about 1.0 mL to a tube made from a suitable material such as polypropylene. Prepare a 1 mg/mL solution of *trypsin for peptide mapping R* in *0.05 M tris-hydrochloride buffer solution pH 7.5 R* and add 30 µL to the solution of the preparation to be examined. Cap the tube and place in a water-bath at 37 °C for 4 h. Remove from the water-bath and stop the reaction immediately, for example by freezing. If analysed immediately using an automatic injector, maintain at 2-8 °C.

NOTE: If a 2 mg/mL somatropin concentration is not obtainable, a similar digest relationship (micrograms of trypsin per milligram of somatropin) may be used.

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Reference solution Prepare at the same time and in the same manner as for the test solution, but using somatropin CRS instead of the preparation to be examined.

CHROMATOGRAPHIC SEPARATION Liquid chromatography (2.2.29).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5-10 µm) with a pore size of 30 nm;

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dilute 1 mL of trifluoroacetic acid R to 1000 mL with water for chromatography R;

— *mobile phase B*: to 100 mL of water for chromatography R, add 1 mL of trifluoroacetic acid R and dilute to 1000 mL with acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100 → 80	0 → 20
20 - 40	80 → 75	20 → 25
40 - 65	75 → 50	25 → 50
65 - 70	50 → 20	50 → 80

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 100 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of somatropin digest supplied with somatropin CRS.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

D. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

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Related proteins

Liquid chromatography (2.2.29): use the normalisation procedure. *Maintain the solutions at 2-8 °C and use within 24 h.*

Solution A Dilute 5 µL of *strong hydrogen peroxide solution R* to 100 mL with *0.025 M phosphate buffer solution pH 7.0 R*.

Test solution Dilute the preparation to be examined with an appropriate buffer, for example *0.025 M phosphate buffer solution pH 7.0 R*, to obtain a concentration of 1.6 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 1.6 mg/mL.

Reference solution (b) Dissolve the contents of a vial of *somatropin CRS* in solution A to obtain a concentration of 1.6 mg/mL. Allow to stand for 1-7 days to obtain a sufficient amount of sulfoxide forms.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm) with a pore size of 100 nm;

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: dissolve 82.6 g of *ammonium sulfate R* and 34.5 g of *sodium dihydrogen phosphate monohydrate R* in 2950 mL of *water for chromatography R*; add 25.0 mL of *perchloric acid R* and 2000 mL of *acetonitrile R1*, and dilute to 5000 mL with *water for chromatography R*;

— *mobile phase B*: to 4000 mL of *acetonitrile R1*, add 1000 mL of *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	77 → 72	23 → 28
60 - 61	72 → 77	28 → 23
61 - 72	77	23

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Autosampler Set at 2-8 °C.

Injection 20 µL.

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Relative retention With reference to somatropin (retention time = about 40 min): [MetO^{125}]somatropin (double peak) = about 0.40; [β-Asp^{107}]somatropin = about 0.78; [MetO^{14}]somatropin = about 0.91; 130,131-anhydrosomatropin = about 1.27; [seco-130/131]somatropin = about 1.31.

If necessary, adjust the percentage of mobile phase B in the gradient so that the main peak elutes at about 40 min.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to [MetO^{14}]somatropin and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to somatropin.

Limit:

— *total*: maximum 6.0 per cent.

Dimer and related substances of higher molecular mass

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Test solution Dilute the preparation to be examined in *0.025 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 1.0 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Place 1 vial of *somatropin CRS* in an oven at 50 °C for a period sufficient to generate 1-2 per cent of dimer (typically 12-24 h). Dissolve its contents in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 5000 to 150 000.

Mobile phase *2-propanol R*, *0.063 M phosphate buffer solution pH 7.0 R* (3:97 *V/V*); filter and degas.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Relative retention With reference to somatropin monomer (retention time = 12 min to 17 min): related substances of higher molecular mass = about 0.65; somatropin dimer = about 0.9.

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System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

Limit:

— *sum of the peaks with retention times less than that of the principal peak*: maximum 4.0 per cent.

Charged variants

Capillary electrophoresis (2.2.47).

Test solution (a) Dilute the preparation to be examined to obtain a concentration of 1 mg/mL.

Test solution (b) Mix equal volumes of test solution (a) and the reference solution.

Reference solution Dissolve the contents of a vial of *somatropin CRS* in *0.05 M tris-hydrochloride buffer solution pH 7.5 R* and dilute with the same solvent to obtain a concentration of 1 mg/mL.

Capillary:

— *material*: uncoated fused silica;

— *size*: effective length = at least 70 cm, Ø = 50 µm.

Temperature 30 °C.

CZE buffer 13.2 g/L solution of *ammonium phosphate R* adjusted to pH 6.0 with *phosphoric acid R* and filtered.

Detection Spectrophotometer at 200 nm.

Set the autosampler to store the samples at 4 °C during analysis.

Preconditioning of the capillary Rinse with *1 M sodium hydroxide* for 20 min, with *water R* for 10 min and with the CZE buffer for 20 min.

Between-run rinsing Rinse with *0.1 M sodium hydroxide* for 2 min and with the CZE buffer for 6 min.

NOTE: rinsing times may be adapted according to the length of the capillary and the equipment used.

Injection Test solution (a) and the reference solution; under pressure or vacuum, using the following sequence: sample injection for at least 3 s then CZE buffer injection for 1 s. The injection time and pressure may be adapted in order to meet the system suitability criteria.

Migration Apply a field strength of 217 V/cm (20 kV for capillaries of 92 cm total length) for 80 min, using the CZE buffer as the electrolyte in both buffer reservoirs.

Relative migration With reference to somatropin: deamidated forms = 1.02 to 1.11.

System suitability Reference solution:

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— the electropherogram obtained is similar to the electropherogram of somatropin supplied with *somatropin CRS*. The peak due to deamidated somatropin, I_4, elutes after and is completely separated from the peak due to somatropin, with a relative migration time (RMT) of at least 1.02. Other commonly observed peaks may include: I_1 (RMT = 0.93 – 0.96), I_2 (RMT = 0.96 – 0.98) and I_3 (RMT = 1.01 – 1.03).

NOTE: peak I_2 corresponds to the cleaved form and peak I_4 corresponds to the deamidated forms, eluting as a doublet.

Limits:

— *deamidated forms*: maximum 5.0 per cent;

— *any other impurity*: for each impurity, maximum 2.0 per cent;

— *total*: maximum 10.0 per cent.

Bacterial endotoxins (*2.6.14*)

Less than 5 IU in the volume that contains 1 mg of somatropin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Size-exclusion chromatography (*2.2.30*) as described in the test for dimer and related substances of higher molecular mass with the following modification.

Injection Test solution and reference solution (a).

Calculate the content of somatropin ($C_{990}H_{1528}N_{262}O_{300}S_7$) from the assigned content of $C_{990}H_{1528}N_{262}O_{300}S_7$ in *somatropin CRS*.

STORAGE

In an airtight container at a temperature of -20 °C. Avoid repeated freezing and thawing. If the solution is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states:

— the content of somatropin in milligrams per millilitre;

— the name and concentration of any excipient.

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Somatropin Injection

General Notices

Superseded upon implementation of European Pharmacopoeia 11.2 by Somatropin Injection (02370)

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Somatropin Powder for Injection

General Notices

Somatropin for Injection

(Ph. Eur. monograph 0952)

```
FPTIPLSRLF  DNAMLRAHRL  HQLAFDTYQE  FEEAYIPKEQ   40
KYSFLQNPQT  SLCFSESIPT  PSNREETQQK  SNLELLRISL   80
LLIQSWLEPV  QFLRSVFANS  LVYGASDSNV  YDLLKDLEEG  120
IQTLMGRLED  GSPRTGQIFK  QTYSKFDTNS  HNDDALLKNY  160
GLLYCFRKDM  DKVETFLRIV  QCRSVEGSCG  F           191
```

disulfide bridges: 53-165, 182-189.

$C_{990}H_{1528}N_{262}O_{300}S_7$ 22 125

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DEFINITION

Freeze-dried, sterile preparation of a protein having the structure (191 amino-acid residues) of the major component of growth hormone produced by the human pituitary.

Content

89.0 per cent to 105.0 per cent of the amount of somatropin stated on the label.

By convention, for the purpose of labelling somatropin preparations, 1 mg of anhydrous somatropin ($C_{990}H_{1528}N_{262}O_{300}S_7$) is equivalent to 3.0 IU of biological activity.

Somatropin powder for injection complies with the requirements of the monograph *Parenteral preparations (0520)*.

PRODUCTION

Somatropin powder for injection is prepared either from *Somatropin (0951)* or from *Somatropin concentrated solution (0950)*. The purified preparation, to which buffers and stabilisers may be added, is filtered through a bacteria-retentive filter, aseptically distributed in sterile containers of glass type I (*3.2.1*) and freeze-dried. The containers are immediately sealed so as to exclude microbial contamination and moisture.

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CHARACTERS

Appearance

White or almost white powder.

IDENTIFICATION

A. Examine the chromatograms obtained in the test for related proteins.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related proteins

Liquid chromatography (2.2.29): use the normalisation procedure. *Maintain the solutions at 2-8 °C and use within 24 h*.

Solution A Dilute 5 µL of *strong hydrogen peroxide solution R* to 100 mL with *0.025 M phosphate buffer solution pH 7.0 R*.

Test solution Prepare a solution of the preparation to be examined in an appropriate buffer, for example *0.025 M phosphate buffer solution pH 7.0 R*, to obtain a concentration of 1.6 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 1.6 mg/mL.

Reference solution (b) Dissolve the contents of a vial of *somatropin CRS* in solution A to obtain a concentration of 1.6 mg/mL. Allow to stand for 1-7 days to obtain a sufficient amount of sulfoxide forms.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm) with a pore size of 100 nm;

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: dissolve 82.6 g of *ammonium sulfate R* and 34.5 g of *sodium dihydrogen phosphate monohydrate R* in 2950 mL of *water for chromatography R*; add 25.0 mL of *perchloric acid R* and 2000 mL of *acetonitrile R1*, and dilute to 5000 mL with *water for chromatography R*;

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— *mobile phase B*: to 4000 mL of *acetonitrile R1*, add 1000 mL of *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	77 → 72	23 → 28
60 - 61	72 → 77	28 → 23
61 - 72	77	23

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Autosampler Set at 2-8 °C.

Injection 20 µL.

Relative retention With reference to somatropin (retention time = about 40 min): [MetO^{125}]somatropin (double peak) = about 0.40; [β-Asp^{107}]somatropin = about 0.78; [MetO^{14}]somatropin = about 0.91; 130,131-anhydrosomatropin = about 1.27; [seco-130/131]somatropin = about 1.31.

If necessary, adjust the percentage of mobile phase B in the gradient so that the main peak elutes at about 40 min.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to [MetO^{14}]somatropin and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to somatropin.

Limit:

— *total*: maximum 10 per cent.

Dimer and related substances of higher molecular mass

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Prepare a solution of the preparation to be examined in *0.025 M phosphate buffer solution pH 7.0 R* to obtain a concentration of 1.0 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Place 1 vial of *somatropin CRS* in an oven at 50 °C for a period sufficient to generate 1-2 per cent of dimer (typically 12-24 h). Dissolve its contents in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

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Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 5000 to 150 000.

Mobile phase *2-propanol R*, *0.063 M phosphate buffer solution pH 7.0 R* (3:97 *V/V*); filter and degas.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Relative retention With reference to somatropin monomer (retention time = 12 min to 17 min): related substances of higher molecular mass = about 0.65; somatropin dimer = about 0.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

Limit:

— *sum of the peaks with retention times less than that of the principal peak*: maximum 6.0 per cent.

Charged variants

Capillary electrophoresis (*2.2.47*).

Test solution Prepare a solution of the preparation to be examined containing 1 mg/mL of somatropin.

Reference solution Dissolve the contents of a vial of *somatropin CRS* in *0.05 M tris-hydrochloride buffer solution pH 7.5 R* and dilute with the same solvent to obtain a concentration of 1 mg/mL.

Capillary:

— *material*: uncoated fused silica;

— *size*: effective length = at least 70 cm, Ø = 50 µm.

Temperature 30 °C.

CZE buffer 13.2 g/L solution of *ammonium phosphate R* adjusted to pH 6.0 with *phosphoric acid R* and filtered.

Detection Spectrophotometer at 200 nm.

Set the autosampler to store the samples at 4 °C during analysis.

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Preconditioning of the capillary Rinse with *1 M sodium hydroxide* for 20 min, with *water R* for 10 min and with the CZE buffer for 20 min.

Between-run rinsing Rinse with *0.1 M sodium hydroxide* for 2 min and with the CZE buffer for 6 min.

NOTE rinsing times may be adapted according to the length of the capillary and the equipment used.

Injection Test solution and the reference solution; under pressure or vacuum, using the following sequence: sample injection for at least 3 s then CZE buffer injection for 1 s.

The injection time and pressure may be adapted in order to meet the system suitability criteria.

Migration Apply a field strength of 217 V/cm (20 kV for capillaries of 92 cm total length) for 80 min, using CZE buffer as the electrolyte in both buffer reservoirs.

Relative migration With reference to somatropin: deamidated forms = 1.02 to 1.11.

System suitability Reference solution:

— the electropherogram obtained is similar to the electropherogram of somatropin supplied with *somatropin CRS*. The peak due to deamidated somatropin, I_4, elutes after and is completely separated from the peak due to somatropin, with a relative migration time (RMT) of at least 1.02. Other commonly observed peaks may include: I_1 (RMT = 0.93 – 0.96), I_2 (RMT = 0.96 – 0.98) and I_3 (RMT = 1.01 – 1.03).

NOTE peak I_2 corresponds to the cleaved form and peak I_4 corresponds to the deamidated forms, eluting as a doublet.

Limits:

— *deamidated forms*: maximum 6.5 per cent;

— *any other impurity*: for each impurity, maximum 2.0 per cent;

— *total*: maximum 11.5 per cent.

Water (*2.5.32*)

Maximum 3.0 per cent, unless otherwise justified and authorised.

Bacterial endotoxins (*2.6.14*)

Less than 5 IU/mg.

ASSAY

Size-exclusion chromatography (*2.2.30*) as described in the test for dimer and related substances of higher molecular mass with the following modification.

Injection Test solution and reference solution (a).

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Calculate the content of somatropin ($C_{990}H_{1528}N_{262}O_{300}S_7$) from the assigned content of $C_{990}H_{1528}N_{262}O_{300}S_7$ in *somatropin CRS*.

STORAGE

In a sterile, airtight, tamper-evident container, at a temperature of 2 °C to 8 °C.

LABELLING

The label states:

— the content of somatropin in the container, in milligrams;

— the composition and volume of the liquid to be added for reconstitution;

— the time within which the reconstituted solution shall be used and the storage conditions during this period;

— the name and quantity of any excipient;

— the storage temperature;

— that the preparation shall not be shaken during reconstitution.

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Sorafenib Tablets

General Notices

(Ph. Eur. monograph 3022)

Action and use

Inhibitor of multiple tyrosine kinases; antineoplastic.

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DEFINITION

Tablets containing *Sorafenib tosilate (2931)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solution A Dissolve 1.0 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*. Adjust to pH 2.4 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Solvent mixture *water R* previously adjusted to pH 2.4 with *phosphoric acid R*, mobile phase B (25:75 *V/V*).

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Test solution Cut 5 tablets and place the cut tablets in a flask. Add 150 mL of the solvent mixture and shake mechanically for not less than 1 h until disintegration and dispersion are complete. Dilute to 250.0 mL, shake and sonicate for 30 min. Centrifuge for 5 min or filter. Dilute 2.0 mL of the clear supernatant or filtrate to 50.0 mL with the solvent mixture to obtain a concentration of sorafenib of 0.16 mg/mL.

Reference solution (a) Dissolve 22.0 mg of *sorafenib tosilate CRS* in the solvent mixture using sonication and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *sorafenib impurity H CRS* in 100 mL of the solvent mixture using sonication. Dilute 1 mL of the solution to 50 mL with the test solution.

Reference solution (d) Dissolve 4 mg of *sorafenib for peak identification CRS* (containing impurities A and D) in the solvent mixture and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *anhydrous ethanol R*, *acetonitrile for chromatography R*, solution A (16:24:60 *V/V/V*);

— *mobile phase B*: *anhydrous ethanol R*, *acetonitrile for chromatography R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 14	100 → 33	0 → 67

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity H; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity D.

Relative retention With reference to sorafenib (retention time = about 9 min): toluenesulfonic acid = about 0.1; impurity D = about 0.46; impurity H = about 0.97.

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System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity H and sorafenib.

Calculation of percentage contents:

— for each impurity, use the concentration of sorafenib in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.1 per cent; disregard the peaks due to toluenesulfonic acid and impurity D.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium 10.0 g/L solution of *sodium laurilsulfate R* in a 10.3 g/L solution of *hydrochloric acid R*. Use 900 mL of the medium.

Rotation speed 100 r/min.

Time 15 min.

Analysis Ultraviolet and visible absorption spectrophotometry (*2.2.25*), using a path length of 1 mm.

Test solutions Samples withdrawn from the dissolution vessel and filtered.

Reference solution Dissolve 30.0 mg of *sorafenib tosilate CRS* in 2.5 mL of *methanol R* and dilute to 100.0 mL with the dissolution medium.

When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 10-fold dilution for 200 mg tablets).

Measure the absorbance of the solutions at 280 nm.

Calculate the amount of dissolved sorafenib ($C_{21}H_{16}ClF_3N_4O_3$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *sorafenib tosilate CRS* and applying a conversion factor of 0.7297.

Acceptance criterion:

— *Q* = 75 per cent after 15 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

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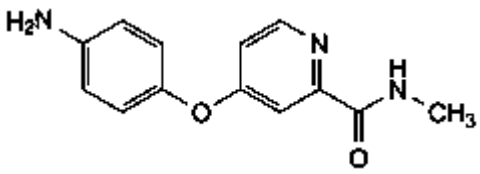
— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

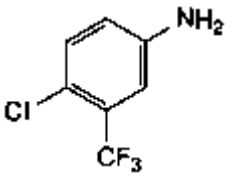
Calculate the percentage content of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) taking into account the assigned content of *sorafenib tosilate CRS* and applying a conversion factor of 0.7297.

IMPURITIES

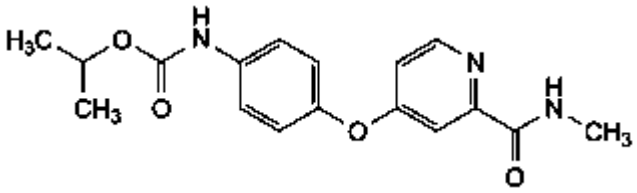
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, C, D, E, F, G, H.*



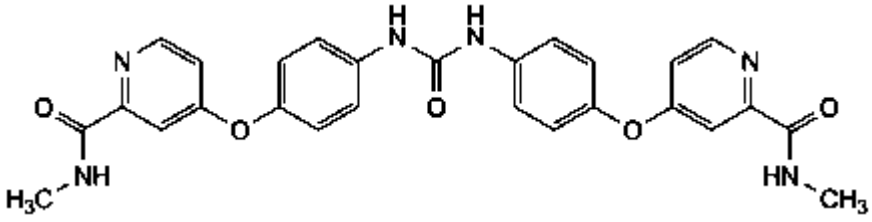
A. 4-(4-aminophenoxy)-*N*-methylpyridine-2-carboxamide,



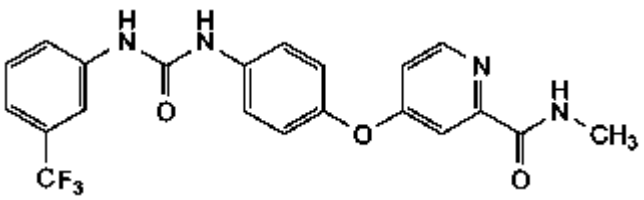
C. 4-chloro-3-(trifluoromethyl)aniline,



D. propan-2-yl [4-[[2-(methylcarbamoyl)pyridin-4-yl]oxy]phenyl]carbamate,



E. 4,4′-[carbonylbis(azanediyl-4,1-phenyleneoxy)]bis(*N*-methylpyridine-2-carboxamide),



F. *N*-methyl-4-[4-[[[3-(trifluoromethyl)phenyl]carbamoyl]amino]phenoxy]pyridine-2-carboxamide,

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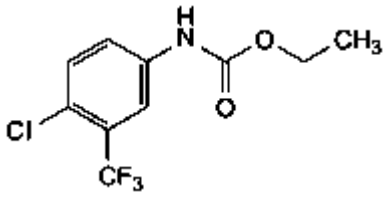
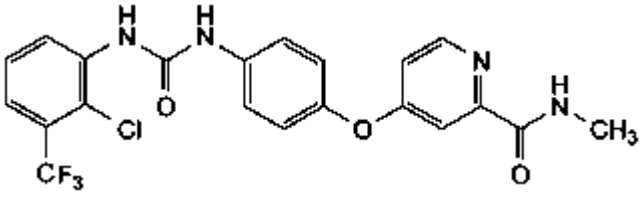


G. ethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate,



H. 4-[4-[[[2-chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]phenoxy]-*N*-methylpyridine-2-carboxamide.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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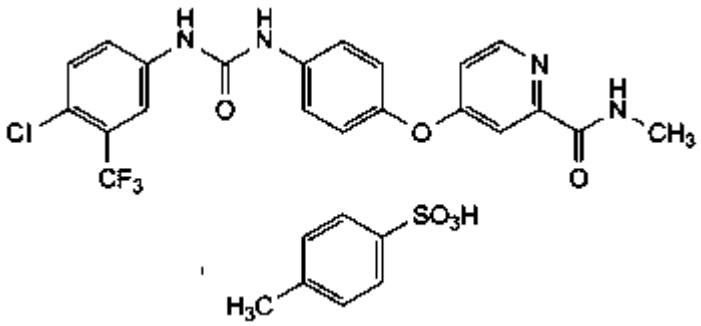
Sorafenib Tosilate

General Notices

(Ph. Eur. monograph 2931)



$C_{28}H_{24}ClF_3N_4O_6S$ 637 *475207-59-1*

Action and use

Inhibitor of multiple tyrosine kinases; antineoplastic.

Preparation

Sorafenib Tablets

Ph Eur

DEFINITION

4-[4-[[[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]phenoxy]-*N*-methylpyridine-2-carboxamide 4-methylbenzene-1-sulfonate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl toluenesulfonate esters are genotoxic and are potential impurities in sorafenib tosilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method *2.5.40. Methyl, ethyl and isopropyl toluenesulfonate in active substances* is available to assist manufacturers.

CHARACTERS

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Appearance

White or slightly yellowish or brownish powder.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sorafenib tosilate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture *phosphoric acid R*, *acetonitrile R*, *dimethyl sulfoxide R* (0.1:15:85 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of *sorafenib tosilate CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *sorafenib impurity H CRS* in 100 mL of the solvent mixture using sonication. Dilute 1 mL of the solution to 20 mL with the test solution.

Reference solution (d) Dissolve 5 mg of *sorafenib for peak identification CRS* (containing impurities A and D) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 75 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *potassium dihydrogen phosphate R* and 1.0 mL of *phosphoric acid R* in *water for chromatography R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: *anhydrous ethanol R*, *acetonitrile for chromatography R* (40:60 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	95	5
2 - 24	95 → 56.5	5 → 43.5
24 - 32	56.5 → 10	43.5 → 90
32 - 37	10	90

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 3 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity H; use the chromatogram supplied with *sorafenib for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A and D.

Relative retention With reference to sorafenib (retention time = about 27 min): toluenesulfonic acid = about 0.07; impurity A = about 0.1; impurity D = about 0.7; impurity H = about 0.98.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurity H and sorafenib.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 0.7;

— for each impurity, use the concentration of sorafenib tosilate in reference solution (b).

Limits:

— *impurities A, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to toluenesulfonic acid.

Water (*2.5.32*)

Maximum 1.0 per cent, determined on 0.200 g by direct sample introduction.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

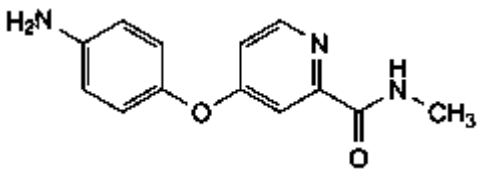
Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{28}H_{24}ClF_3N_4O_6S$ taking into account the assigned content of *sorafenib tosilate CRS*.

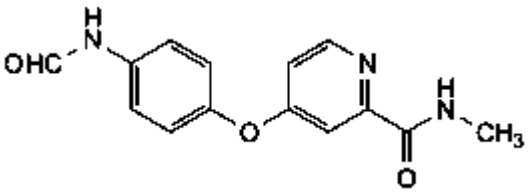
IMPURITIES

Specified impurities *A, D.*

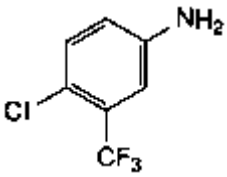
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, E, F, G, H.*



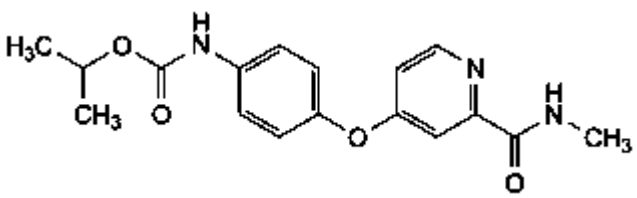
A. 4-(4-aminophenoxy)-*N*-methylpyridine-2-carboxamide,



B. 4-(4-formamidophenoxy)-*N*-methylpyridine-2-carboxamide,



C. 4-chloro-3-(trifluoromethyl)aniline,



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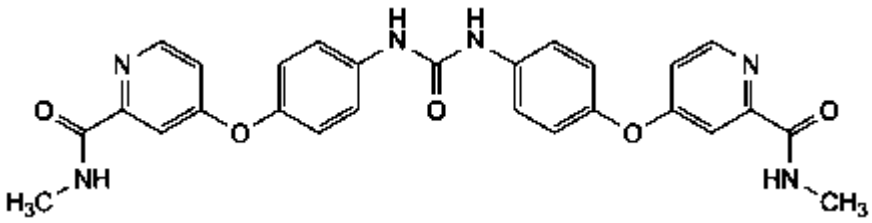
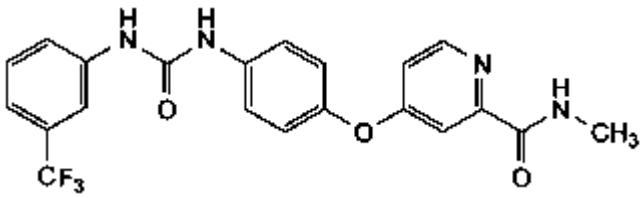
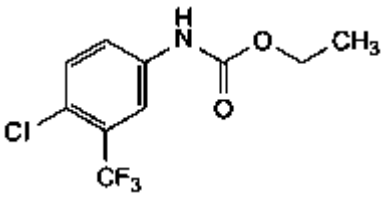
D. propan-2-yl [4-[[2-(methylcarbamoyl)pyridin-4-yl]oxy]phenyl]carbamate,



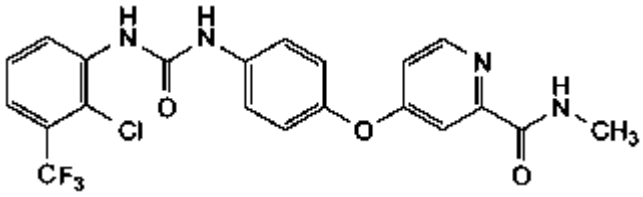
E. 4,4′-[carbonylbis(azanediyl-4,1-phenyleneoxy)]bis(*N*-methylpyridine-2-carboxamide),



F. *N*-methyl-4-[4-[[[3-(trifluoromethyl)phenyl]carbamoyl]amino]phenoxy]pyridine-2-carboxamide,



G. ethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate,



H. 4-[4-[[[2-chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]phenoxy]-*N*-methylpyridine-2-carboxamide.

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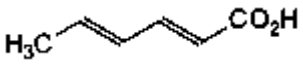
Sorbic Acid

General Notices

(Ph. Eur. monograph 0592)



$C_6H_8O_2$ 112.1 *110-44-1*

Action and use

Antimicrobial preservative.

Ph Eur

DEFINITION

(*E,E*)-Hexa-2,4-dienoic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 132 °C to 136 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

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Test solution Dissolve 50.0 mg in *water R* and dilute to 250.0 mL with the same solvent. Dilute 2.0 mL of this solution to 200.0 mL with *0.1 M hydrochloric acid*.

Spectral range 230-350 nm.

Absorption maximum At 264 nm.

Specific absorbance at the absorption maximum 2150 to 2550.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sorbic acid CRS*.

D. Dissolve 0.2 g in 2 mL of *ethanol (96 per cent) R* and add 0.2 mL of *bromine water R*. The solution is decolorised.

TESTS

Solution S

Dissolve 1.25 g in *ethanol (96 per cent) R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Aldehydes

Maximum 0.15 per cent, calculated as C_2H_4O.

Dissolve 1.0 g in a mixture of 30 mL of *water R* and 50 mL of *2-propanol R*, adjust to pH 4 with *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* and dilute to 100 mL with *water R*. To 10 mL of this solution add 1 mL of *decolorised fuchsin solution R* and allow to stand for 30 min. Any colour in the solution is not more intense than that in a standard prepared at the same time by adding 1 mL of *decolorised fuchsin solution R* to a mixture of 1.5 mL of *acetaldehyde standard solution (100 ppm C_2H_4O) R*, 4 mL of *2-propanol R* and 4.5 mL of *water R*.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 2.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.1000 g in 20 mL of *ethanol (96 per cent) R*. Using 0.2 mL of *phenolphthalein solution R* as indicator, titrate with *0.1 M sodium hydroxide* until a pink colour is obtained.

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1 mL of *0.1 M sodium hydroxide* is equivalent to 11.21 mg of $C_6H_8O_2$.

STORAGE

Protected from light.

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Sorbitan Laurate

General Notices

(Ph. Eur. monograph 1040)

Action and use

Non-ionic surfactant.

When sorbitan monolaurate is demanded, Sorbitan Laurate shall be supplied.

Ph Eur

DEFINITION

Mixture usually obtained by partial esterification of sorbitol and its mono- and di-anhydrides with lauric (dodecanoic) acid.

CHARACTERS

Appearance

Brownish-yellow, viscous liquid.

Solubility

Practically insoluble but dispersible in water, miscible with ethanol (96 per cent).

Relative density

About 0.98.

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Iodine value (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 7.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

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330 to 358.

Iodine value (2.5.4)

Maximum 10.

Peroxide value (2.5.5)

Maximum 5.0.

Saponification value (2.5.6)

158 to 170.

Carry out the saponification for 1 h.

Composition of fatty acids

Gas chromatography (2.4.22, Method C).

Prepare reference solution (a) as indicated in tables 2.4.22.-1 and 2.4.22.-2.

Composition of the fatty acid fraction of the substance:

- *caproic acid*: maximum 1.0 per cent;
- *caprylic acid*: maximum 10.0 per cent;
- *capric acid*: maximum 10.0 per cent;
- *lauric acid*: 40.0 per cent to 60.0 per cent;
- *myristic acid*: 14.0 per cent to 25.0 per cent;
- *palmitic acid*: 7.0 per cent to 15.0 per cent;
- *stearic acid*: maximum 7.0 per cent;
- *oleic acid*: maximum 11.0 per cent;
- *linoleic acid*: maximum 3.0 per cent.

Water (2.5.12)

Maximum 1.5 per cent, determined on 1.00 g.

Total ash (2.4.16)

Maximum 0.5 per cent.

STORAGE

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Protected from light.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitan laurate used as emulsifier and co-solubiliser in creams.

Composition of fatty acids

(see Tests).

Hydroxyl value

(see Tests).

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Sorbitan Oleate

General Notices

(Ph. Eur. monograph 1041)

Action and use

Non-ionic surfactant.

When sorbitan mono-oleate is demanded, Sorbitan Oleate shall be supplied.

Ph Eur

DEFINITION

Mixture usually obtained by esterification of 1 mole of sorbitol and its mono-and di-anhydrides per mole of oleic ((9*Z*)-octadec-9-enoic) acid. A suitable antioxidant may be added.

CHARACTERS

Appearance

Brownish-yellow, viscous liquid.

Solubility

Practically insoluble but dispersible in water, soluble in fatty oils producing a hazy solution, miscible with ethanol (96 per cent).

Relative density

About 0.99.

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Iodine value (see Tests).

C. Composition of fatty acids (see Tests).

Margaric acid Maximum 0.2 per cent for oleic acid of vegetable origin and maximum 4.0 per cent for oleic acid of animal origin.

TESTS

Acid value (*2.5.1*)

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Maximum 8.0, determined on 5.0 g.

Hydroxyl value (2.5.3, Method A)

190 to 210.

Iodine value (2.5.4)

62 to 76.

Peroxide value (2.5.5)

Maximum 10.0.

Saponification value (2.5.6)

145 to 160.

Carry out the saponification for 1 h.

Composition of fatty acids

Gas chromatography (2.4.22, Method C).

Composition of the fatty acid fraction of the substance:

— *myristic acid*: maximum 5.0 per cent;

— *palmitic acid*: maximum 16.0 per cent;

— *palmitoleic acid*: maximum 8.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: 65.0 per cent to 88.0 per cent;

— *linoleic acid*: maximum 18.0 per cent;

— *linolenic acid*: maximum 4.0 per cent;

— *fatty acids with chain length greater than* C_{18}: maximum 4.0 per cent.

Water (2.5.12)

Maximum 1.5 per cent, determined on 1.00 g.

Total ash (2.4.16)

Maximum 0.5 per cent, determined on 1.5 g.

STORAGE

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Protected from light.

LABELLING

The label states the origin of the oleic acid used (animal or vegetable).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitan oleate used as emulsifier and co-solubiliser in creams.

Composition of fatty acids

(see Tests).

Hydroxyl value

(see Tests).

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Sorbitan Palmitate

General Notices

(Ph. Eur. monograph 1042)

Action and use

Non-ionic surfactant.

When sorbitan monopalmitate is demanded, Sorbitan Palmitate shall be supplied.

Ph Eur

DEFINITION

Mixture usually obtained by partial esterification of sorbitol and its mono- and di-anhydrides with palmitic (hexadecanoic) acid.

CHARACTERS

Appearance

Yellow or yellowish powder, waxy flakes or hard masses.

Solubility

Practically insoluble in water, soluble in fatty oils, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.15*): 44 °C to 51 °C.

Introduce the melted substance into the glass capillary tubes and allow to stand at a temperature below 10 °C for 24 h.

B. Hydroxyl value (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 8.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

270 to 305.

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Peroxide value (2.5.5)

Maximum 5.0.

Saponification value (2.5.6)

140 to 155.

Carry out the saponification for 1 h.

Composition of fatty acids

Gas chromatography (2.4.22, Method C).

Composition of the fatty acid fraction of the substance:

— *palmitic acid*: minimum 92.0 per cent;

— *stearic acid*: maximum 6.0 per cent.

Water (2.5.12)

Maximum 1.5 per cent, determined on 1.00 g.

Total ash (2.4.16)

Maximum 0.5 per cent.

STORAGE

Protected from light.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitan palmitate used as emulsifier and co-solubiliser in creams.

Composition of fatty acids

(see Tests).

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Hydroxyl value

(see Tests).

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Sorbitan Sesquioleate

General Notices

(Ph. Eur. monograph 1916)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture usually obtained by esterification of 2 moles of sorbitol and its mono- and di-anhydrides per 3 moles of oleic ((9*Z*)-octadec-9-enoic) acid. A suitable antioxidant may be added.

CHARACTERS

Appearance

Pale yellow or slightly brownish-yellow paste, which becomes a viscous, oily, brownish-yellow liquid at about 25 °C.

Solubility

Dispersible in water, soluble in fatty oils, slightly soluble in ethanol (96 per cent).

Relative density

About 0.99.

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Iodine value (see Tests).

C. Composition of fatty acids (see Tests).

Margaric acid Maximum 0.2 per cent for oleic acid of vegetable origin and maximum 4.0 per cent for oleic acid of animal origin.

TESTS

Acid value (*2.5.1*)

Maximum 16.0, determined on 5.0 g.

Hydroxyl value (*2.5.3. Method A*)

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Hydroxyl value (*2.5.3, Method A*)

180 to 215.

Iodine value (*2.5.4*)

70 to 95.

Peroxide value (*2.5.5*)

Maximum 10.0.

Saponification value (*2.5.6*)

145 to 166.

Carry out the saponification for 1 h.

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*).

Composition of the fatty acid fraction of the substance:

— *myristic acid*: maximum 5.0 per cent;

— *palmitic acid*: maximum 16.0 per cent;

— *palmitoleic acid*: maximum 8.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: 65.0 per cent to 88.0 per cent;

— *linoleic acid*: maximum 18.0 per cent;

— *linolenic acid*: maximum 4.0 per cent;

— *fatty acids with chain length greater than* C_{18}: maximum 4.0 per cent.

Water (*2.5.12*)

Maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

Maximum 0.5 per cent, determined on 1.5 g.

STORAGE

Protected from light.

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LABELLING

The label states the origin of the oleic acid used (animal or vegetable).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitan sesquioleate used as emulsifier and co-solubiliser in creams.

Composition of fatty acids

(see Tests).

Hydroxyl value

(see Tests).

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Sorbitan Stearate

General Notices

(Ph. Eur. monograph 1043)

Action and use

Non-ionic surfactant.

When sorbitan monostearate is demanded, Sorbitan Stearate shall be supplied.

Ph Eur

DEFINITION

Mixture usually obtained by partial esterification of sorbitol and its mono- and di-anhydrides with *Stearic acid 50 (1474)* or *Stearic acid 70 (1474)*.

CHARACTERS

Appearance

Pale yellow, waxy solid.

Solubility

Practically insoluble but dispersible in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.15*): 50 °C to 60 °C.

Introduce the melted substance into the capillary tubes and allow to stand at a temperature below 10 °C for 24 h.

B. Hydroxyl value (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 10.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

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235 to 260.

Peroxide value (2.5.5)

Maximum 5.0.

Saponification value (2.5.6)

147 to 157.

Carry out the saponification for 1 h.

Composition of fatty acids

Gas chromatography (2.4.22, Method C).

Composition of the fatty acid fraction of the substance:

	Type of fatty acid used	Composition of fatty acids
Sorbitan stearate (type I)	Stearic acid 50	*Stearic acid*: 40.0 per cent to 60.0 per cent, *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent.
Sorbitan stearate (type II)	Stearic acid 70	*Stearic acid*: 60.0 per cent to 80.0 per cent, *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent.

Water (2.5.12)

Maximum 1.5 per cent, determined on 1.00 g.

Total ash (2.4.16)

Maximum 0.5 per cent.

STORAGE

Protected from light.

LABELLING

The label states the type of sorbitan stearate.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related

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characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitan stearate used as emulsifier and co-solubiliser in creams.

Composition of fatty acids

(see Tests).

Hydroxyl value

(see Tests).

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Sorbitan Trioleate

General Notices

(Ph. Eur. monograph 1044)

Action and use

Non-ionic surfactant.

Ph Eur

DEFINITION

Mixture usually obtained by esterification of 1 mole of sorbitol and its mono-anhydride per 3 moles of oleic ((9*Z*)-octadec-9-enoic) acid. A suitable antioxidant may be added.

CHARACTERS

Appearance

Pale yellow, light yellowish or brown solid, which becomes a viscous, oily, brownish-yellow liquid at about 25 °C.

Solubility

Practically insoluble but dispersible in water, soluble in fatty oils, slightly soluble in ethanol (96 per cent).

Relative density

About 0.98.

IDENTIFICATION

A. Hydroxyl value (see Tests).

B. Iodine value (see Tests).

C. Composition of fatty acids (see Tests).

Margaric acid Maximum 0.2 per cent for oleic acid of vegetable origin and maximum 4.0 per cent for oleic acid of animal origin.

TESTS

Acid value (*2.5.1*)

Maximum 16.0, determined on 5.0 g.

Hydroxyl value (*2.5.3. Method A*)

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Hydroxyl value (*2.5.3, Method A*)

55 to 75.

Iodine value (*2.5.4*)

76 to 90.

Peroxide value (*2.5.5*)

Maximum 10.0.

Saponification value (*2.5.6*)

170 to 190.

Carry out the saponification for 1 h.

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*).

Composition of the fatty acid fraction of the substance:

— *myristic acid*: maximum 5.0 per cent;

— *palmitic acid*: maximum 16.0 per cent;

— *palmitoleic acid*: maximum 8.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: 65.0 per cent to 88.0 per cent;

— *linoleic acid*: maximum 18.0 per cent;

— *linolenic acid*: maximum 4.0 per cent;

— *fatty acids with chain length greater than* C_{18}: maximum 4.0 per cent.

Water (*2.5.12*)

Maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

Maximum 0.5 per cent, determined on 1.5 g.

STORAGE

Protected from light.

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LABELLING

The label states the origin of the oleic acid used (animal or vegetable).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitan trioleate used as emulsifier and co-solubiliser in creams.

Composition of fatty acids

(see Tests).

Hydroxyl value

(see Tests).

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Sorbitol

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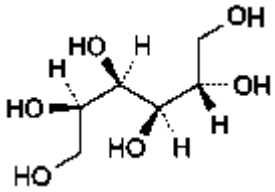
(Ph. Eur. monograph 0435)



$C_6H_{14}O_6$ 182.2 *50-70-4*

Action and use

Used for parenteral nutrition.

Ph Eur

DEFINITION

D-Glucitol (D-sorbitol).

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

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A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

B. Dissolve 0.5 g with heating in a mixture of 0.5 mL of *pyridine R* and 5 mL of *acetic anhydride R*. After 10 min, pour the solution into 25 mL of *water R* and allow to stand in iced water for 2 h. The precipitate, recrystallised from a small volume of *ethanol (96 per cent) R* and dried *in vacuo*, melts (*2.2.14*) at 98 °C to 104 °C.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *sorbitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 25 mg of *mannitol CRS* and 25 mg of *sorbitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *ethyl acetate R*, *propanol R* (10:20:70 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *4-aminobenzoic acid solution R*; dry in a current of cold air until the acetone is removed; heat at 100 °C for 15 min; allow to cool and spray with a 2 g/L solution of *sodium periodate R*; dry in a current of cold air; heat at 100 °C for 15 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Specific optical rotation (*2.2.7*): + 4.0 to + 7.0 (anhydrous substance).
Dissolve 5.00 g of the substance to be examined and 6.4 g of *disodium tetraborate R* in 40 mL of *water R*. Allow to stand for 1 h, shaking occasionally, and dilute to 50.0 mL with *water R*. Filter if necessary.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 5 g in *water R* and dilute to 50 mL with the same solvent.

Conductivity (*2.2.38*)

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Maximum 20 µS·cm^{-1}.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Reducing sugars

Maximum 0.2 per cent, expressed as glucose equivalent.

Dissolve 5.0 g in 6 mL of *water R* with the aid of gentle heat. Cool and add 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 5.0 g of the substance to be examined in 20 mL of *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 0.50 g of *sorbitol CRS* in 2 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 100.0 mL with *water R*.

Reference solution (d) Dissolve 0.5 g of *sorbitol R* and 0.5 g of *mannitol R* (impurity A) in 5 mL of *water R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 85 ± 1 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time Twice the retention time of sorbitol.

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Relative retention With reference to sorbitol (retention time = about 27 min): impurity C = about 0.6; impurity A = about 0.8; impurity B = about 1.1.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to impurity A and sorbitol.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Water (2.5.12)

Maximum 1.5 per cent, determined on 1.00 g. Use a mixture of 1 volume of *formamide R1* and 2 volumes of *anhydrous methanol R* as solvent.

Microbial contamination

If intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

If not intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^3 CFU/g (2.6.12);

— TYMC: acceptance criterion 10^2 CFU/g (2.6.12);

— absence of *Escherichia coli* (2.6.13);

— absence of *Salmonella* (2.6.13).

Bacterial endotoxins (2.6.14)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins:

— less than 4 IU/g for parenteral preparations having a concentration of less than 100 g/L of sorbitol;

— less than 2.5 IU/g for parenteral preparations having a concentration of 100 g/L or more of sorbitol.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

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Injection Test solution and reference solution (a).

Calculate the percentage content of $C_6H_{14}O_6$ taking into account the assigned content of *sorbitol CRS*.

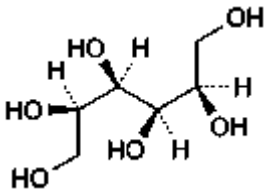
LABELLING

The label states:

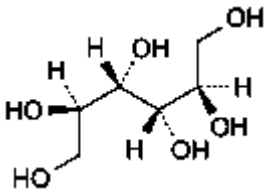
— where applicable, the maximum concentration of bacterial endotoxins;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

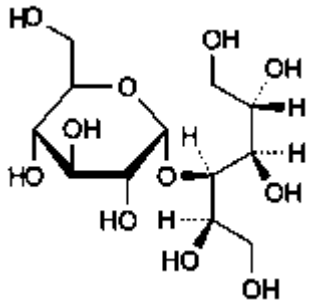
IMPURITIES



A. D-mannitol,



B. D-iditol,



C. 4-*O*-α-D-glucopyranosyl-D-glucitol (D-maltitol).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process

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and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitol used as filler and binder in tablets.

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

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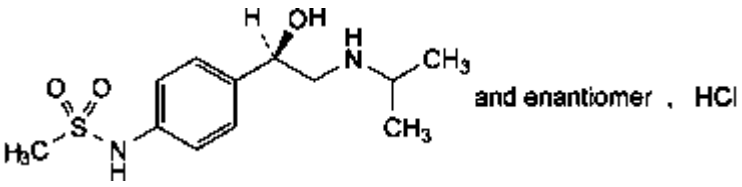
Sotalol Hydrochloride

General Notices

(Ph. Eur. monograph 2004)



$C_{12}H_{21}ClN_2O_3S$ 308.8 *959-24-0*

Action and use

Beta-adrenoceptor antagonist; class II and class III antiarrhythmic.

Ph Eur

DEFINITION

N-[4-[(1*RS*)-1-Hydroxy-2-[(propan-2-yl)amino]ethyl]phenyl]methanesulfonamide hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sotalol hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

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TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*)

4.0 to 5.0.

Dilute 5.0 mL of solution S to 10.0 mL with *carbon dioxide-free water R*.

Optical rotation (*2.2.7*)

-0.10° to + 0.10°.

Dilute 25.0 mL of solution S to 50.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 3.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 8.0 mg of *sotalol impurity B CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 100.0 mL with the mobile phase.

Reference solution (d) Dilute 1.5 mL of reference solution (b) to 100 mL with the mobile phase. To 1 mL of this solution add 1 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 2 g of *sodium octanesulfonate R* in 790 mL of *water for chromatography R*, adjust to pH 3.0 with *phosphoric acid R* and add 210 mL of *acetonitrile for chromatography R*.

Flow rate 1 mL/min.

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Detection Spectrophotometer at 228 nm.

Injection 10 µL of the test solution and reference solutions (a), (c) and (d).

Run time 2.5 times the retention time of sotalol.

System suitability Reference solution (d):

— *resolution*: minimum 4.0 between the peaks due to sotalol and impurity B.

Limits:

— *impurity B*: not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), and not more than 1 such peak has an area greater than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total of other impurities*: not more than 1.65 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.17 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating during the titration, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.250 g in 10 mL of *anhydrous formic acid R*, using sonication if necessary. Add 40 mL of *acetic anhydride R* and titrate immediately with *0.1 M perchloric acid*. Determine the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 30.88 mg of $C_{12}H_{21}ClN_2O_3S$.

STORAGE

Protected from light.

IMPURITIES

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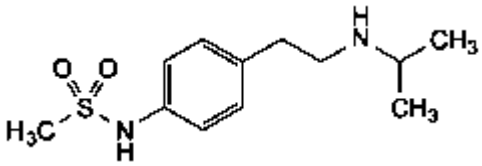
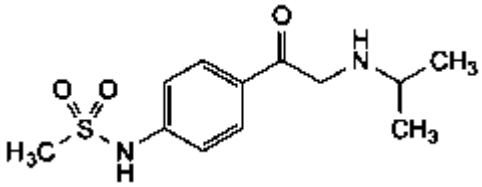
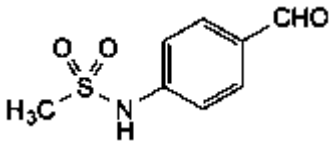


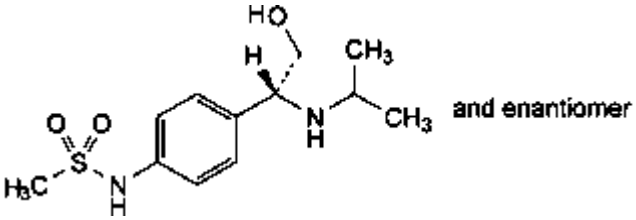
A. *N*-[4-[2-[(propan-2-yl)amino]ethyl]phenyl]methanesulfonamide,



B. *N*-[4-[[(propan-2-yl)amino]acetyl]phenyl]methanesulfonamide,



C. *N*-(4-formylphenyl)methanesulfonamide,



D. *N*-[4-[(1*RS*)-2-hydroxy-1-[(propan-2-yl)amino]ethyl]phenyl]methanesulfonamide.

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Sotalol Injection

General Notices

Action and use

Beta-adrenoceptor antagonist; class II and class III antiarrhythmic.

DEFINITION

Sotalol Injection is a sterile solution of Sotalol Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sotalol hydrochloride, $C_{12}H_{20}N_2O_3S,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm, of the final solution obtained in the Assay exhibits a maximum only at 249 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the injection with *water* to produce a solution containing 0.2% w/v of Sotalol Hydrochloride.

(2) 0.2% w/v of *sotalol hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below in a tank saturated with ammonia vapour.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry it in a current of air for at least 5 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

30 volumes of *methanol* and 70 volumes of *chloroform*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection with the mobile phase to produce a solution containing 0.2% w/v of Sotalol Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 3 volumes of this solution to 10 volumes with the mobile phase.

(3) 0.0008% w/v of *4'-(2-isopropylaminoethyl)methanesulfonanilide hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 228 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

210 volumes of *acetonitrile* and 790 volumes of a 0.2% w/v solution of *sodium octanesulfonate*, adjusted to pH 3.0 with *orthophosphoric acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4′-(2-isopropylaminoethyl)methanesulfonanilide is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any *secondary peaks* is not greater than 1.65 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

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Dilute a volume of the injection containing 20 mg of Sotalol Hydrochloride to 100 mL with *water*. To 10 mL of this solution add 20 mL of 1M *sodium hydroxide* and sufficient *water* to produce 200 mL. Measure the *absorbance* of the resulting solution at the maximum at 249 nm, Appendix II B, using 0.1M *sodium hydroxide* in the reference cell. Calculate the content of $C_{12}H_{20}N_2O_3S$,HCl taking 480 as the value of A(1%, 1 cm) at the maximum at 249 nm.

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Sotalol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist; class II and class III antiarrhythmic.

DEFINITION

Sotalol Tablets contain Sotalol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sotalol hydrochloride, $C_{12}H_{20}N_2O_3S,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm, of the final solution obtained in the Assay exhibits a maximum only at 249 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Sotalol Hydrochloride with 25 mL of *methanol* for 15 minutes, centrifuge and use the supernatant liquid.

(2) 0.2% w/v of *sotalol hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below in a tank saturated with ammonia vapour.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry it in a current of air for at least 5 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

30 volumes of *methanol* and 70 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, size and intensity to that in the chromatogram obtained with solution (2).

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Sotalol Hydrochloride with 25 mL of the mobile phase for 15 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 3 volumes of this solution to 10 volumes with the mobile phase.

(3) 0.0008% w/v of *4′-(2-isopropylaminoethyl)methanesulfonanilide hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 228 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

210 volumes of *acetonitrile* and 790 volumes of a 0.2% w/v solution of *sodium octanesulfonate*, adjusted to pH 3.0 with *orthophosphoric acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4′-(2-isopropylaminoethyl)methanesulfonanilide is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any *secondary peaks* is not more than 1.65 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing 50 mg of Sotalol Hydrochloride with 175 mL of *water* for 15 minutes, add sufficient *water* to produce 250 mL and centrifuge. To 10 mL of the supernatant liquid add 20 mL of 1M *sodium hydroxide* and sufficient *water* to produce 200 mL. Measure the *absorbance* of the resulting solution at the maximum at 249 nm, Appendix II B, using 0.1M *sodium hydroxide* in the reference cell. Calculate the content of $C_{12}H_{20}N_2O_3S$,HCl taking 480 as the value of A(1%, 1 cm) at the maximum at 249 nm.

STORAGE

Sotalol Tablets should be protected from light.

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Soya Phospholipids for Injection

General Notices

(Ph. Eur. monograph 2316)

Soya lecithins *8030-76-0*

Soya phosphatidylcholines *97281-47-5*

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DEFINITION

Mixture of natural phospholipids of soya, and fractions thereof, for injection. A suitable stabiliser such as α-tocopherol may be added.

Content

— *phosphatidylcholine*: minimum 60.0 per cent (anhydrous substance);

— *phosphatidylethanolamine*: maximum 12.0 per cent (anhydrous substance);

— *lysophosphatidylcholine*: maximum 4.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Light yellow or brownish, porous agglomerates or waxy solid mass.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent) and in heptane.

IDENTIFICATION

Carry out either test A or test B. If N-acyl-phosphatidylethanolamine is not detected with test A or B, carry out test C.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *phosphatidylethanolamine from soya bean CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

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Reference solution (b) Dissolve 20 mg of *lysophosphatidylcholine from soya bean CRS* and 20 mg of *N-acyl-phosphatidylethanolamine from soya bean CRS* in *methanol R* and dilute to 20.0 mL with the same solvent.

Reference solution (c) Dissolve 15 mg of *phosphatidylcholine from soya bean CRS* in *methanol R*, add 3 mL of reference solution (a) and 1 mL of reference solution (b) and dilute to 50.0 mL with *methanol R*.

Plate *TLC silica gel plate R* (2-10 µm).

Mobile phase *water R*, *methanol R*, *chloroform R* (4:25:65 *V/V/V*).

Application 4 µL of the test solution and reference solution (c), as slim bands.

Development Over 2/3 of the plate.

Detection Spray with *copper sulfate solution R1* and heat at 170 °C for 5-15 min; the phospholipids appear as brownish-grey bands.

Retardation factors Lysophosphatidylcholine = about 0.15; phosphatidylcholine = about 0.3; phosphatidylethanolamine = about 0.6; *N*-acyl-phosphatidylethanolamine = about 0.8.

System suitability Reference solution (c):

— the chromatogram shows 4 clearly separated bands.

Results:

— the principal band in the chromatogram obtained with the test solution is similar in position and colour to the band due to phosphatidylcholine in the chromatogram obtained with reference solution (c);

— the band due to *N*-acyl-phosphatidylethanolamine is visible in the chromatogram obtained with the test solution.

B. Liquid chromatography (*2.2.29*) as described in the assay with the following modifications.

Injection Test solution and reference solution (h).

Identification of peaks Use the chromatogram obtained with reference solution (h) to identify the peak due to *N*-acyl-phosphatidylethanolamine.

Relative retention With reference to phosphatidylcholine (retention time = about 9 min): *N*-acyl-phosphatidylethanolamine = about 0.2 (may be eluted as 1 or 2 peaks).

Results:

— the principal peak in the chromatogram obtained with the test solution is due to phosphatidylcholine;

— the peak due to *N*-acyl-phosphatidylethanolamine in the chromatogram obtained with the test solution has a signal-to-noise ratio not less than 3.

C. Composition of fatty acids (*2.4.22, Method B*). Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the substance:

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— *linoleic acid (C18:2)*: 59 per cent to 71 per cent;

— *palmitic acid (C16:0)*: 10 per cent to 17 per cent;

— *oleic acid (C18:1)*: 6 per cent to 15 per cent;

— *α-linolenic acid (C18:3)*: 4 per cent to 9 per cent;

— *stearic acid (C18:0)*: 2 per cent to 5 per cent.

TESTS

Acid value (2.5.1)

Maximum 12.

Dissolve 2.00 g in 50 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *ether R*, previously neutralised with *0.1 M potassium hydroxide*, using 0.5 mL of *phenolphthalein solution R1* as indicator.

Peroxide value (2.5.5, Method A)

Maximum 5.

Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (2.2.20).

Iodine value (2.5.4, Method A)

Minimum 83.

Free fatty acids

Thin-layer chromatography (2.2.27). *Carry out the test at room temperature.*

Solvent mixture *water R*, *heptane R*, *2-propanol R* (8:40:50 *V/V/V*).

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution Dissolve 10.0 mg of *oleic acid R* and 10 mg of *refined soya-bean oil R* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *acetic acid R*, *ether R*, *heptane R* (1:30:70 *V/V/V*).

Application 20 µL.

Development Over 2/3 of the plate.

Detection Spray with *copper sulfate solution R1* and heat at 170 °C for 5-15 min.

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Retardation factors Oleic acid = about 0.3; soya-bean oil = about 0.5.

System suitability Reference solution:

— the chromatogram shows 2 clearly separated spots.

Limit Any spot due to oleic acid is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.5 per cent).

Water (2.5.12)

Maximum 2.0 per cent, determined on 0.500-1.00 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

Bacterial endotoxins (2.6.14, Method A)

Less than 6 IU/g. The suitability of the method must be verified and a risk assessment must be carried out according to general chapter 5.1.10. *Guidelines for using the test for bacterial endotoxins* since the phospholipids can interfere with the test.

ASSAY

Liquid chromatography (2.2.29).

Solvent mixture Mix 8 volumes of *water R* and 46 volumes of *2-propanol R*, then add 46 volumes of *hexane R*.

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

NOTE: if saturation of the peak due to phosphatidylcholine is observed, the test solution may be diluted with the solvent mixture to quantify this compound.

Reference solution (a_1) Dissolve 60 mg of *phosphatidylcholine from soya bean CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solutions (b_1), (c_1), (d_1), (e_1), (f_1) Dilute reference solution (a_1) with the solvent mixture to obtain 5 reference solutions, the concentrations of which span 60 per cent to 140 per cent of the expected content of phosphatidylcholine in the test solution.

Reference solution (a_2) Dissolve 40 mg of *phosphatidylethanolamine from soya bean CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solutions (b_2), (c_2), (d_2), (e_2), (f_2) Dilute reference solution (a_2) with the solvent mixture to obtain 5 reference solutions, the concentrations of which span 60 per cent to 140 per cent of the expected content of phosphatidylethanolamine in the test solution.

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Reference solution (a_3) Dissolve 40 mg of *lysophosphatidylcholine from soya bean CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solutions (b_3), (c_3), (d_3), (e_3), (f_3) Dilute reference solution (a_3) with the solvent mixture to obtain 5 reference solutions, the concentrations of which span 60 per cent to 140 per cent of the expected content of lysophosphatidylcholine in the test solution.

Reference solution (g) Mix 5 mL of reference solution (a_1) and 5 mL of reference solution (a_2).

Reference solution (h) Dissolve 5 mg of *N-acyl-phosphatidylethanolamine from soya bean CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *diol silica gel for chromatography R* (5 µm);

— *temperature*: 55 °C.

Mobile phase:

— *mobile phase A*: mix 0.08 volumes of *triethylamine R*, 1.5 volumes of *glacial acetic acid R*, 17 volumes of *2-propanol R* and 81.42 volumes of *hexane R*;

— *mobile phase B*: mix 0.08 volumes of *triethylamine R*, 1.5 volumes of *glacial acetic acid R*, 14 volumes of *water for chromatography R* and 84.42 volumes of *2-propanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.0	95	5
2.0 - 7.0	95 → 80	5 → 20
7.0 - 10.5	80 → 60	20 → 40
10.5 - 17.0	60 → 0	40 → 100
17.0 - 19.5	0	100

Flow rate 1.0 mL/min.

Detection Evaporative light-scattering detector; the following settings have been found to be suitable; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criteria:

— *carrier gas*: *nitrogen R*;

— *flow rate*: 2.5 mL/min;

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— *evaporation temperature*: 50 °C.

Injection 20 µL of the test solution and reference solutions ($b_{1,2,3}$), ($c_{1,2,3}$), ($d_{1,2,3}$), ($e_{1,2,3}$), ($f_{1,2,3}$) and (g).

Identification of peaks Use the chromatograms obtained with reference solutions (f_1), (f_2) and (f_3) to identify the peaks due to phosphatidylcholine, phosphatidylethanolamine and lysophosphatidylcholine.

Relative retention With reference to phosphatidylcholine (retention time = about 9 min): phosphatidylethanolamine = about 0.8; lysophosphatidylcholine = about 1.2.

Establish calibration curves with the logarithm of the concentration of phosphatidylcholine, phosphatidylethanolamine and lysophosphatidylcholine in reference solutions ($b_{1,2,3}$), ($c_{1,2,3}$), ($d_{1,2,3}$), ($e_{1,2,3}$) and ($f_{1,2,3}$) as the abscissa and the logarithm of the corresponding peak areas as the ordinate.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to phosphatidylethanolamine and phosphatidylcholine in the chromatogram obtained with reference solution (g);

— *phosphatidylcholine*:

— *repeatability*: maximum relative standard deviation of 5.0 per cent determined on 6 injections of reference solution (f_1);

— *correlation coefficient*: minimum 0.995;

— *phosphatidylethanolamine*:

— *repeatability*: maximum relative standard deviation of 5.0 per cent determined on 6 injections of reference solution (f_2);

— *correlation coefficient*: minimum 0.995;

— *lysophosphatidylcholine*:

— *repeatability*: maximum relative standard deviation of 5.0 per cent determined on 6 injections of reference solution (f_3);

— *correlation coefficient*: minimum 0.99.

Calculate the percentage contents of phosphatidylcholine, phosphatidylethanolamine and lysophosphatidylcholine using the calibration curves.

STORAGE

Under nitrogen, protected from light, at -15 °C or below.

LABELLING

The label states:

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— the specified content range of phosphatidylcholine;

— the specified content range of phosphatidylethanolamine.

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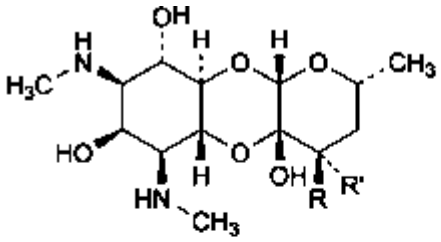
Spectinomycin Dihydrochloride Pentahydrate

General Notices

(Ph. Eur. monograph 1152)



, 2 HCl , 5 H_2O

Compound	R	R'	Molec. Formula	M_r
spectinomycin	R + R' = O		$C_{14}H_{26}Cl_2N_2O_7,5H_2O$	495.4
(4*R*)-dihydro-spectinomycin	OH	H	$C_{14}H_{28}Cl_2N_2O_7,5H_2O$	497.4

Action and use

Aminocyclotol antibacterial.

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DEFINITION

Mixture of (2*R*,4a*R*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)decahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one dihydrochloride pentahydrate (spectinomycin dihydrochloride pentahydrate) and of (2*R*,4*R*,4a*S*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)-2-methyl-6,8-bis(methylamino)decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxine-4,4a,7,9-tetrol dihydrochloride pentahydrate ((4*R*)-dihydrospectinomycin dihydrochloride pentahydrate).

It is produced by *Streptomyces spectabilis* or by any other means.

Content

— *(4R)-dihydrospectinomycin dihydrochloride*: maximum 9.0 per cent (anhydrous substance);

— *sum of the contents of spectinomycin dihydrochloride and (4R)-dihydrospectinomycin dihydrochloride*: 93.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

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White or almost white, slightly hygroscopic powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *spectinomycin hydrochloride CRS*.

B. Dilute 1.0 mL of solution S (see Tests) to 10 mL with *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dilute 2.0 mL of solution S to 20.0 mL with *water R*.

pH (*2.2.3*)

3.8 to 5.6 for solution S.

Specific optical rotation (*2.2.7*)

+ 15.0 to + 21.0 (anhydrous substance), determined on solution S within 20 min of preparation.

Related substances

Liquid chromatography (*2.2.29*). *In order to avoid formation of anomers, prepare the solutions immediately before use.*

Test solution Dissolve 15.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 3 mg of *spectinomycin for system suitability CRS* in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 3.0 mL of reference solution (b) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: ambient and constant.

Mobile phase Dissolve 4.2 g of *oxalic acid R* and 2.0 mL of *heptafluorobutyric acid R* in *water R* and dilute to 1000 mL with *water R*; adjust to pH 3.2 with *sodium hydroxide solution R*, add 105 mL of *acetonitrile R* and mix; filter through a membrane filter (nominal pore size 0.45 µm) and degas with *helium for chromatography R* for 10 min.

Flow rate 1.0 mL/min.

Post-column solution *carbonate-free sodium hydroxide solution R* diluted with *carbon dioxide-free water R* to obtain a final concentration of NaOH of 21 g/L. Degas the solution with *helium for chromatography R* for 10 min before use. Add it pulse-less to the column effluent using a 375 µL polymeric mixing coil.

Post-column flow rate 0.5 mL/min.

Detection Pulsed amperometric detection or equivalent with a gold indicator electrode having preferably a diameter of 1.4 mm or greater, a suitable reference electrode and a stainless steel counter electrode, held at + 0.12 V detection, + 0.70 V oxidation and -0.60 V reduction potentials respectively, with pulse durations according to the instrument used. Keep the detection cell at ambient and constant temperature. Clean the gold indicator electrode with an eraser and damp precision wipe prior to start-up of the system to enhance the detector sensitivity and increase the signal-to-noise ratio.

Injection 20 µL.

Run time 1.5 times the retention time of spectinomycin.

Identification of impurities Use the chromatogram supplied with *spectinomycin for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, D and E.

Relative retention With reference to spectinomycin (retention time = 11 min to 20 min): impurity A = about 0.5; impurity F = about 0.53; impurity G = about 0.6; impurity D = about 0.7; impurity E = about 0.9; (4*R*)-dihydrospectinomycin = about 1.3; impurity C = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity E and spectinomycin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.4;

— *impurities A, C, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurities D, E*: for each impurity, not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (4.0 per cent);

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— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (6.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent); disregard the peak due to (4*R*)-dihydrospectinomycin.

Water (2.5.12)

16.0 per cent to 20.0 per cent, determined on 0.100 g.

Sulfated ash (2.4.14)

Maximum 1.0 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 0.09 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. Prepare the solutions using a 0.42 per cent *m/m* solution of *sodium hydrogen carbonate R*.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Test solution Dissolve 40.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent. Allow to stand for not less than 15 h and not more than 72 h (formation of anomers). Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution Dissolve 40.0 mg of *spectinomycin hydrochloride CRS* (containing (4*R*)-dihydrospectinomycin) in *water R* and dilute to 50.0 mL with the same solvent. Allow to stand for the same period of time as the test solution (formation of anomers). Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

System suitability:

— *repeatability*: maximum relative standard deviation of 3.0 per cent for the principal peak determined on 6 injections of the reference solution.

Calculate the sum of the percentage contents of spectinomycin dihydrochloride and (4*R*)-dihydrospectinomycin dihydrochloride taking into account the assigned contents of the sum of $C_{14}H_{26}Cl_2N_2O_7$ and $C_{14}H_{28}Cl_2N_2O_7$ in *spectinomycin hydrochloride CRS*. Calculate the percentage content of (4*R*)-dihydrospectinomycin dihydrochloride taking into account the assigned contents of the sum of $C_{14}H_{26}Cl_2N_2O_7$ and $C_{14}H_{28}Cl_2N_2O_7$ in *spectinomycin hydrochloride CRS*.

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

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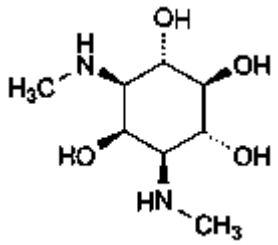
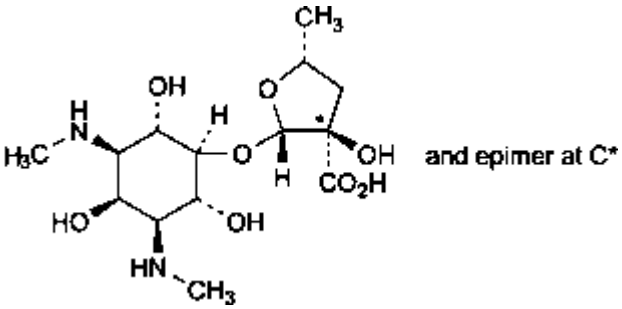
IMPURITIES

Specified impurities A, C, D, E, F, G.

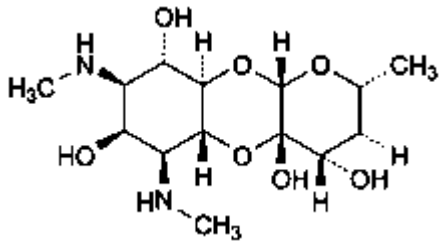
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



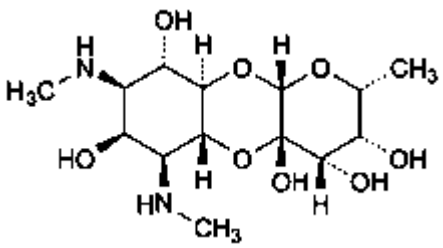
A. 1,3-dideoxy-1,3-bis(methylamino)-*myo*-inositol (actinamine),



B. (2*S*,3*RS*,5*R*)-3-hydroxy-5-methyl-2-[[(1*r*,2*R*,3*S*,4*r*,5*R*,6*S*)-2,4,6-trihydroxy-3,5-bis(methylamino)cyclohexyl]oxy]tetrahydrofuran-3-carboxylic acid (actinospectinoic acid),



C. (2*R*,4*S*,4a*S*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)-2-methyl-6,8-bis(methylamino)decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxine-4,4a,7,9-tetrol ((4*S*)-dihydrospectinomycin),



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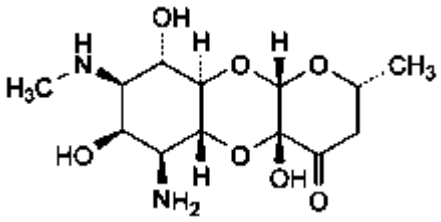
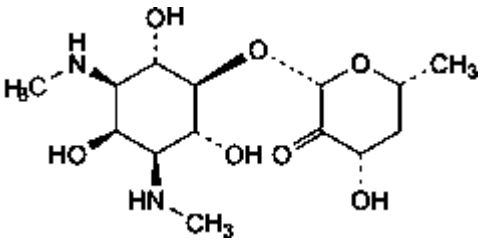
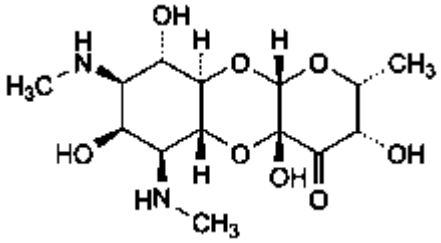
D. (2*R*,3*R*,4*S*,4a*S*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)-2-methyl-6,8-bis(methylamino)decahydro-2*H*-pyrano[2,3-*b*][1,4]benzodioxine-3,4,4a,7,9-pentol (dihydroxyspectinomycin),



E. (2*R*,4a*R*,5a*R*,6*S*,7*R*,8*R*,9*S*,9a*R*,10a*S*)-6-amino-4a,7,9-trihydroxy-2-methyl-8-(methylamino)decahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one (*N*-desmethylspectinomycin),



F. (2*S*,4*S*,6*R*)-4-hydroxy-6-methyl-2-[[(1*r*,2*R*,3*S*,4*r*,5*R*,6*S*)-2,4,6-trihydroxy-3,5-bis(methylamino)cyclohexyl]oxy]dihydro-2*H*-pyran-3(4*H*)-one (triol spectinomycin),



G. (2*R*,3*S*,4a*R*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)-3,4a,7,9-tetrahydroxy-2-methyl-6,8-bis(methylamino)decahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one (tetrahydroxyspectinomycin).

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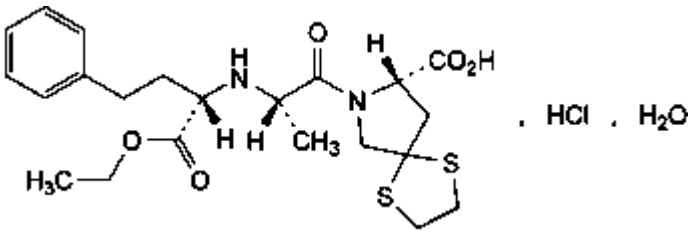
Spirapril Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 1766)



$C_{22}H_{31}ClN_2O_5S_2,H_2O$ 521.1

Action and use

Angiotensin-converting enzyme inhibitor.

Ph Eur

DEFINITION

(8*S*)-7-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid hydrochloride monohydrate.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, fine crystalline powder.

Solubility

Very slightly soluble in water, soluble in methanol, slightly soluble in acetonitrile, practically insoluble in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *spirapril hydrochloride monohydrate CRS*.

C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Specific optical rotation (*2.2.7*)

-13.0 to -11.0 (anhydrous substance).

Dissolve 0.200 g in *dimethylformamide R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R1*, *water R* (20:80 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 6 mg of *spirapril for system suitability CRS* (containing impurities B and D) in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 70 °C.

Mobile phase:

— *mobile phase A*: dissolve 4.5 g of *tetramethylammonium hydroxide R* in 900 mL of *water R*, add 100 mL of *acetonitrile R1* and adjust to pH 2.2 with *phosphoric acid R*;

— *mobile phase B*: dissolve 4.5 g of *tetramethylammonium hydroxide R* in 400 mL of *water R*, add 600 mL of *acetonitrile R1* and adjust to pH 2.2 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	90	10

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
4 - 14	90 → 10	10 → 90
14 - 20	10	90

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Relative retention With reference to spirapril (retention time = about 10 min): impurity C = about 0.6; impurity B = about 0.7; impurity A = about 1.26; impurity D = about 1.38.

System suitability Reference solution (a):

— *resolution*: minimum 3.5 between the peaks due to impurity B and spirapril, and minimum 5.5 between the peaks due to spirapril and impurity D.

Limits:

— *impurity D*: not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity B*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities A, C*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (*2.5.12*)

3.0 per cent to 4.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Liquid chromatography (2.2.29).

Solvent mixture Mix equal volumes of acetonitrile R1 and water R.

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of spirapril hydrochloride monohydrate CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 6.0 mg of spirapril for system suitability CRS (spirapril spiked with impurity B and impurity D) in a mixture of 2 volumes of acetonitrile R and 8 volumes of water R and dilute to 20 mL with the same mixture of solvents.

Solution A Dissolve 4.5 g of tetramethylammonium hydroxide R in 900 mL of water R, adjust to pH 1.75 with phosphoric acid R and add 100 mL of acetonitrile R1.

Solution B Dissolve 4.5 g of tetramethylammonium hydroxide R in 400 mL of water R, adjust to pH 1.75 with phosphoric acid R and add 600 mL of acetonitrile R1.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 70 °C.

Mobile phase Solution A, solution B (45:55 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Retention time Spirapril = 1.6 min to 2.9 min; impurity D = about 13 min. Adjust the proportion of solution B in the mobile phase if necessary.

System suitability Reference solution (b):

— *resolution*: minimum 15 between the peaks due to spirapril and impurity D.

Calculate the percentage content of $C_{22}H_{31}ClN_2O_5S_2$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of spirapril hydrochloride monohydrate CRS.

STORAGE

In an airtight container, protected from light.

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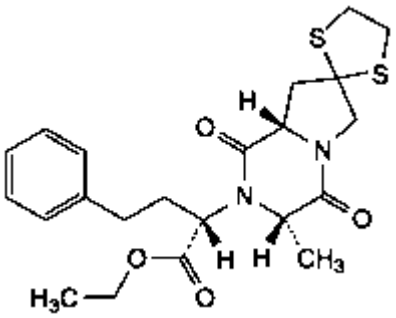
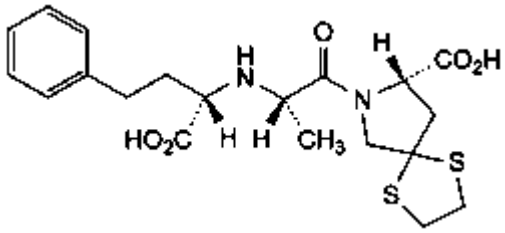
IMPURITIES

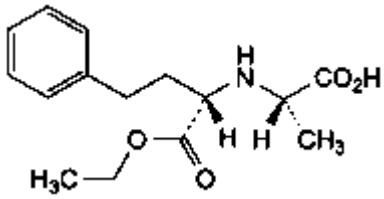
Specified impurities *A, B, C, D.*



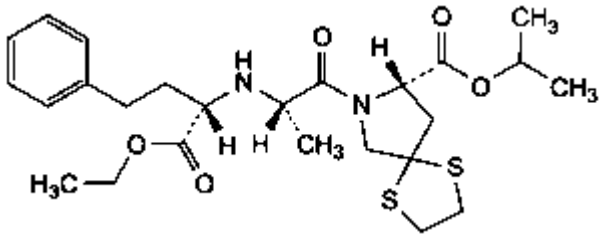
A. ethyl (2*S*)-2-[(3′*S*,8′a*S*)-3′-methyl-1′,4′-dioxohexahydrospiro[1,3-dithiolane-2,7′(6′*H*)-pyrrolo[1,2-*a*]pyrazin]-2′-yl]-4-phenylbutanoate,



B. (8*S*)-7-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid (spiraprilat),



C. (2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



D. 1-methylethyl (8*S*)-7-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylate.

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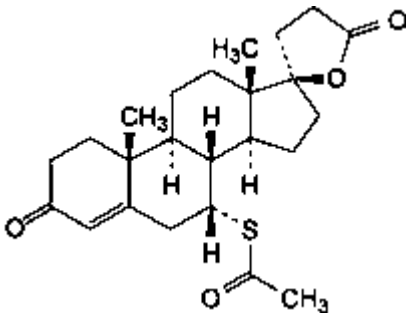
Spironolactone

General Notices

(Ph. Eur. monograph 0688)



$C_{24}H_{32}O_4S$ 416.6 *52-01-7*

Action and use

Aldosterone receptor antagonist; potassium-sparing diuretic.

Preparations

Spironolactone Oral Suspension

Spironolactone Tablets

Ph Eur

DEFINITION

S-[(2′*R*)-3,5′-Dioxo-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethanethioate.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

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Practically insoluble in water, soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *spironolactone CRS*.

If the spectra obtained in the solid state shows differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *spironolactone CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *cyclohexane R*, *ethyl acetate R* (1:24:75 *V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To about 10 mg add 2 mL of a 50 per cent *V/V* solution of *sulfuric acid R* and shake. An orange solution with an intense yellowish-green fluorescence is produced. Heat the solution gently; the colour becomes deep red and hydrogen sulfide, which blackens *lead acetate paper R*, is evolved. Add the solution to 10 mL of *water R*; a greenish-yellow solution is produced, showing opalescence or a precipitate.

TESTS

Specific optical rotation (2.2.7)

-46 to -41 (dried substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

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Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in 2.5 mL of tetrahydrofuran R and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (b) to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve with the aid of ultrasound the contents of a vial of spironolactone for system suitability CRS (containing impurities A, C, D, E and I) in 1.0 mL of the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of spironolactone CRS in 2.5 mL of tetrahydrofuran R and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5.0 mg of canrenone CRS (impurity F) in 2.5 mL of tetrahydrofuran R and dilute to 25.0 mL with the solvent mixture. Dilute 3.0 mL of this solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 40 °C.

Mobile phase acetonitrile R, tetrahydrofuran R, methanol R1, water for chromatography R (15:20:425:540 *V/V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (d).

Run time 2.5 times the retention time of spironolactone.

Identification of impurities Use the chromatogram supplied with spironolactone for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C, D, E and I; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to spironolactone (retention time = about 26 min): impurity A = about 0.95; impurity F = about 1.2; impurity C = about 1.5; impurity D = about 1.6; impurity E = about 1.7; impurity I = about 1.9.

System suitability Reference solution (b):

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— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to spironolactone.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 2.3;

— *impurity I*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities E, F*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities A, C*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Free thiol compounds

To 2.0 g add 20 mL of *water R*, shake for 1 min and filter. To 10 mL of the filtrate add 0.05 mL of *0.01 M iodine* and 0.1 mL of *starch solution R* and mix. A blue colour develops.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{24}H_{32}O_4S$ from the assigned content of *spironolactone CRS*.

STORAGE

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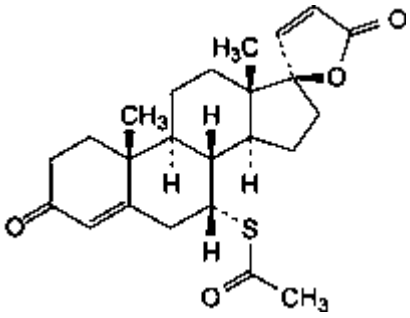
Protected from light.

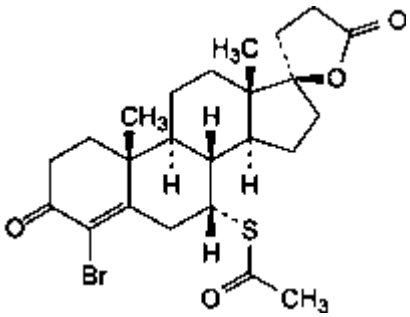
IMPURITIES

Specified impurities *A, C, D, E, F, I.*

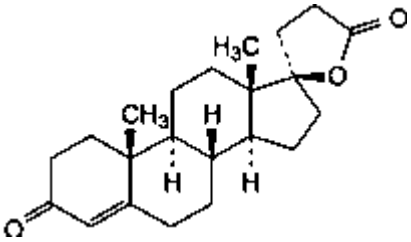
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, G, H.*



A. *S*-[(2′*R*)-3,5′-dioxo-5′*H*-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethanethioate (Δ20-spironolactone),



B. *S*-[(2′*R*)-4-bromo-3,5′-dioxo-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethanethioate (4-bromospironolactone),



C. (2′*R*)-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-3,5′-dione (aldone),

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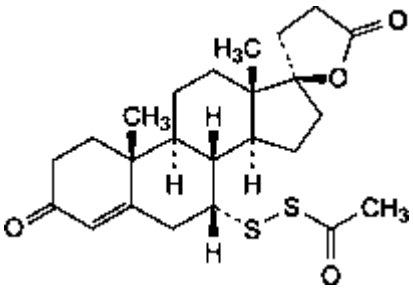
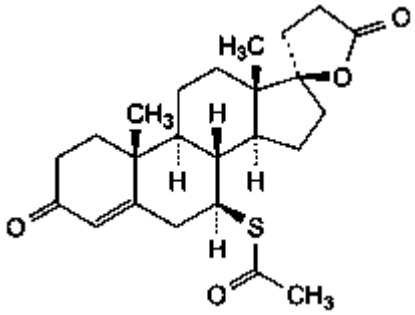
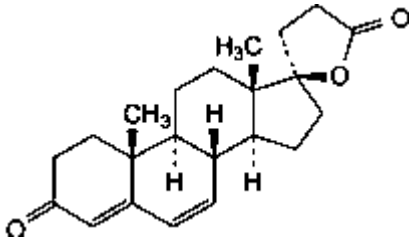


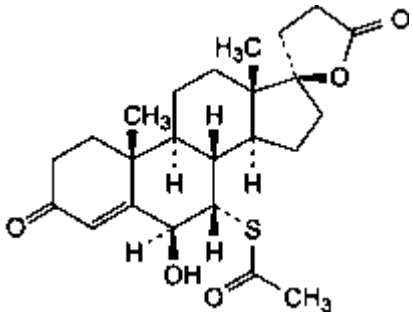
D. *S*-[(2′*R*)-3,5′-dioxo-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethane(dithioperoxate) (disulfanyl-spironolactone),



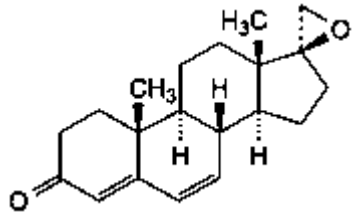
E. *S*-[(2′*R*)-3,5′-dioxo-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-7β-yl] ethanethioate (7β-spironolactone),



F. (2′*R*)-3′,4′-dihydro-5′*H*-spiro[androst-4,6-diene-17,2′-furan]-3,5′-dione (canrenone),



G. *S*-[(2′*R*)-6β-hydroxy-3,5′-dioxo-3′,4′-dihydro-5′*H*-spiro[androst-4-ene-17,2′-furan]-7α-yl] ethanethioate (6β-hydroxy-spironolactone),



H. (2′*S*)-spiro[androst-4,6-diene-17,2′-oxiran]-3-one,

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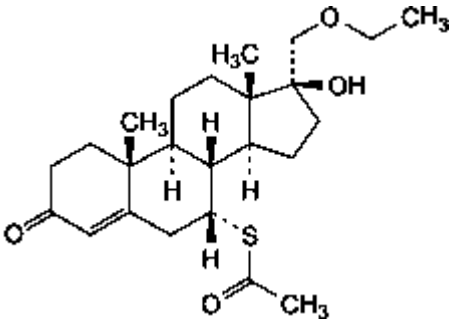

I. *S*-[17α-(ethoxymethyl)-17β-hydroxy-3-oxoandrost-4-en-7α-yl] ethanethioate.

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Spironolactone Oral Suspension

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Aldosterone receptor antagonist; potassium-sparing diuretic.

DEFINITION

Spironolactone Oral Suspension is a suspension containing Spironolactone in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of spironolactone, $C_{24}H_{32}O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the oral suspension containing 20 mg of Spironolactone with sufficient *dichloromethane* to produce a solution containing 0.1% w/v and filter (Whatman GF/C is suitable).

(2) 0.1% w/v of *spironolactone BPCRS* in *dichloromethane*.

(3) 0.01% w/v of each of *spironolactone BPCRS* and *canrenone EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *water*, 24 volumes of *cyclohexane* and 75 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

The requirement stated under Unlicensed Medicines, Oral Suspensions does not apply to Spironolactone Oral Suspension.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Mix 10 volumes of *methanol*, 20 volumes of a 0.0029% w/v solution of *orthophosphoric acid*, 20 volumes of *water* and 50 volumes of *acetonitrile* (solution A).

(1) Transfer a quantity of the oral suspension containing 50 mg of Spironolactone to a 500 mL volumetric flask. Add 200 mL of a 1.25% w/v solution of *sodium chloride* and shake. Add 50 mL of *methanol* and 100 mL of *acetonitrile*; dilute to volume with *acetonitrile*. Mix with the aid of ultrasound for 5 minutes and shake for a further 10 minutes. Allow the flocculate to settle at the bottom of the flask and filter the solution through a nylon filter (0.45-µm).
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) Dilute 1 volume of solution (2) to 10 volumes with solution A.
(4) 0.00001% w/v of each of *spironolactone BPCRS* and *canrenone EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable) fitted with a guard column (4 mm × 3 mm) packed with the same material.
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile*, 35 volumes of *methanol* and 60 volumes of *water*.

Mobile phase B 25 volumes of *acetonitrile*, 35 volumes of *methanol* and 40 volumes of *water*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-35	100→0	0→100	linear gradient
35-43	0	100	isocratic
43-44	0→100	100→0	linear gradient
44-49	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to spironolactone and canrenone is at least 2.0;

the *signal-to-noise ratio* of the peaks due to spironolactone and canrenone is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to canrenone using solution (4) and multiply the area of this peak by the following correction factor: 1.7;

the area of any peak corresponding to canrenone is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Mix 10 volumes of *methanol*, 20 volumes of a 0.0029% w/v solution of *orthophosphoric acid*, 20 volumes of *water* and 50 volumes of *acetonitrile* (solution A).

(1) Transfer a weighed quantity of the oral suspension containing 50 mg of Spironolactone to a 500 mL volumetric flask. Add 200 mL of a 1.25% w/v solution of *sodium chloride* and shake. Add 50 mL of *methanol* and 100 mL of *acetonitrile*; dilute to volume with *acetonitrile*. Mix with the aid of ultrasound for 5 minutes and shake for a further 10 minutes. Allow the flocculate to settle at the bottom of the flask and filter the solution through a nylon filter (0.45-µm).

(2) 0.01% w/v of *spironolactone BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{24}H_{32}O_4S$, weight in volume, using the declared content of $C_{24}H_{32}O_4S$ in *spironolactone BPCRS*.

STORAGE

Spironolactone Oral Suspension should be protected from light.

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Spironolactone Tablets

General Notices

Action and use

Aldosterone receptor antagonist; potassium-sparing diuretic.

DEFINITION

Spironolactone Tablets contain Spironolactone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of spironolactone, $C_{24}H_{32}O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 0.125 g of Spironolactone with two 10 mL quantities of *chloroform*, filter, evaporate the combined filtrates to dryness and dissolve the residue in 2.5 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of spironolactone (*RS 321*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 1 volume of *water*, 24 volumes of *cyclohexane* and 75 volumes of *ethyl acetate* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 20 mg of Spironolactone with 10 mL of *dichloromethane*. Solution (2) contains 0.2% w/v of *spironolactone BPCRS* in *dichloromethane*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 1000 mL of *0.1M hydrochloric acid* containing 0.1% w/v *sodium dodecyl sulfate* and rotate the paddle at 75 revolutions per minute. Withdraw a sample of 10 mL of the medium, filter and measure the *absorbance* of the filtrate, suitably diluted if necessary, at the maximum at 242 nm, Appendix II B. Calculate the total content of $C_{24}H_{32}O_4S$ in the medium taking 445 as the value of A(1%, 1 cm) at the maximum at 242 nm.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) disperse a quantity of the powdered tablets containing 62.5 mg of Spironolactone with 25 mL of *chloroform*, place in an ultrasonic bath for 5 minutes, shake for 10 to 15 minutes, centrifuge and filter the supernatant liquid through glass fibre paper (Whatman GF/C is suitable). Repeat the procedure on the residue with a further 25 mL of *chloroform*. Combine the chloroform extracts and evaporate to dryness using a rotary evaporator. Add 2.5 mL of *tetrahydrofuran* and 22.5 mL of the mobile phase to the residue. For solution (2) dilute 1 mL of solution (1) to 100 mL with the mobile phase. For solution (3) dissolve 25 mg of *canrenone EPCRS* in 1 mL of *tetrahydrofuran* and dilute to 10 mL with the mobile phase. For solution (4) dilute 1 mL of solution (3) to 100 mL with the mobile phase. For solution (5) mix 1 mL each of solutions (1) and (3) and dilute to 100 mL with the mobile phase. For solution (6) dilute 0.5 mL of solution (2) to 10 mL with the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Spherisorb C8 is suitable), (b) a mixture of 8 volumes of *acetonitrile*, 18 volumes of *tetrahydrofuran* and 74 volumes of *water* as the mobile phase with a flow rate of 1.8 mL per minute and (c) detection wavelengths of 254 nm and 283 nm as directed below.

Inject separately 20 µL of each of solutions (1), (2), (5) and (6) and record the chromatograms for twice the retention time of spironolactone using a detection wavelength of 254 nm. In the chromatogram obtained with solution (1), the sum of the areas of any *secondary peaks*, other than any peak corresponding to canrenone, is not greater than the area of the peak due to spironolactone in the chromatogram obtained with solution (2) (1%). Disregard any peak the area of which is less than that of the principal peak in the chromatogram obtained with solution (6).

Inject 20 µL of each of solutions (1) and (4) and record the chromatograms using a detection wavelength of 283 nm. The test is not valid unless (a) the chromatogram obtained with solution (5) shows two peaks due to canrenone and spironolactone with a *resolution factor* greater than 1.4 and (b) the principal peak in the chromatogram obtained with solution (6) has a *signal-to-noise ratio* of at least 6.

In the chromatogram obtained with solution (1) the area of any peak corresponding to canrenone is not greater than that of the peak due to canrenone in the chromatogram obtained with solution (4) (1%). Calculate the percentage content of canrenone found when recording at 283 nm and the percentage content of the other related substances found when recording at 254 nm. The sum is not greater than 1.0%.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 25 mg of Spironolactone add 100 mL of *methanol* and heat just to boiling, with swirling. Cool, add sufficient *methanol* to produce 250 mL, dilute 10 mL to 100 mL with *methanol* and measure the *absorbance* of the resulting solution at the maximum at 238 nm, Appendix II B. Calculate the content of $C_{24}H_{32}O_4S$ taking 470 as the value of A(1%, 1 cm) at the maximum at 238 nm.

STORAGE

Spironolactone Tablets should be protected from light.

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Spray-dried Liquid Glucose

General Notices

(Ph. Eur. monograph 1525)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of glucose, oligosaccharides and polysaccharides, obtained by the partial hydrolysis of starch.

The degree of hydrolysis, expressed as dextrose equivalent (DE), is not less than 20 (nominal value).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder or granules.

Solubility

Freely soluble in water.

IDENTIFICATION

A. Dissolve 0.1 g in 2.5 mL of *water R* and heat with 2.5 mL of *cupri-tartaric solution R*. A red precipitate is formed.

B. Dip, for 1 s, a suitable stick with a reactive pad containing glucose-oxidase, peroxidase and a hydrogen-donating substance, such as tetramethylbenzidine, in a 5 g/L solution of the substance to be examined. Observe the colour of the reactive pad; within 60 s the colour changes from yellow to green or blue.

C. It is a powder or granules.

D. Dextrose equivalent (see Tests).

TESTS

Solution S

Dissolve 12.5 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

pH (*2.2.3*)

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4.0 to 7.0.

Mix 1 mL of a 223.6 g/L solution of *potassium chloride R* and 30 mL of solution S.

Sulfur dioxide (*2.5.29*)

Maximum 20 ppm.

Loss on drying (*2.2.32*)

Maximum 6.0 per cent, determined on 10.00 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

Dextrose equivalent

(DE): within 10 per cent of the nominal value.

Weigh an amount of the substance to be examined equivalent to 2.85-3.15 g of reducing carbohydrates, calculated as dextrose equivalent, into a 500 mL volumetric flask. Dissolve in *water R* and dilute to 500.0 mL with the same solvent. Transfer the solution to a 50 mL burette.

Pipette 25.0 mL of *cupri-tartaric solution R* into a 250 mL flask and add 18.5 mL of the test solution from the burette, mix and add a few glass beads. Place the flask on a hot plate, previously adjusted so that the solution begins to boil after 2 min ± 15 s. Allow to boil for exactly 120 s, add 1 mL of a 1 g/L solution of *methylene blue R* and titrate with the test solution (V_1) until the blue colour disappears. Maintain the solution at boiling throughout the titration.

Standardise the cupri-tartaric solution using a 6.00 g/L solution of *glucose R* (V_0).

Calculate the dextrose equivalent using the following expression:

$$\frac{300 \times V_0 \times 100}{V_1 \times M \times D}$$

V_0	=	total volume of glucose standard solution, in millilitres;
V_1	=	total volume of test solution, in millilitres;
M	=	mass of the sample, in grams;
D	=	percentage content of dry matter in the substance.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

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Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

LABELLING

The label states the dextrose equivalent (DE) (= nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for spray-dried liquid glucose used as filler or binder for wet granulation.

Dextrose equivalent

(see Tests).

Particle-size distribution (2.9.31 or 2.9.38)

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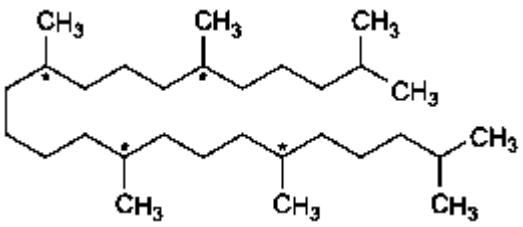
Squalane

General Notices

(Ph. Eur. monograph 1630)



$C_{30}H_{62}$ 422.8 *111-01-3*

Action and use

Excipient; emollient.

Ph Eur

DEFINITION

(6Ξ,10Ξ,15Ξ,19Ξ)-2,6,10,15,19,23-Hexamethyltetracosane (perhydrosqualene). It may be of vegetable (unsaponifiable matter of olive oil), animal (shark liver oil) or synthetic origin.

Content

96.0 per cent to 103.0 per cent.

PRODUCTION

The origin of the squalane (vegetable, animal or synthetic) is stated by the manufacturer.

CHARACTERS

Appearance

Clear, colourless, oily liquid.

Solubility

Practically insoluble in water, miscible with most fats and oils, freely soluble in acetone and in cyclohexane, practically insoluble in ethanol (96 per cent).

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Relative density

About 0.815.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *squalane CRS*.

B. Refractive index (see Tests).

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Refractive index (*2.2.6*)

1.450 to 1.454.

Acid value (*2.5.1*)

Maximum 0.2.

Iodine value (*2.5.4, Method A*)

Maximum 4.0.

Saponification value (*2.5.6*)

Maximum 3.0.

Total ash (*2.4.16*)

Maximum 0.5 per cent, determined on 1.000 g.

ASSAY

Gas chromatography (*2.2.28*).

Internal standard solution To 1.0 mL of *dimethylacetamide R* add 100.0 mL of *heptane R*.

Test solution Dissolve 0.100 g of the substance to be examined in the internal standard solution and dilute to 25.0 mL with the same solution.

Reference solution (a) Dissolve 0.100 g of *squalane CRS* in the internal standard solution and dilute to 25.0 mL with the same solution.

Reference solution (b) To 0.1 mL of *methyl erucate R* add 0.100 g of the substance to be examined, dissolve in the internal standard solution and dilute to 25 mL with the same solution.

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Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.7 mL/min.

Split ratio 1:12.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 39	60 → 290
	39 - 50	290
Injection port		275
Detector		300

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to squalane (retention time = about 41 min): internal standard = about 0.2; methyl erucate = about 0.9; cyclosqualane = 1.05.

System suitability Reference solution (b):

— *resolution*: minimum 5 between the peaks due to methyl erucate and squalane.

Calculate the percentage content of $C_{30}H_{62}$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *squalane CRS*.

LABELLING

The label states the origin of squalane (vegetable, animal or synthetic).

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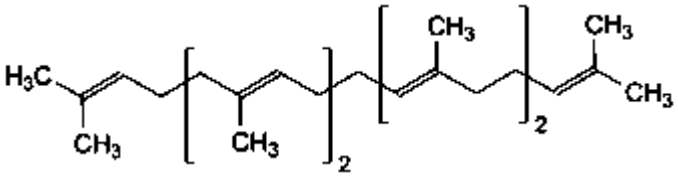
Squalene

General Notices

(Ph. Eur. monograph 2805)



$C_{30}H_{50}$ 410.7

111-02-4

Ph Eur

DEFINITION

(6*E*,10*E*,14*E*,18*E*)-2,6,10,15,19,23-Hexamethyltetracosa-2,6,10,14,18,22-hexaene. It may be of vegetable or animal origin.

Content

97.0 per cent to 103.0 per cent (anhydrous substance).

This monograph applies to squalene used as an adjuvant in vaccines.

CHARACTERS

Appearance

Clear, colourless or light yellow, oily liquid.

Solubility

Practically insoluble in water, freely soluble in acetone and in cyclohexane, soluble in ethanol (96 per cent).

Relative density

About 0.86.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

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Comparison *squalene CRS*.

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Refractive index (*2.2.6*)

1.491 to 1.499.

Acid value (*2.5.1*)

Maximum 1.0.

Iodine value (*2.5.4, Method B*)

350 to 450, determined on 0.06 g.

Peroxide value (*2.5.5, Method A*)

Maximum 5.0.

Saponification value (*2.5.6*)

Maximum 5.0.

Water (*2.5.32*)

Maximum 0.2 per cent, determined on 2.00 g.

ASSAY

Gas chromatography (*2.2.28*). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.100 g of the substance to be examined in *heptane R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 0.100 g of *squalene CRS* in *heptane R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 0.100 g of the substance to be examined and 0.100 g of *methyl lignocerate R* in *heptane R* and dilute to 100.0 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 1 µm).

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Carrier gas *helium for chromatography R*.

Flow rate 1.7 mL/min.

Split ratio 1:12.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 12	290
Injection port		275
Detector		300

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to squalene (retention time = about 8.1 min): methyl lignocerate = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to methyl lignocerate and squalene.

Calculate the percentage content of $C_{30}H_{50}$ taking into account the assigned content of *squalene CRS*.

STORAGE

In an airtight container, protected from light.

LABELLING

The label states the origin of squalene (vegetable or animal).

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Stannous Chloride Dihydrate

General Notices

(Ph. Eur. monograph 1266)

$SnCl_2,2H_2O$ 225.6 *10025-69-1*

Ph Eur

DEFINITION

Content

98.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, efflorescent in air.

Solubility

Freely soluble in water (the solution becomes cloudy after standing or on dilution), freely soluble in ethanol (96 per cent). It dissolves in dilute hydrochloric acid.

IDENTIFICATION

A. To 1 mL of solution S1 (see Tests) add 5 mL of *water R* and 0.05 mL of *mercuric chloride solution R*. A blackish-grey precipitate is formed.

B. Dissolve 1.0 g in 3.0 mL of *water R*. Add 0.5 mL of *dilute sodium hydroxide solution R* to the cloudy solution; a yellowish flocculent precipitate is formed. Add 6.5 mL of *water R*. To 1.0 mL of the previously shaken suspension add 1.0 mL of *strong sodium hydroxide solution R*; the precipitate dissolves and the resulting solution is clear and colourless.

C. Dissolve 10 mg in 2 mL of *dilute nitric acid R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S1

To 0.40 g add 1 mL of *dilute hydrochloric acid R* and dilute to 20 mL with *distilled water R*.

Solution S2

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Dissolve 1.0 g in *dilute hydrochloric acid R* and dilute to 30 mL with the same acid. Heat to boiling. Add 30 mL of *thioacetamide solution R* and boil for 15 min (solution A). Take 5 mL, filter and heat the filtrate to boiling. Add 5 mL of *thioacetamide solution R* and boil for 15 min. If a precipitate is formed, add the remainder of solution A (solution A′) to the mixture. Add 10 mL of *thioacetamide solution R* and boil. Repeat the series of operations from “Take 5 mL” until a precipitate is no longer formed on addition of *thioacetamide solution R* to the filtrate obtained from the 5 mL of solution A (solution A′, solution A″, etc. respectively). If no precipitate is formed or if no more precipitate is formed combine the solution obtained with the remainder of solution A (solution A′, solution A″, etc. respectively), filter and wash the precipitate with 10 mL of *water R*. Heat the filtrate until the resulting vapour no longer turns a moistened piece of *lead acetate paper R* blackish-grey. Allow to cool and dilute to 50 mL with *water R*.

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 10.0 g in *dilute hydrochloric acid R* and dilute to 20 mL with the same acid.

Substances not precipitated by thioacetamide

Maximum 0.2 per cent.

Evaporate 25 mL of solution S2 to dryness and ignite at 600 ± 50 °C. The residue weighs a maximum of 1 mg.

Sulfates (*2.4.13*)

Maximum 500 ppm, determined on solution S1.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 5 mL of solution S2 to 10 mL with *water R*.

ASSAY

Dissolve 0.100 g in 50 mL of *water R*, freed from oxygen by purging with carbon dioxide or nitrogen for 15 min. Add 1.5 mL of *hydrochloric acid R1*, 5 g of *sodium potassium tartrate R*, 10 g of *sodium hydrogen carbonate R* and 1 mL of *starch solution R*. Titrate immediately with *0.05 M iodine*. Carry out a blank titration.

1 mL of *0.05 M iodine* is equivalent to 11.28 mg of $SnCl_2,2H_2O$.

STORAGE

In an airtight container.

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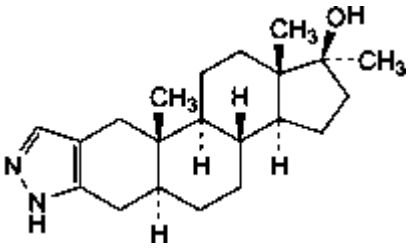
Stanozolol

General Notices

(Ph. Eur. monograph 1568)



$C_{21}H_{32}N_2O$ 328.5 *10418-03-8*

Action and use

Anabolic steroid; androgen.

Ph Eur

DEFINITION

17-Methyl-2′*H*-5α-androst-2-eno[3,2-*c*]pyrazol-17β-ol.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Practically insoluble in water, soluble in dimethylformamide, slightly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *stanozolol CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness at room temperature under an air-stream and record new spectra using the residues.

B. Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Specific optical rotation (*2.2.7*)

+ 37 to + 41 (dried substance).

Dissolve 60.0 mg in *methanol R* and dilute to 20.0 mL with the same solvent.

Impurities A and B

Thin-layer chromatography (*2.2.27*).

Solvent mixture *methanol R1*, *methylene chloride R* (10:90 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in 1.0 mL of the solvent mixture.

Reference solution Dissolve 2 mg of *stanozolol CRS*, 2.0 mg of *stanozolol impurity A CRS* and 2.0 mg of *stanozolol impurity B CRS* in 1.0 mL of the solvent mixture. Dilute 0.1 mL of the solution to 2.0 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *ethyl acetate R*, *cyclohexane R* (2:48:50 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with *vanillin reagent R* and heat at 120 °C.

System suitability Reference solution:

— the chromatogram shows 3 clearly separated spots, due to stanozolol, impurity A and impurity B, in order of increasing R_F value.

Limits:

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— *impurity A*: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.5 per cent);

— *impurity B*: any spot due to impurity B is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.5 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 15.0 mg of the substance to be examined in methanol R and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with methanol R. Dilute 1.0 mL of this solution to 10.0 mL with methanol R.

Reference solution (b) Dissolve 1 mg of stanozolol CRS and 1 mg of stanozolol impurity B CRS in methanol R and dilute to 20 mL with the same solvent.

Reference solution (c) Dissolve 15.0 mg of stanozolol CRS in methanol R and dilute to 5.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R1 (5 µm).

Mobile phase 1 g/L solution of sodium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R, methanol R1 (30:70 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 228 nm.

Injection 25 µL of the test solution and reference solutions (a) and (b).

Run time 3 times the retention time of stanozolol.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to stanozolol (retention time = about 12 min): impurity B = about 1.3.

System suitability Reference solution (b):

— resolution: minimum 4.0 between the peaks due to stanozolol and impurity B.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

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— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying at 105 °C at a pressure not exceeding 0.7 kPa.

ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

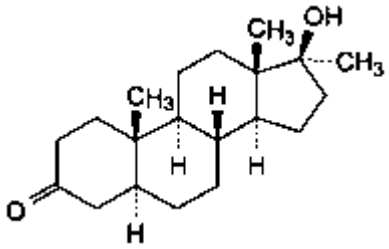
1 mL of *0.1 M perchloric acid* is equivalent to 32.85 mg of $C_{21}H_{32}N_2O$.

STORAGE

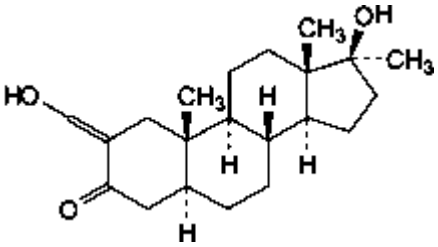
In an airtight container, protected from light.

IMPURITIES

Specified impurities A, B.



A. 17β-hydroxy-17-methyl-5α-androstan-3-one (mestanolone),



B. 17β-hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one (oxymetholone).

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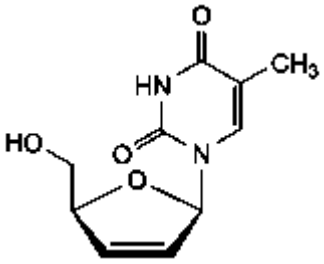
Stavudine

General Notices

(Ph. Eur. monograph 2130)



$C_{10}H_{12}N_2O_4$ 224.2 *3056-17-5*

Action and use

Nucleoside reverse transciptase inhibitor; antiviral (HIV).

Ph Eur

DEFINITION

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Soluble in water, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Specific optical rotation (*2.2.7*): -45.9 to -39.5 (anhydrous substance).

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Dissolve 0.100 g in *water R* and dilute to 10.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *stavudine CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or store them at 2-8 °C until use*.

Test solution Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 0.5 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dilute 20.0 mL of reference solution (a) to 100.0 mL with *water R*.

Reference solution (c) Dissolve 5 mg of *stavudine for system suitability CRS* (containing impurities A, B, C, E and G) in *water R* and dilute to 10.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 35 volumes of *acetonitrile for chromatography R* and 965 volumes of a 0.77 g/L solution of *ammonium acetate R*;

— *mobile phase B*: mix 250 volumes of *acetonitrile for chromatography R* and 750 volumes of a 0.77 g/L solution of *ammonium acetate R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 20	100 → 0	0 → 100
20 - 30	0	100

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 254 nm.

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Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *stavudine for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, E and G.

Relative retention With reference to stavudine (retention time = about 10 min): impurity A = about 0.3; impurity B = about 0.50; impurity C = about 0.53; impurity E = about 1.1; impurity G = about 1.9.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B; minimum 1.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to stavudine.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.7;

— for impurity A, use the concentration of stavudine in reference solution (a);

— for impurities other than A, use the concentration of stavudine in reference solution (b).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity G*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Impurity I

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C until use.*

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *stavudine impurity I CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

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— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 30 volumes of *acetonitrile for chromatography R* and 70 volumes of a 1.15 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 6.8 with *triethylamine R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 266 nm.

Injection 20 µL.

Run time 7 times the retention time of stavudine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity I.

Relative retention With reference to stavudine (retention time = about 3 min): impurity I = about 6.0.

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 40 for the principal peak.

Calculation of percentage content:

— *correction factor*: multiply the peak area of impurity I by 1.7;

— for impurity I, use the concentration of stavudine in reference solution (b).

Limit:

— *impurity I*: maximum 0.15 per cent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or store them at 2-8 °C until use*.

Test solution Dissolve 10.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 50.0 mL with *water R*.

Reference solution (a) Dissolve 10.0 mg of *stavudine CRS* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 50.0 mL with *water R*.

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Reference solution (b) Dissolve 5 mg of *thymine R* (impurity A) and 7.5 mg of *thymidine R* (impurity C) in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.033 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Mix 5 volumes of *acetonitrile for chromatography R* and 95 volumes of a 0.77 g/L solution of *ammonium acetate R*.

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 25 µL.

Run time Twice the retention time of stavudine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to stavudine (retention time = about 4 min): impurity A = about 0.4; impurity C = about 0.6.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurities A and C in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.6 for the peak due to stavudine in the chromatogram obtained with reference solution (a).

Calculate the percentage content of $C_{10}H_{12}N_2O_4$ using the chromatograms obtained with the test solution and reference solution (a) and taking into account the assigned content of *stavudine CRS*.

STORAGE

Protected from light and humidity.

IMPURITIES

Specified impurities *A, G, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, H.*

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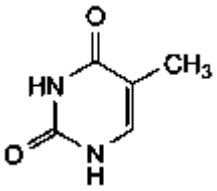
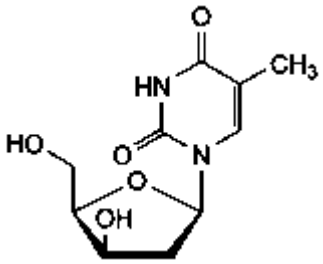
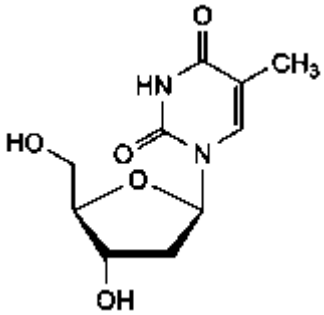


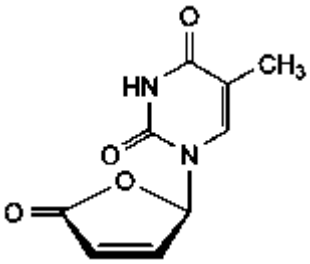
A. 5-methylpyrimidine-2,4(1*H*,3*H*)-dione (thymine),



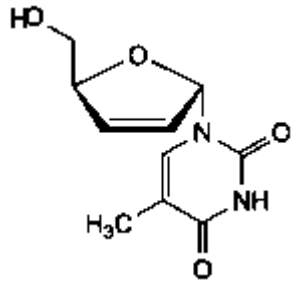
B. 1-(2-deoxy-β-D-*threo*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (3′-epithymidine),



C. 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (thymidine),



D. 1-[(2*R*)-5-oxo-2,5-dihydrofuran-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione,



E. 1-(2,3-dideoxy-α-D-*glycero*-pent-2-enofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (stavudine anomer α),

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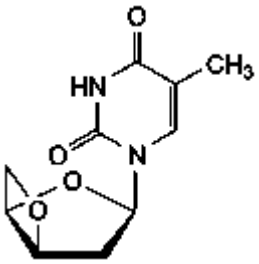
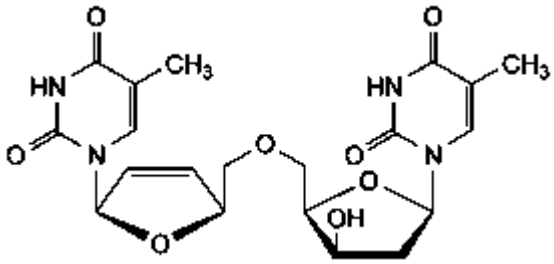
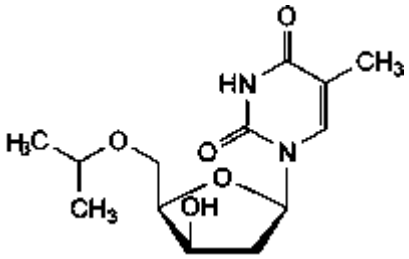


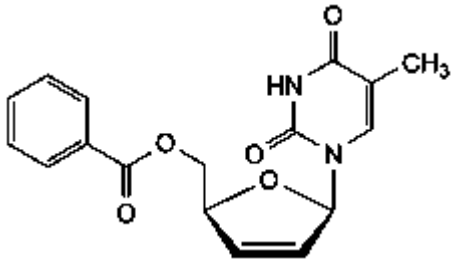
F. 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione,



G. 1-[2-deoxy-5-*O*-[[(2*S*,5*R*)-5-[5-methyl-2,4-dioxo-3,4-dihydropyrimidine-1(2*H*)-yl]-2,5-dihydrofuran-2-yl]methyl]-β-D-*threo*-pentofuranosyl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione,



H. 1-[2-deoxy-5-*O*-(1-methylethyl)-β-D-*threo*-pentofuranosyl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione,



I. 1-(5-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione.

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This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Stearic Acid[1]

General Notices

(Ph. Eur. monograph 1474)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture consisting mainly of stearic (octadecanoic) acid ($C_{18}H_{36}O_2$; M_r 284.5) and palmitic (hexadecanoic) acid ($C_{16}H_{32}O_2$; M_r 256.4) obtained from fats or oils of vegetable or animal origin.

Content

Stearic acid 50	*Stearic acid*: 40.0 per cent to 60.0 per cent. *Sum of the contents of stearic and palmitic acids*: minimum 90.0 per cent.
Stearic acid 70	*Stearic acid*: 60.0 per cent to 80.0 per cent. *Sum of the contents of stearic and palmitic acids*: minimum 90.0 per cent.
Stearic acid 95	*Stearic acid*: minimum 90.0 per cent. *Sum of the contents of stearic and palmitic acids*: minimum 96.0 per cent.

♦ CHARACTERS

Appearance

White or almost white, waxy, flaky crystals, white or almost white hard masses, or white or yellowish-white powder.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent) and in light petroleum (bp: 50-70 °C).♦

IDENTIFICATION

A. Freezing point (see Tests).

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B. Acid value (*2.5.1*): 194 to 212, determined on 0.5 g.

C. Examine the chromatograms obtained in the assay.

Results The principal peaks in the chromatogram obtained with the test solution are similar in retention time to those in the chromatogram obtained with the reference solution.

TESTS

◊ Appearance

Heat the substance to be examined to about 75 °C. The resulting liquid is not more intensely coloured than reference solution Y_7 or BY_7 (*2.2.2, Method I*). ◊

Acidity

Melt 5.0 g, shake for 2 min with 10 mL of hot *carbon dioxide-free water R*, cool slowly and filter. To the filtrate add 0.05 mL of *methyl orange solution R*. No red colour develops.

Iodine value (*2.5.4*)

See Table 1474.-1.

Freezing point

See Table 1474.-1.

Measure the freezing point according to general chapter *2.2.18* or using the following method.

Apparatus

Use the apparatus illustrated in Figure 1474.-1.

Method

Place in the sample container (B) a sufficient quantity of the liquid or previously melted substance to be examined to reach the marked line (C). Adjust the immersion line (H) of the thermometer (F) to the level of the meniscus of the sample and determine the approximate freezing point by cooling rapidly.

Place the sample container (B) in a bath about 5 °C above the approximate freezing point until all but the last traces of crystals are melted. Fill the bath (D) with water or a saturated solution of sodium chloride, at a temperature about 5 °C lower than the expected freezing point, insert the sample container (B) into the cylinder (A), ensuring that some seed crystals are present, and stir thoroughly until solidification takes place. Note the highest temperature observed during solidification.

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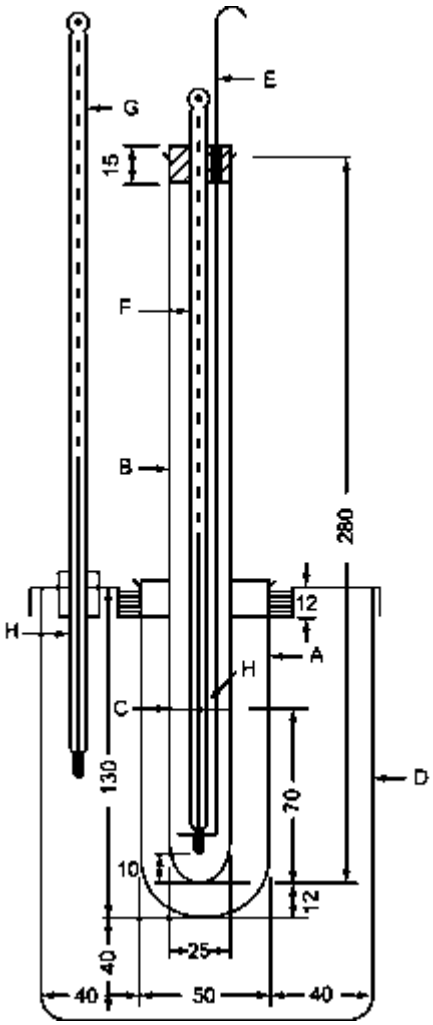

Figure 1474.-1. – *Apparatus for the determination of freezing point*

Dimensions in millimetres

A. Cylinder made of glass (the tube is painted with silicone oil on both sides of the wall to prevent clouding).

B. Sample container (a borosilicate-glass test-tube, which is painted with silicone oil to prevent clouding, except at the region of the wall in contact with the sample; it is inserted into the cylinder (A) and fixed with a cork stopper).

C. Marked line.

D. Bath made of glass or plastic.

E. Stirring rod made of glass or stainless steel (3 mm in diameter; the lower end is bent to make a loop about 18 mm in diameter).

F. Thermometer with an immersion line.

G. Thermometer with an immersion line or a total immersion thermometer.

H. Immersion line.

Table 1474.-1.

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Type	Iodine value	Freezing point (°C)
Stearic acid 50	maximum 4.0	53 - 59
Stearic acid 70	maximum 4.0	57 - 64
Stearic acid 95	maximum 1.5	64 - 69

ASSAY

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution In a conical flask fitted with a reflux condenser, dissolve 0.100 g of the substance to be examined in 5 mL of *boron trifluoride-methanol solution R*. Boil under reflux for 10 min. Add 4.0 mL of *heptane R* through the condenser and boil again under reflux for 10 min. Allow to cool. Add 20 mL of a saturated solution of *sodium chloride R*. Shake and allow the layers to separate. Remove about 2 mL of the organic layer and dry it over 0.2 g of *anhydrous sodium sulfate R*. Dilute 1.0 mL of this solution to 10.0 mL with *heptane R*.

Reference solution Prepare the reference solution in the same manner as the test solution using 50 mg of *palmitic acid CRS* and 50 mg of *stearic acid CRS* instead of the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.4 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	70
	2 - 36	70 → 240
	36 - 41	240
Injection port		220
Detector		260

Detection Flame ionisation.

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Injection 1 µL.

Relative retention With reference to methyl stearate: methyl palmitate = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to methyl palmitate and methyl stearate;

— *repeatability*: maximum relative standard deviation of 3.0 per cent for the areas of the peaks due to methyl palmitate and methyl stearate, determined on 6 injections; maximum 1.0 per cent for the ratio of the areas of the peaks due to methyl palmitate to the areas of the peaks due to methyl stearate, determined on 6 injections.

LABELLING

The label states the type of stearic acid (50, 70, 95).

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for stearic acid used as a lubricant in tablets and capsules.

Particle-size distribution (*2.9.31*)

Specific surface area

(*2.9.26, Method I*).◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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Stearoyl Macrogolglycerides

General Notices

(Ph. Eur. monograph 1268)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of macrogols with a mean relative molecular mass between 300 and 4000.

They are obtained by partial alcoholysis of saturated oils containing mainly triglycerides of stearic (octadecanoic) acid, using macrogol, or by esterification of glycerol and macrogol with saturated fatty acids, or by mixing glycerol esters and condensates of ethylene oxide with the fatty acids of these hydrogenated oils.

The hydroxyl value is within 15 units of the nominal value. The saponification value is within 10 units of the nominal value.

CHARACTERS

Appearance

Pale yellow waxy solid.

Solubility

Dispersible in warm water and in warm liquid paraffin, freely soluble in methylene chloride, soluble in warm anhydrous ethanol.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

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Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine B R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The chromatogram shows a spot due to triglycerides with an R_F value of about 0.9 (R_{st} 1) and spots due to 1,3-diglycerides (R_{st} 0.7), to 1,2-diglycerides (R_{st} 0.6), to monoglycerides (R_{st} 0.1) and to esters of macrogol (R_{st} 0).

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 2.0, determined on 2.0 g.

Hydroxyl value (*2.5.3, Method A*)

Within 15 units of the nominal value, determined on 1.0 g.

Peroxide value (*2.5.5, Method A*)

Maximum 6.0, determined on 2.0 g.

Saponification value (*2.5.6*)

Within 10 units of the nominal value, determined on 2.0 g.

Alkaline impurities

Introduce 5.0 g into a test-tube and carefully add a mixture, neutralised if necessary with *0.01 M hydrochloric acid* or with *0.01 M sodium hydroxide*, of 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*, 0.3 mL of *water R* and 10 mL of *ethanol (96 per cent) R*. Shake and allow to stand. Not more than 1.0 mL of *0.01 M hydrochloric acid* is required to change the colour of the upper layer to yellow.

Free glycerol

Maximum 3.0 per cent.

Dissolve 1.20 g in 25.0 mL of *methylene chloride R*. Heat if necessary. After cooling, add 100 mL of *water R*. Shake and add 25.0 mL of *periodic acetic acid solution R*. Shake and allow to stand for 30 min. Add 40 mL of a 75 g/L solution of *potassium iodide R*. Allow to stand for 1 min. Add 1 mL of *starch solution R*. Titrate the iodine with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 2.3 mg of glycerol.

Composition of fatty acids

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Gas chromatography (*2.4.22, Method A*).

Composition of the fatty-acid fraction of the substance:

— *lauric acid*: maximum 5.0 per cent;

— *myristic acid*: maximum 5.0 per cent;

— *stearic acid and palmitic acid*: different nominal amounts and minimum 90.0 per cent for the sum of $C_{18}H_{36}O_2$ and $C_{16}H_{32}O_2$.

Ethylene oxide and dioxan (*2.4.25*)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use a mixture of 30 volumes of *anhydrous methanol R* and 70 volumes of *methylene chloride R* as solvent.

Total ash (*2.4.16*)

Maximum 0.2 per cent.

LABELLING

The label states:

— the nominal hydroxyl value;

— the nominal saponification value;

— the type of the macrogol used (mean relative molecular mass) or the number of moles of ethylene oxide reacted per mole of substance (nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for stearoyl macrogolglycerides used as self-emulsifying agents, solubilisers, modified-release agents and wetting agents.

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Hydroxyl value

(see Tests).

Saponification value

(see Tests).

Composition of fatty acids

(see Tests).

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Stearyl Alcohol

General Notices

(Ph. Eur. monograph 0753)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of solid alcohols, mainly octadecan-1-ol ($C_{18}H_{38}O$; M_r 270.5), of animal or vegetable origin.

Content

Minimum 95.0 per cent of $C_{18}H_{38}O$.

CHARACTERS

Appearance

White or almost white, unctuous flakes, granules or mass.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent). When melted, it is miscible with fatty oils, with liquid paraffin and with melted wool fat.

IDENTIFICATION

Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

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Dissolve 0.50 g in 20 mL of boiling *ethanol (96 per cent) R*. Allow to cool.

Melting point (*2.2.14*)

57 °C to 60 °C.

Acid value (*2.5.1*)

Maximum 1.0.

Hydroxyl value (*2.5.3, Method A*)

197 to 217.

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Dissolve 2.00 g in *methylene chloride R*, warming if necessary and dilute to 25 mL with the same solvent.

Saponification value (*2.5.6*)

Maximum 2.0.

ASSAY

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 0.100 g of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *cetyl alcohol R* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 50 mg of *stearyl alcohol CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Reference solution (c) Mix 1 mL of reference solution (a) and 1 mL of reference solution (b) and dilute to 10 mL with *ethanol (96 per cent) R*.

Column:

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *methylpolysiloxane R* (1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 20	150 → 250
	20 - 40	250
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL of the test solution and reference solutions (b) and (c).

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to cetyl alcohol and stearyl alcohol.

Calculate the percentage content of $C_{18}H_{38}O$.

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Streptokinase Concentrated Solution

General Notices

Streptokinase Bulk Solution

(Ph. Eur. monograph 0356)

Action and use

Plasminogen activator; fibrinolytic.

Preparation

Streptokinase Injection

Ph Eur

DEFINITION

Streptokinase concentrated solution is a preparation of a protein obtained from culture filtrates of certain strains of haemolytic *Streptococcus* group C; it has the property of combining with human plasminogen to form plasminogen activator. It may contain buffer salts and other excipients. The potency is not less than 510 IU per microgram of nitrogen.

CHARACTERS

Appearance

Clear, colourless liquid.

IDENTIFICATION

A. Place 0.5 mL of citrated human plasma in a polystyrene tube maintained in a water-bath at 37 °C. Add 0.1 mL of a dilution of the preparation to be examined containing 10 000 IU of streptokinase activity per millilitre in *phosphate buffer solution pH 7.2 R* and 0.1 mL of a solution of *human thrombin R* containing 20 IU/mL in *phosphate buffer solution pH 7.2 R*. Mix immediately. A clot forms and lyses within 30 min. Repeat the procedure using citrated bovine plasma. The clot does not lyse within 60 min.

B. Perform an immunochemical test using double immunodiffusion techniques (2.7.1). Place in the central cavity about 80 µL of goat or rabbit antistreptokinase serum containing about 10 000 units of antistreptokinase activity per millilitre; place in each of the surrounding cavities about 80 µL of a dilution of the preparation to be examined containing 125 000 IU of streptokinase activity per millilitre. Allow the plates to stand in a humidified tank for 24 h. Only one precipitation arc appears and it is well defined.

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TESTS

pH (*2.2.3*)

6.8 to 7.5.

Dilute the preparation to be examined in *carbon dioxide-free water R* to obtain a solution containing at least 1000 000 IU of streptokinase activity per millilitre.

Streptodornase

Maximum 10 IU of streptodornase activity per 100 000 IU of streptokinase activity.

Test solution Dilute the preparation to be examined in *imidazole buffer solution pH 6.5 R* to obtain a solution containing 150 000 IU of streptokinase activity per millilitre.

Reference solution Dissolve in *imidazole buffer solution pH 6.5 R* a reference preparation of streptodornase, calibrated in International Units against the International Standard of streptodornase, to obtain a solution containing 20 IU of streptodornase activity per millilitre. The equivalence in International Units of the International Standard is stated by the World Health Organization.

To each of 8 numbered centrifuge tubes, add 0.5 mL of a 1 g/L solution of *sodium deoxyribonucleate R* in *imidazole buffer solution pH 6.5 R*. To tube number 1 and tube number 2 add 0.25 mL of *imidazole buffer solution pH 6.5 R*, 0.25 mL of the test solution and, immediately, 3.0 mL of perchloric acid (25 g/L $HClO_4$). Mix, centrifuge at about 3000 *g* for 5 min and measure the absorbances (*2.2.25*) of the supernatant at 260 nm, using as the compensation liquid a mixture of 1.0 mL of *imidazole buffer solution pH 6.5 R* and 3.0 mL of perchloric acid (25 g/L $HClO_4$) (absorbances A_1 and A_2). To the other 6 tubes (numbers 3 to 8) add 0.25 mL, 0.25 mL, 0.125 mL, 0.125 mL, 0 mL and 0 mL respectively of *imidazole buffer solution pH 6.5 R*; add to each tube 0.25 mL of the test solution and 0 mL, 0 mL, 0.125 mL, 0.125 mL, 0.25 mL and 0.25 mL respectively of the reference solution. Mix the contents of each tube and heat at 37 °C for 15 min. To each tube add 3.0 mL of perchloric acid (25 g/L $HClO_4$), mix and centrifuge. Measure the absorbances (*2.2.25*) of the supernatant at 260 nm using the compensation liquid described above (absorbances A_3 to A_8). The absorbances comply with the following requirement:

$$\left(A_3 + A_4\right) - \left(A_1 + A_2\right) < \frac{\left(A_5 + A_6 + A_7 + A_8\right)}{2} - \left(A_3 + A_4\right)$$

Streptolysin

In a polystyrene tube, use a quantity of the preparation to be examined equivalent to 500 000 IU of streptokinase activity and dilute to 0.5 mL with a mixture of 1 volume of *phosphate buffer solution pH 7.2 R* and 9 volumes of a 9 g/L solution of *sodium chloride R*. Add 0.4 mL of a 23 g/L solution of *sodium thioglycollate R*. Heat in a water-bath at 37 °C for 10 min. Add 0.1 mL of a solution of a reference preparation of human antistreptolysin O containing 5 IU/mL. Heat at 37 °C for 5 min. Add 1 mL of *rabbit erythrocyte suspension R*. Heat at 37 °C for 30 min. Centrifuge at about 1000 *g*. In the same manner, prepare a polystyrene tube in which the solution of the preparation to be examined has been replaced by 0.5 mL of a mixture of 1 volume of *phosphate buffer solution pH 7.2 R* and 9 volumes of a 9 g/L solution of *sodium chloride R*. Measure the absorbances (*2.2.25*) of the supernatant at 550 nm. The absorbance of the test solution is not more than 50 per cent greater than that of the reference solution.

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Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dilute the preparation to be examined with water R to obtain a concentration of about 0.5-1 g/L, depending on the chromatographic system used.

Reference solution Dilute 1 volume of streptokinase for system suitability CRS with 49 volumes of water R.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: styrene-divinylbenzene copolymer R (10 µm) with a pore size of 200 nm;

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: trifluoroacetic acid R, water for chromatography R (1:1000 *V/V*); degas;

— *mobile phase B*: trifluoroacetic acid R, acetonitrile for chromatography R (1:1000 *V/V*); degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	68	32
1 - 4	68 → 52	32 → 48
4 - 5	52	48
5 - 7	0	100
7 - 10	68	32

The above conditions may be modified to improve the separation efficiency of the chromatographic system.

Flow rate 5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Retention time: streptokinase = 2.3 min to 2.8 min.

System suitability Reference solution:

— symmetry factor: maximum 1.9 for the peak due to streptokinase;

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— *peak-to-valley ratio*: minimum 2, where H_p = height above the baseline of the 1st peak eluting after the principal peak and H_v = height above the baseline of the lowest point of the curve separating this peak from the 2nd peak eluting after the principal peak;

— the chromatogram obtained with the reference solution is similar to the chromatogram supplied with *streptokinase for system suitability CRS*.

Limit:

— *total*: maximum 5 per cent.

Bacterial endotoxins (2.6.14)

Less than 0.02 IU per 100 IU of streptokinase activity, if intended for use without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Nitrogen (2.5.9)

Potency

The potency of streptokinase is determined by comparing its capacity to activate plasminogen to form plasmin with the same capacity of a reference preparation of streptokinase calibrated in International Units; the formation of plasmin is determined using a suitable chromogenic substrate.

The International Unit is the activity of a stated amount of the International Standard for streptokinase. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Reference and test solutions

Prepare 2 independent series of at least 3 dilutions of each of the preparation to be examined and of the reference preparation of streptokinase in *tris(hydroxymethyl)aminomethane sodium chloride buffer solution pH 7.4 R1*, in the linear range of the assay (a range of 0.5-4.0 IU/mL has been found suitable). Prepare and maintain all solutions at 37 °C.

Substrate solution

Mix 1.0 mL of *tris(hydroxymethyl)aminomethane buffer solution pH 7.4 R* with 1.0 mL of *chromogenic substrate R3*. Add 5 µL of a 100 g/L solution of *polysorbate 20 R*. Keep at 37 °C in a water-bath. Immediately before commencing the activation assay, add 45 µL of a 1 mg/mL solution of *human plasminogen R*.

Method

Analyse each streptokinase dilution, maintained at 37 °C, in duplicate. Initiate the activation reaction by adding 60 µL of each dilution to 40 µL of substrate solution. For blank wells, use 60 µL of *tris(hydroxymethyl)aminomethane sodium chloride buffer solution pH 7.4 R1* instead of the reference and test solutions. Allow the reaction to proceed at 37 °C for 20 min and read the absorbance (2.2.25) at 405 nm. If a suitable thermostatted plate reader is available, this may be used to monitor the reaction. Alternatively, it may be necessary to stop the

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reaction after 20 min using 50 µL of a 50 per cent *V/V* solution of *glacial acetic acid R*. Best results are obtained when the absorbance for the highest streptokinase concentration is between 0.1 and 0.2 (after blank subtraction). If necessary, adjust the time of incubation in order to reach this range of absorbances.

Calculate the regression of the absorbance on log concentrations of the solutions of the preparation to be examined and of the reference preparation of streptokinase and calculate the potency of the preparation to be examined using a suitable statistical method, for example the parallel-line assay (*5.3*).

The estimated potency is not less than 90 per cent and not more than 111 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

STORAGE

In an airtight container, protected from light and at a temperature of -20 °C. If the preparation is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states:

— the number of International Units of streptokinase activity per milligram, calculated with reference to the dried preparation;

— that the preparation is suitable for use in the manufacture of parenteral preparations.

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Streptokinase Injection

General Notices

Action and use

Plasminogen activator; Fibrinolytic.

DEFINITION

Streptokinase Injection is a sterile solution of Streptokinase Concentrated Solution in Water for Injections. It is prepared by dissolving Streptokinase for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Streptokinase Injection should be used immediately after preparation.

STREPTOKINASE FOR INJECTION

DEFINITION

Streptokinase for Injection is a freeze-dried sterile material prepared from Streptokinase Concentrated Solution with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Potency

The estimated potency is not less than 90% and not more than 111% of the stated potency.

CHARACTERISTICS

A white powder or a white friable solid; hygroscopic.

Freely soluble in *water*.

IDENTIFICATION

A. Place 0.5 mL of citrated human, canine or rabbit plasma in a haemolysis tube maintained in a water bath at 37°. Add 0.1 mL of a solution of the preparation being examined containing 10,000 IU of streptokinase activity per mL in *citro-phosphate buffer pH 7.2* and

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0.1 mL of a solution of *thrombin* containing 20 IU per mL in *citro-phosphate buffer pH 7.2* and shake immediately. A clot forms and lyses within 30 minutes. Repeat the procedure using citrated bovine plasma. Lysis does not occur within 60 minutes.

B. Comply with test B for Identification described under Streptokinase Concentrated Solution.

TESTS

Acidity or alkalinity

pH, 6.8 to 7.5, Appendix V L.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 0.02 IU per 100 IU of streptokinase activity.

ASSAY

Carry out the Assay described under Streptokinase Concentrated Solution. The fiducial limits of error are not less than 80% and not more than 125% of the stated potency.

STORAGE

The sealed container should be protected from light and stored below 25°. Do not freeze.

LABELLING

The label of the sealed container states the total number of IU (Units) contained in it.

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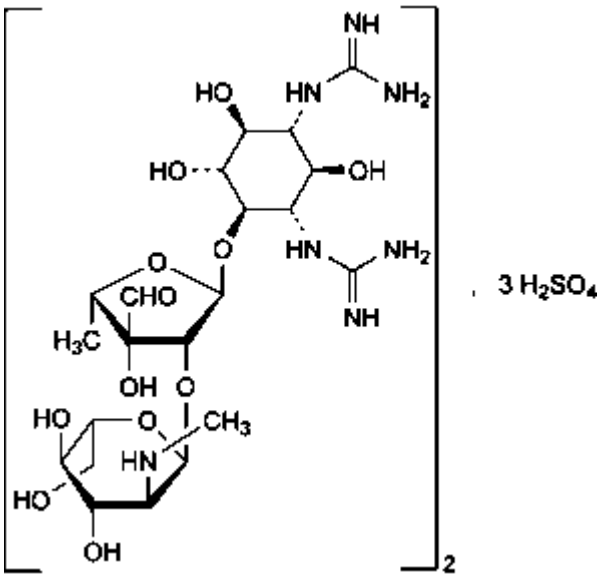
Streptomycin Sulfate

General Notices

Streptomycin Sulphate

(Ph. Eur. monograph 0053)



$C_{42}H_{84}N_{14}O_{36}S_3$ 1457 *3810-74-0*

Action and use

Aminoglycoside antibacterial; antituberculosis drug.

Preparation

Streptomycin Injection

Ph Eur

DEFINITION

Bis[N^1,N^3-dicarbamimidoyl-4-*O*-[5-deoxy-2-*O*-[2-deoxy-2-(methylamino)-α-L-glucopyranosyl]-3-*C*-formyl-α-L-lyxofuranosyl]-D-streptamine] trisulfate, a substance produced by the growth of certain strains of *Streptomyces griseus* or obtained by any other means. Stabilisers may be added. The potency is not less than 720 IU/mg, calculated with reference to the dried substance.

PRODUCTION

It is produced by methods of manufacture designed to eliminate or minimise substances lowering blood pressure.

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CHARACTERS

A white or almost white powder, hygroscopic, very soluble in water, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. Examine by thin-layer chromatography (2.2.27), using a plate coated with a 0.75 mm layer of the following mixture: mix 0.3 g of *carbomer R* with 240 mL of *water R* and allow to stand, with moderate shaking, for 1 h; adjust to pH 7 by the gradual addition, with continuous shaking, of *dilute sodium hydroxide solution R* and add 30 g of *silica gel H R*.
Heat the plate at 110 °C for 1 h, allow to cool and use immediately.

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *streptomycin sulfate for identification CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *kanamycin monosulfate CRS*, 10 mg of *neomycin sulfate CRS* and 10 mg of *streptomycin sulfate for identification CRS* in *water R* and dilute to 10 mL with the same solvent.

Apply separately to the plate 10 µL of each solution. Develop over a path of 12 cm using a 70 g/L solution of *potassium dihydrogen phosphate R*. Dry the plate in a current of warm air, and spray with a mixture of equal volumes of a 2 g/L solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and a 460 g/L solution of *sulfuric acid R*. Heat at 150 °C for 5 min to 10 min. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. Dissolve 5 mg to 10 mg in 4 mL of *water R* and add 1 mL of *1 M sodium hydroxide*. Heat in a water-bath for 4 min. Add a slight excess of *dilute hydrochloric acid R* and 0.1 mL of *ferric chloride solution R1*. A violet colour develops.
C. Dissolve 0.1 g in 2 mL of *water R*, add 1 mL of *α-naphthol solution R* and 2 mL of a mixture of equal volumes of *strong sodium hypochlorite solution R* and *water R*. A red colour develops.
D. Dissolve about 10 mg in 5 mL of *water R* and add 1 mL of *1 M hydrochloric acid*. Heat in a water-bath for 2 min. Add 2 mL of a 5 g/L solution of *α-naphthol R* in *1 M sodium hydroxide* and heat in a water-bath for 1 min. A faint yellow colour develops.
E. It gives the reactions of sulfates (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is not more intensely coloured than intensity 3 of the range of reference solutions of the most appropriate colour (2.2.2, *Method II*). Allow to stand protected from light, at a temperature of about 20 °C for 24 h. Solution S is not more opalescent than reference suspension II (2.2.1).

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pH

(2.2.3): 4.5 to 7.0 for solution S.

Specific absorbance (2.2.25)

10.0 to 12.4, determined at the absorption maximum at 525 nm (dried substance).

Dissolve 0.100 g in *water R* and dilute to 100.0 mL with the same solvent. Introduce separately 5.0 mL of the solution, and 5.0 mL of *water R* (blank) into 2 volumetric flasks. To each flask add 5.0 mL of *0.2 M sodium hydroxide* and heat for exactly 10 min in a water-bath.

Cool in ice for exactly 5 min, add 3 mL of a 15 g/L solution of *ferric ammonium sulfate R* in *0.5 M sulfuric acid*, dilute to 25.0 mL with *water R* and mix. Exactly 20 min after the addition of the ferric ammonium sulfate solution, measure the absorbance of the test solution in a 2 cm cell, using the blank as compensation liquid.

Methanol

Examine by gas chromatography (2.2.28).

Test solution Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution Dilute 12.0 mg of *methanol R* to 100.0 mL with *water R*.

The chromatographic procedure may be carried out using:

— a column 1.5 m to 2.0 m long and 2 mm to 4 mm in internal diameter, packed with *ethylvinylbenzene-divinylbenzene copolymer R* (150 µm to 180 µm);

— *nitrogen for chromatography R* as the carrier gas at a constant flow rate of 30 mL to 40 mL per minute;

— a flame-ionisation detector.

Maintain the column at a constant temperature between 120 °C and 140 °C and the injection port and the detector at a temperature at least 50 °C higher than that of the column. Inject the test solution and the reference solution. The area of the peak due to methanol in the chromatogram obtained with the test solution is not greater than the area of the peak in the chromatogram obtained with the reference solution (0.3 per cent).

Streptomycin B

Examine by thin-layer chromatography (2.2.27), using *silica gel G R* as the coating substance.

Test solution Dissolve 0.2 g of the substance to be examined in a freshly prepared mixture of 3 volumes of *sulfuric acid R* and 97 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents. Heat under a reflux condenser for 1 h, cool, rinse the condenser with *methanol R* and dilute to 20 mL with the same solvent (10 g/L solution).

Reference solution Dissolve 36 mg of *mannose R* in a freshly prepared mixture of 3 volumes of *sulfuric acid R* and 97 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents. Heat under a reflux condenser for 1 h, cool, rinse the condenser with

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methanol R and dilute to 50 mL with the same solvent. Dilute 5 mL of the solution to 50 mL with *methanol R* (0.3 g/L solution expressed as streptomycin B; 1 mg of *mannose R* is equivalent to 4.13 mg of streptomycin B).

Apply separately to the plate 10 µL of each solution. Develop over a path of 13 cm to 15 cm using a mixture of 25 volumes of *glacial acetic acid R*, 25 volumes of *methanol R* and 50 volumes of *toluene R*. Allow the plate to dry in air and spray with a freshly prepared mixture of equal volumes of a 2 g/L solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and a 20 per cent *V/V* solution of *sulfuric acid R* and heat at 110 °C for 5 min. Any spot corresponding to streptomycin B in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (3.0 per cent).

Sulfate

18.0 per cent to 21.5 per cent of sulfate (dried substance).

Dissolve 0.250 g in 100 mL of *water R* and adjust the solution to pH 11 using *concentrated ammonia R*. Add 10.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate*, adding 50 mL of *ethanol (96 per cent) R* when the colour of the solution begins to change and continuing the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of sulfate (SO_4).

Loss on drying

(*2.2.32*): maximum 7.0 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.1 kPa for 24 h.

Sulfated ash

(*2.4.14*): maximum 1.0 per cent, determined on 1.000 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.25 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *streptomycin sulfate CRS* as the chemical reference substance.

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

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Streptomycin Sulfate for Injection

General Notices

Action and use

Aminoglycoside antibacterial; antituberculosis drug.

DEFINITION

Streptomycin Sulfate for Injection is a sterile material consisting of Streptomycin Sulfate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of the sealed container with *water* to produce a solution containing the equivalent of 0.08% w/v of streptomycin.

(2) 0.1% w/v of *streptomycin sulfate for identification EPCRS* in *water*.

(3) 0.1% w/v of *streptomycin sulfate for identification EPCRS*, 0.1% w/v of *neomycin sulfate EPCRS* and 0.1% w/v of *kanamycin monosulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a plate prepared in the following manner. Mix 0.3 g of *carbomer* (Carbopol 934 is suitable) with 240 mL of *water*, allow to stand with moderate shaking for 1 hour, adjust to pH 7 by the gradual addition, with constant shaking, of 2M *sodium hydroxide* and add 30 g of *silica gel H*. Spread a uniform layer of the resulting suspension, 0.75 mm thick. Heat the plate at 110° for 1 hour, allow to cool and use immediately.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol* (*96%*) and a 46% w/v solution of *sulfuric acid* and heat at 150° for 5 to 10 minutes.

MOBILE PHASE

A 7% w/v solution of *potassium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated principal spots.

CONFIRMATION

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CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Dissolve 5 to 10 mg in 4 mL of *water* and add 1 mL of 1M *sodium hydroxide*. Heat in a water bath for 4 minutes. Add a slight excess of 2M *hydrochloric acid* and 0.1 mL of *Iron(iii) Chloride Solution R1*. A violet colour develops.

C. Yield the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 25% w/v of streptomycin, 4.5 to 7.0, Appendix V L.

Streptomycin B

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of the sealed container containing the equivalent of 0.16 g of streptomycin in sufficient of a freshly prepared mixture of 3 volumes of *sulfuric acid* and 97 volumes of *methanol* to produce 5 mL, heat under a reflux condenser for 1 hour, cool, rinse the condenser with *methanol* and add sufficient *methanol* to produce 20 mL (1% w/v solution).

(2) Dissolve 36 mg of *D-mannose* in sufficient of a freshly prepared mixture of 3 volumes of *sulfuric acid* and 97 volumes of *methanol* to produce 5 mL, heat under a reflux condenser for 1 hour, cool, rinse the condenser with *methanol* and add sufficient *methanol* to produce 50 mL. Dilute 5 mL of the resulting solution to 50 mL with *methanol*; this solution contains the equivalent of 0.03% w/v of streptomycin B (1 mg of D-mannose is equivalent to 4.13 mg of streptomycin B).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 13 to 15 cm.

(e) After removal of the plate, allow it to dry in air and spray with a freshly prepared mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol* (*96%*) and a 20% v/v solution of *sulfuric acid* and heat at 110° for 5 minutes.

MOBILE PHASE

25 volumes of *glacial acetic acid*, 25 volumes of *methanol* and 50 volumes of *toluene*.

LIMITS

Any spot corresponding to streptomycin B in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (3%).

Loss on drying

When dried over *phosphorus pentoxide* at 60° at a pressure not exceeding 0.1 kPa for 24 hours, lose not more than 7.0% of their weight. Use 1 g.

Bacterial endotoxins

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Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the powder for injection with *water BET* to give a solution containing the equivalent of 10 mg of streptomycin per mL (solution A). The endotoxin limit concentration of solution A is 2.5 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Dissolve a quantity of the mixed contents of the 10 containers containing the equivalent of 0.33 g of streptomycin in sufficient *water for injections* to produce 100 mL and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. Calculate the content of streptomycin in the injection, taking each 1000 IU found to be equivalent to 1 mg of streptomycin. For a container of average content weight, the upper fiducial limit of error is not less than 95.0% and the lower fiducial limit of error is not more than 115.0% of the stated content.

LABELLING

The label of the sealed container states the quantity of streptomycin sulfate contained in it in terms of the equivalent amount of streptomycin.

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Strong Ammonia Solution

General Notices

(Ammonia Solution, Concentrated, Ph. Eur. monograph 0877)

NH_3 17.03

Preparation

Dilute Ammonia Solution

Ph Eur

DEFINITION

Content

25.0 per cent *m/m* to 30.0 per cent *m/m*.

CHARACTERS

Appearance

Clear, colourless liquid, very caustic.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Relative density (*2.2.5*): 0.892 to 0.910.

B. It is strongly alkaline (*2.2.4*).

C. To 0.5 mL add 5 mL of *water R*. Bubble air through the solution and lead the gaseous mixture obtained over the surface of a solution containing 1 mL of *0.1 M hydrochloric acid* and 0.05 mL of *methyl red solution R*. The colour changes from red to yellow. Add 1 mL of *sodium cobaltinitrite solution R*. A yellow precipitate is formed.

TESTS

Solution S

Evaporate 220 mL almost to dryness on a water-bath. Cool, add 1 mL of *dilute acetic acid R* and dilute to 20 mL with *distilled water R*.

Appearance of solution

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The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

To 2 mL add 8 mL of *water R*.

Oxidisable substances

Cautiously add, whilst cooling, 8.8 mL to 100 mL of *dilute sulfuric acid R*. Add 0.75 mL of *0.002 M potassium permanganate*. Allow to stand for 5 min. The solution remains faintly pink.

Pyridine and related substances

Maximum 2 ppm, calculated as pyridine.

Measure the absorbance (*2.2.25*) at 252 nm using *water R* as the compensation liquid. The absorbance is not greater than 0.06.

Carbonates

Maximum 60 ppm.

To 10 mL in a test-tube with a ground-glass neck add 10 mL of *calcium hydroxide solution R*. Stopper immediately and mix. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of a 0.1 g/L solution of *anhydrous sodium carbonate R*.

Chlorides (*2.4.4*)

Maximum 1 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 5 ppm.

Dilute 3 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 0.25 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Residue on evaporation

Maximum 20 mg/L.

Evaporate 50 mL to dryness on a water-bath and dry at 100-105 °C for 1 h. The residue weighs a maximum of 1 mg.

ASSAY

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Weigh accurately a flask with a ground-glass neck containing 50.0 mL of *1 M hydrochloric acid*. Add 2 mL of the substance to be examined and re-weigh. Add 0.1 mL of *methyl red solution R* as indicator. Titrate with *1 M sodium hydroxide* until the colour changes from red to yellow.

1 mL of *1 M hydrochloric acid* is equivalent to 17.03 mg of NH_3.

STORAGE

Protected from air, at a temperature not exceeding 20 °C.

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Strong Ammonium Acetate Solution

General Notices

DEFINITION

Ammonium Bicarbonate	470 g
Glacial Acetic Acid	453 g
Strong Ammonia Solution	A sufficient quantity
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Ammonium Bicarbonate by adding gradually to the Glacial Acetic Acid diluted with 350 mL of Purified Water. Add Strong Ammonia Solution until 0.05 mL of the resulting solution diluted with 0.5 mL of *water* gives a full blue colour with 0.05 mL of *bromothymol blue solution R3* and a full yellow colour with 0.05 mL of *thymol blue solution*; about 100 mL of Strong Ammonia Solution is required. Add sufficient Purified Water to produce 1000 mL.

Content of ammonium acetate, $C_2H_7NO_2$

55.0 to 60.0% w/v.

TESTS

Acidity or alkalinity

pH of a 10% v/v solution, 7.0 to 8.0, Appendix V L.

Weight per mL

1.085 to 1.095 g, Appendix V G.

ASSAY

To 5 mL add 50 mL of *water* and 12 mL of *formaldehyde solution* previously neutralised to *phenolphthalein solution R1* and titrate with *1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *1M sodium hydroxide VS* is equivalent to 77.08 mg of $C_2H_7NO_2$.

STORAGE

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Strong Ammonium Acetate Solution should be kept in lead-free glass containers.

LABELLING

When ammonium acetate solution or dilute ammonium acetate solution is prescribed or demanded, Strong Ammonium Acetate Solution diluted to eight times its volume with freshly boiled and cooled Purified Water, shall be dispensed or supplied.

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Strong Cetrimide Solution

General Notices

Action and use

Antiseptic.

Preparation

Cetrimide Solution

DEFINITION

Strong Cetrimide Solution is an aqueous solution of cetrimide. It contains 20 to 40% w/v of cetrimide, calculated as $C_{17}H_{38}BrN$. It contains Ethanol (96 per cent) or Isopropyl Alcohol or both. It may be perfumed and may contain colouring matter.

PRODUCTION

In making Strong Cetrimide Solution, Ethanol (96 per cent) may be replaced by Industrial Methylated Spirit, provided that the law and the statutory regulations governing the use of Industrial Methylated Spirit are observed.

Content of cetrimide $C_{17}H_{38}BrN$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a volume of the solution containing 0.1 g of cetrimide to 5 mL with *water* and add 2 mL of a 5% w/v solution of *potassium hexacyanoferrate(III)*. A yellow precipitate is produced.

B. Shake together 5 mL of *water*, 1 mL of 2M *sulfuric acid*, 2 mL of *chloroform* and 0.05 mL of *methyl orange solution*; the chloroform layer is colourless. Add 0.1 mL of the solution being examined and shake; a yellow colour is produced slowly in the chloroform layer.

C. Yields reaction A characteristic of *bromides*, Appendix VI.

TESTS

Acidity or alkalinity

Dilute a volume of the solution containing 10 g of cetrimide to 100 mL and add 0.1 mL of *bromocresol purple solution*. Not more than 1.0 mL of either *0.1M hydrochloric acid VS* or *0.1M sodium hydroxide VS* is required to change the colour of the solution.

Miscibility with ethanol

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Mix a volume of the solution containing 1.6 g of cetrimide with a mixture of 2 mL of *water* and 16 mL of *ethanol (96%)*. The solution remains *clear*, Appendix IV A.

Neutral substances

To a volume of the solution containing 10 g of cetrimide add 25 mL of *ethanol (50%)*, acidify to *bromophenol blue solution* by the drop wise addition of *hydrochloric acid* and add 0.05 mL in excess. Transfer quantitatively to the extraction compartment of an apparatus designed for continuous liquid-liquid extraction by fluids of a lesser density than water, washing out the beaker with 10 mL *ethanol (50%)* and adding the washings to the bulk of the solution in the extractor. Add sufficient *ethanol (50%)*, if necessary, to half-fill the extraction chamber to the level of the overflow limb. Add sufficient *purified hexane* to fill the extraction chamber, secure an overflow volume of about 30 mL in the ebullition flask and heat using an electrically heated mantle. Ensure that a continuous flow of hexane through the aqueous ethanol layer is observed and continue the extraction for 16 hours. Transfer the hexane extract to a separating funnel, washing out the flask with 10 mL of *purified hexane*. Shake the combined extract and washings with 25 mL of *ethanol (50%)* and discard the aqueous ethanol layer. Filter the hexane layer through a dry filter paper (Whatman No. 1 is suitable) into a tared flask and remove the solvent using a rotary evaporator at 40° and then at room temperature at a pressure not exceeding 0.7 kPa for 2 hours. The residue weighs not more than 0.4 g.

Non-quaternised amines

To a volume of the solution containing 10 g of cetrimide add a mixture of 100 mL of *propan-2-ol*, 0.1 mL of *hydrochloric acid* and 20 mL of *methanol*. Titrate with 0.1M *tetrabutylammonium hydroxide VS* passing a slow current of *nitrogen* through the solution and determining the end point potentiometrically using a platinum-glass electrode system. Inflections in the titration curve indicate (A) neutralisation of excess hydrochloric acid and (B) neutralisation of non-quaternised amine salts. The difference between the volumes corresponding to A and B is not more than 10 mL (2.4%, calculated as $C_{16}H_{35}N$).

Ethanol; Isopropyl alcohol

Carry out one or both of the following methods according to the declared alcohol content of the solution being examined.

Ethanol Not more than 10.0% v/v, by the method for the *determination of ethanol*, Appendix VIII F. Use on-column injection and do not heat the injection port.

Isopropyl alcohol Not more than 10.0% v/v, by the method for the *determination of ethanol*, Appendix VIII F, with the following modifications. For solution (1) use a solution containing 5.0% v/v of *propan-2-ol* and 5.0% v/v of *propan-1-ol* (internal standard). For solution (2) use the solution being examined, diluted with *water*, if necessary, to contain about 5.0% v/v of isopropyl alcohol. Maintain the column temperature at 170°, use on-column injection and do not heat the injection port.

ASSAY

Dilute a volume containing 4 g of cetrimide with sufficient *water* to produce 100 mL. Transfer 25 mL of the solution to a separating funnel and add 25 mL of *chloroform*, 10 mL of 0.1M *sodium hydroxide* and 10 mL of a freshly prepared 8.0% w/v solution of *potassium iodide*. Shake well, allow to separate and discard the chloroform layer. Wash the aqueous layer with three 10 mL quantities of *chloroform* and discard the washings. Add 40 mL of *hydrochloric acid*, cool and titrate with *0.05M potassium iodate VS* until the deep brown colour is almost discharged. Add 2 mL of *chloroform* and continue the titration, with shaking, until the chloroform layer becomes colourless. Carry out a blank titration on a mixture of 10 mL of the freshly prepared potassium iodide solution, 20 mL of *water* and 40 mL of *hydrochloric acid*. The

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difference between the titrations represents the amount of potassium iodate required. Each mL of *0.05M potassium iodate VS* is equivalent to 33.64 mg of $C_{17}H_{38}BrN$.

STORAGE

Strong Cetrimide Solution should be stored at a temperature above 15°.

LABELLING

The label states whether Ethanol, Isopropyl Alcohol or both are present and the percentage of cetrimide, weight in volume.

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Strong Coal Tar Solution

General Notices

DEFINITION

Coal Tar	400 g
Polysorbate 80	50 g
Ethanol (96 per cent)	Sufficient to produce 1000 mL

In making Strong Coal Tar Solution the Ethanol (96 per cent) may be replaced by Industrial Methylated Spirit[1].

Extemporaneous preparation

The following directions apply.

Mix the Coal Tar, warmed if necessary to render it fluid, with the Polysorbate 80, pour this mixture in a thin stream into 700 mL of Ethanol (96 per cent) in a closed vessel fitted with an agitator; continue agitation throughout the addition of the mixture and for 1 hour thereafter. Allow the mixture to stand for not less than 24 hours, decant and filter the supernatant liquid, wash the vessel and filter with Ethanol (96 per cent), combine the filtrate and washings and add sufficient Ethanol (96 per cent) to produce 1000 mL.

TESTS

Ethanol content

70 to 80% v/v, Appendix VIII F.

1 The law and the statutory regulations governing the use of Industrial Methylated Spirit must be observed.

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Strong Glutaraldehyde Solution

General Notices

$C_5H_8O_2$ 100.1 (anhydrous) *111-30-8*

Action and use

Used in treatment of warts.

Preparation

Glutaraldehyde Solution

DEFINITION

Strong Glutaraldehyde Solution is an aqueous solution of glutaraldehyde (pentanedial). It contains not less than 47.0% and not more than 53.0% w/w of glutaraldehyde, $C_5H_8O_2$.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Heat 1 mL with 10 mL of a solution containing 1 g of *hydroxylamine hydrochloride* and 2 g of *sodium acetate* in *water* on a water bath for 10 minutes, allow to cool and filter. The *melting point* of the residue, after washing with *water* and drying at 105°, is about 178°, Appendix V A.

B. Add 0.05 mL to 2 mL of *ammoniacal silver nitrate solution* and mix gently for a few minutes. Silver is deposited.

TESTS

Acidity

Dilute 10 mL with 10 mL of *carbon dioxide-free water* and titrate with *0.1M sodium hydroxide VS* using *bromothymol blue solution R3* as indicator. Not more than 5.0 mL of *0.1M sodium hydroxide VS* is required to change the colour of the solution.

Clarity and colour of solution

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Dilute 1 volume with 4 volumes of *water*. The resulting solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* B_6, Appendix IV B, Method I.

Weight per mL

1.126 to 1.134 g, Appendix V G.

ASSAY

Dissolve 4 g in 100 mL of a 7% w/v solution of *hydroxylamine hydrochloride* previously neutralised to *bromophenol blue solution* with *1M sodium hydroxide VS* and allow to stand for 30 minutes. Add 20 mL of *petroleum spirit (boiling range, 40° to 60°)* and titrate with *1M sodium hydroxide VS* until the colour of the aqueous phase matches that of a 7% w/v solution of *hydroxylamine hydrochloride* previously neutralised to *bromophenol blue solution* with *1M sodium hydroxide VS*. Each mL of *1M sodium hydroxide VS* is equivalent to 50.05 mg of $C_5H_8O_2$.

STORAGE

Strong Glutaraldehyde Solution should be stored at a temperature not exceeding 15°.

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Strong Paediatric Alimemazine Oral Solution

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Strong Paediatric Alimemazine Oral Solution is a solution containing 0.6% w/v of Alimemazine Tartrate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of alimemazine tartrate, $C_{36}H_{44}N_4S_2,C_4H_6O_6$

0.54 to 0.66% w/v.

IDENTIFICATION

Dilute 15 mL of the oral solution with 175 mL of *water* and add 7 mL of 1M *sodium hydroxide*. Extract with 100 mL of *ether*, wash the ether layer with 15 mL of *water* and dry over *anhydrous sodium sulfate* (solution A). Evaporate 30 mL of solution A to dryness and dissolve the residue in 0.2 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of alimemazine *(RS 005)*.

TESTS

Related substances

Complies with the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and the following freshly prepared solutions. For solution (1) dilute 5 mL with 15 mL of *water*, add 2 mL of 1M *sodium hydroxide* and extract with two 15 mL quantities of *chloroform*. Dry the chloroform extracts with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. Dissolve the residue as completely as possible in 1 mL of a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine*. For solution (2) dilute 1 volume of solution (1) to 50 volumes with the same solvent mixture.

ASSAY

Carry out the following procedure protected from light. To a weighed quantity containing 30 mg of Alimemazine Tartrate add 25 mL of *water* and 5 mL of a 5% w/v solution of *sodium hydroxide*. Extract the mixture with two 50-mL quantities of *chloroform*, shaking vigorously for 1 minute each time, evaporate the combined extracts to dryness at about 30° at a pressure of 2 kPa and dissolve the residue in sufficient *0.1 M hydrochloric acid* to produce 100 mL (solution B). Dilute 10 mL of solution B to 50 mL with *water* (solution C). To a further 10 mL of solution B add 5 mL of *peroxyacetic acid solution*, allow to stand for 10 minutes and add sufficient *water* to produce 50 mL (solution D).

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Measure the *absorbance* of solution D at the maximum at 342 nm, Appendix II B, using solution C in the reference cell and measure the *absorbance* of solution C at the same wavelength using *water* in the reference cell. Repeat the procedure using a 0.03% w/v solution of *alimemazine tartrate BPCRS* in *0.1M hydrochloric acid* in place of solution B and beginning at the words 'Dilute 10 mL of ...'. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{36}H_{44}N_4S_2,C_4H_6O_6$, weight in volume, using the declared content of $C_{36}H_{44}N_4S_2,C_4H_6O_6$ in *alimemazine tartrate BPCRS*. The result is not valid if the absorbance of solution C is more than 0.10.

STORAGE

Strong Paediatric Alimemazine Oral Solution should be protected from light.

Strong Paediatric Alimemazine Oral Solution contains 30 mg of Alimemazine Tartrate in 5 mL.

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Strong Pholcodine Linctus

General Notices

Strong Pholcodine Oral Solution

Action and use

Opioid receptor agonist; cough suppressant.

DEFINITION

Strong Pholcodine Linctus is an *oral solution* containing 0.2% w/v of Pholcodine and 2% w/v of Citric Acid Monohydrate in a suitable flavoured vehicle.

The linctus complies with the requirements stated under Oral Liquids and with the following requirements.

Content of pholcodine, $C_{23}H_{30}N_2O_4,H_2O$

0.180 to 0.220% w/v.

IDENTIFICATION

To 10 mL add 20 mL of *water*, make alkaline to *litmus paper* with 5M *ammonia*, extract with two 15-mL quantities of *chloroform*, washing each extract with 5 mL of *water*, dry the combined extracts with *anhydrous sodium sulfate*, filter and evaporate to dryness. If necessary add 0.1 mL of *ether* and scratch the side of the vessel with a glass rod to induce crystallisation. The crystals, dried at a pressure not exceeding 2 kPa, comply with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of pholcodine (*RS 273*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.01% w/v solution in 0.01M *sodium hydroxide* exhibits a maximum only at 284 nm.

C. Dissolve the remainder of the crystals in 1 mL of *sulfuric acid* and add 0.05 mL of *ammonium molybdate-sulfuric acid solution*; a pale blue colour is produced. Warm gently; the colour changes to deep blue. Add 0.05 mL of 2M *nitric acid*; the colour changes to brownish red.

ASSAY

To 25 g add sufficient 5M *ammonia* to make the solution alkaline to *litmus paper* and extract with four 25-mL quantities of *chloroform*, washing each extract with the same 5 mL of *water*. Combine the extracts and evaporate until the volume is reduced to 15 mL. Carry out Method I for *non-aqueous titration*, Appendix VIII A, using *0.02M perchloric acid VS* as titrant and *quinaldine red solution* as indicator. Each mL of *0.02M perchloric acid VS* is equivalent to 4.165 mg of $C_{23}H_{30}N_2O_4,H_2O$. Determine the *weight per mL* of the linctus, Appendix V G, and calculate the content of $C_{23}H_{30}N_2O_4,H_2O$, weight in volume.

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STORAGE

Strong Pholcodine Linctus should be protected from light.

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Strong Sodium Hypochlorite Solution

General Notices

DEFINITION

Strong Sodium Hypochlorite Solution is an aqueous solution of sodium hypochlorite containing not less than 8% of available chlorine. It may contain suitable stabilising agents.

Content of available chlorine, Cl

Not less than 8.0% w/w.

Total alkalinity

Not more than 1.8% w/w, calculated as NaOH, when determined by the following method. To 25 mL add 50 mL of *water* and 35 mL of *hydrogen peroxide solution* (*20 vol*) and titrate with *0.5M hydrochloric acid VS* using *methyl orange solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 20 mg of NaOH. Determine the *weight per mL* of the solution, Appendix V G, and calculate the total alkalinity as a percentage weight in weight.

ASSAY

Dilute 10 mL to 250 mL with *water*. Add 10 mL of the resulting solution to a mixture of 50 mL of *water*, 1 g of *potassium iodide* and 12.5 mL of 2M *acetic acid*. Titrate with 0.1M *sodium thiosulfate VS* using *starch solution* as indicator. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 3.545 mg of Cl. Determine the *weight per mL* of the solution, Appendix V G, and calculate the percentage w/w of available chlorine.

STORAGE

Strong Sodium Hypochlorite Solution should be kept in a well-filled container fitted with a glass stopper or a suitable plastic cap and protected from light. It should be stored at a temperature not exceeding 20° and away from acids.

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Substances for Pharmaceutical Use

General Notices

(Ph. Eur. monograph 2034)

Ph Eur

DEFINITION

Substances for pharmaceutical use are any organic or inorganic substances that are used as active substances or excipients for the production of medicinal products for human or veterinary use. They may be obtained from natural sources or produced by extraction from raw materials, fermentation or synthesis.

This general monograph does not apply to herbal drugs, herbal drugs for homoeopathic preparations, herbal drug preparations, herbal drug extracts, or mother tinctures for homoeopathic preparations, which are the subject of separate general monographs (*Herbal drugs (1433)*, *Herbal drugs for homoeopathic preparations (2045)*, *Herbal drug preparations (1434)*, *Herbal drug extracts (0765)*, *Mother tinctures for homoeopathic preparations (2029)*). It does not apply to raw materials for homoeopathic preparations, except where there is an individual monograph for the substance in the non-homoeopathic part of the Pharmacopoeia.

This monograph does not apply to chemical precursors for radiopharmaceutical preparations which are the subject of a separate monograph (*Chemical precursors for radiopharmaceutical preparations (2902)*).

Where a substance for pharmaceutical use not described in an individual monograph of the Pharmacopoeia is used in a medicinal product prepared for the special needs of individual patients, the need for compliance with the present general monograph is decided in the light of a risk assessment that takes account of the available quality of the substance and its intended use.

Where medicinal products are manufactured using substances for pharmaceutical use of human or animal origin, the requirements of chapter *5.1.7*. *Viral safety* apply.

Substances for pharmaceutical use may be used as such or as starting materials for subsequent formulation to prepare medicinal products. Depending on the formulation, certain substances may be used either as active substances or as excipients. Solid substances may be compacted, coated, granulated, powdered to a certain fineness, or processed in other ways. A monograph is applicable to a substance processed with an excipient only where such processing is mentioned in the definition section of the monograph.

Substance for pharmaceutical use of special grade Unless otherwise indicated or restricted in the individual monographs, a substance for pharmaceutical use is intended for human and veterinary use, and is of appropriate quality for the manufacture of all dosage forms in which it can be used.

Polymorphism Individual monographs do not usually specify crystalline or amorphous forms, unless bioavailability is affected. All forms of a substance for pharmaceutical use comply with the requirements of the monograph, unless otherwise indicated.

PRODUCTION

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Substances for pharmaceutical use are manufactured by procedures that are designed to ensure a consistent quality and comply with the requirements of the individual monograph or approved specification.

The manufacture of active substances must take place under conditions of good manufacturing practice.

The provisions of general chapter *5.10* apply to the control of impurities in substances for pharmaceutical use.

Whether or not it is specifically stated in the individual monograph that the substance for pharmaceutical use:

— is a recombinant protein or another substance obtained as a direct gene product based on genetic modification, where applicable, the substance also complies with the requirements of the general monograph *Products of recombinant DNA technology (0784)*;

— is obtained from animals susceptible to transmissible spongiform encephalopathies other than by experimental challenge, where applicable, the substance also complies with the requirements of the general monograph *Products with risk of transmitting agents of animal spongiform encephalopathies (1483)*;

— is a substance derived from a fermentation process, whether or not the micro-organisms involved are modified by traditional procedures or recombinant DNA (rDNA) technology, where applicable, the substance also complies with the requirements of the general monograph *Products of fermentation (1468)*.

If solvents are used during production, they are of suitable quality. In addition, their toxicity and their residual level are taken into consideration (*5.4*). If water is used during production, it is of suitable quality.

The identity of elemental impurities derived from intentionally added catalysts and reagents is known, and strategies for controlling them should be established using the principles of risk management.

If substances are produced or processed to yield a certain form or grade, that specific form or grade of the substance complies with the requirements of the monograph. Certain functionality-related tests may be described to control properties that may influence the suitability of the substance and subsequently the properties of dosage forms prepared from it.

Powdered substances May be processed to obtain a certain degree of fineness (*2.9.35*).

Compacted substances Are processed to increase the particle size or to obtain particles of a specific form and/or to obtain a substance with a higher bulk density.

Coated active substances Consist of particles of the active substance coated with one or more suitable excipients.

Granulated active substances Are particles of a specified size and/or form produced from the active substance by granulation directly or with one or more suitable excipients.

If substances are processed with excipients, these excipients comply with the requirements of the relevant monograph or, where no such monograph exists, the approved specification.

Where active substances have been processed with excipients to produce, for example, coated or granulated substances, the processing is carried out under conditions of good manufacturing practice and the processed substances are regarded as intermediates in the manufacture of a medicinal product.

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CHARACTERS

The statements under the heading Characters (e.g. statements about the solubility or a decomposition point) are not to be interpreted in a strict sense and are not requirements. They are given for information.

Where a substance may show polymorphism, this may be stated under Characters in order to draw this to the attention of the user who may have to take this characteristic into consideration during formulation of a preparation.

IDENTIFICATION

Where under Identification an individual monograph contains subdivisions entitled ‘First identification' and ‘Second identification', the test or tests that constitute the ‘First identification' may be used in all circumstances. The test or tests that constitute the ‘Second identification' may be used in pharmacies only, provided it can be demonstrated that the substance or preparation is fully traceable to a batch certified to comply with all the other requirements of the monograph. The implementation of the tests under the second identification is subject to national regulation.

Certain monographs give two or more sets of tests for the purpose of the first identification, which are equivalent and may be used independently. One or more of these sets usually contain a cross-reference to a test prescribed in the Tests section of the monograph. It may be used to simplify the work of the analyst carrying out the identification and the prescribed tests. For example, one identification set cross-refers to a test for enantiomeric purity while the other set gives a test for specific optical rotation: the intended purpose of the two is the same, that is, verification that the correct enantiomer is present.

TESTS

Polymorphism (*5.9*)

If the nature of a crystalline or amorphous form imposes restrictions on its use in preparations, the nature of the specific crystalline or amorphous form is identified, its morphology is adequately controlled and its identity is stated on the label.

Related substances

Unless otherwise prescribed or justified and authorised, organic impurities in active substances are to be reported, identified wherever possible, and qualified as indicated in Table 2034.-1 or in Table 2034.-2 for peptides obtained by chemical synthesis.

Table 2034.-1. – *Reporting, identification and qualification of organic impurities in active substances*

Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Human use or human and veterinary use	≤ 2 g/day	> 0.05 per cent	> 0.10 per cent or a daily intake of > 1.0 mg (whichever is the lower)	> 0.15 per cent or a daily intake of > 1.0 mg (whichever is the lower)
Human use or human and veterinary use	> 2 g/day	> 0.03 per cent	> 0.05 per cent	> 0.05 per cent

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Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Veterinary use only	Not applicable	> 0.10 per cent	> 0.20 per cent	> 0.50 per cent

Table 2034.-2. – *Reporting, identification and qualification of organic impurities in peptides obtained by chemical synthesis*

Reporting threshold	Identification threshold	Qualification threshold
> 0.1 per cent	> 0.5 per cent	> 1.0 per cent

Specific thresholds may be applied for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects.

For DNA reactive impurities, the requirements of ICH Guideline M7 *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* must be complied with for active substances to be used in medicinal products for human use, in cases defined in the scope of the guideline.

If the individual monograph does not provide suitable control for a new impurity, a suitable test for control must be developed and included in the specification for the substance.

The requirements above do not apply to biological and biotechnological products, oligonucleotides, products of fermentation and semi-synthetic products derived therefrom, to crude products of animal or plant origin or herbal products.

Elemental impurities

Permitted daily exposures for elemental impurities (e.g. as included in the ICH Q3D guideline, the principles of which are reproduced in general chapter *5.20*. *Elemental impurities*) apply to the medicinal product. Individual monographs on substances for pharmaceutical use therefore do not contain specifications for elemental impurities unless otherwise prescribed.

Residual solvents

Are limited according to the principles defined in chapter *5.4*, using general method *2.4.24* or another suitable method. Where a quantitative determination of a residual solvent is carried out and a test for loss on drying is not carried out, the content of residual solvent is taken into account for calculation of the assay content of the substance, the specific optical rotation and the specific absorbance.

Microbiological quality

Individual monographs give acceptance criteria for microbiological quality wherever such control is necessary. Table 5.1.4.-2. – *Acceptance criteria for microbiological quality of non-sterile substances for pharmaceutical use* in chapter *5.1.4*. *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use* gives recommendations on microbiological quality that are of general relevance for substances subject to microbial contamination. Depending on the nature of the substance and its intended use, different acceptance criteria may be justified.

Sterility (*2.6.1*)

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If intended for use in the manufacture of sterile dosage forms without a further appropriate sterilisation procedure, or if offered as sterile grade, the substance for pharmaceutical use complies with the test for sterility.

Bacterial endotoxins (*2.6.14*)

The substance for pharmaceutical use complies with the test for bacterial endotoxins if it is labelled as a bacterial endotoxin-free grade or if it is intended for use in the manufacture of parenteral preparations or preparations for irrigation without a further appropriate procedure for the removal of bacterial endotoxins. The limit, when not indicated in the individual monograph, is determined in accordance with the recommendations of general chapter *5.1.10. Guidelines for using the test for bacterial endotoxins*.

Pyrogens (*2.6.8*)

If the test for pyrogens is justified rather than the test for bacterial endotoxins and if a pyrogen-free grade is offered, the substance for pharmaceutical use complies with the test for pyrogens. The limit and test method are stated in the individual monograph or approved by the competent authority. Based on appropriate test validation for bacterial endotoxins and pyrogens, the test for bacterial endotoxins may replace the test for pyrogens.

Additional properties

Control of additional properties (e.g. physical characteristics, functionality-related characteristics) may be necessary for individual manufacturing processes or formulations. Grades (such as sterile, endotoxin-free, pyrogen-free) may be produced with a view to manufacture of preparations for parenteral administration or other dosage forms and appropriate requirements may be specified in an individual monograph.

ASSAY

Unless justified and authorised, contents of substances for pharmaceutical use are determined. Suitable methods are used.

LABELLING

In general, labelling is subject to supranational and national regulation and to international agreements. The statements under the heading Labelling therefore are not comprehensive and, moreover, for the purposes of the Pharmacopoeia only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory. Any other labelling statements are included as recommendations. When the term ‘label' is used in the Pharmacopoeia, the labelling statements may appear on the container, the package, a leaflet accompanying the package or a certificate of analysis accompanying the article, as decided by the competent authority.

Where appropriate, the label states that the substance is:

— intended for a specific use;

— of a distinct crystalline form;

— of a specific degree of fineness;

— compacted;

— coated;

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— granulated;

— sterile;

— free from bacterial endotoxins;

— free from pyrogens;

— containing gliding agents.

Where applicable, the label states:

— the degree of hydration;

— the name and concentration of any excipient.

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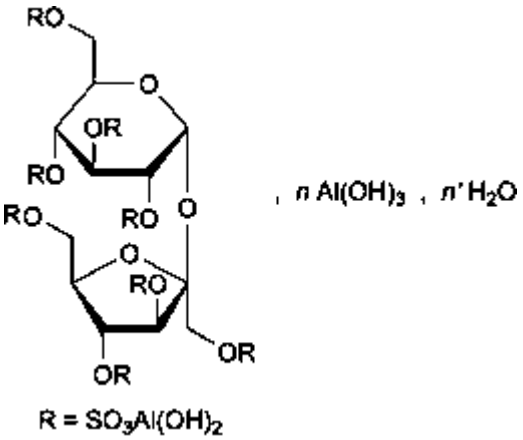
Sucralfate

General Notices

(Ph. Eur. monograph 1796)



$C_{12}H_{30}Al_8O_{51}S_8[Al(OH)_3]_n[H_2O]_{n'}$

in which n = 8 to 10 and n' = 22 to 31

Action and use

Treatment of gastric and duodenal ulcers.

Ph Eur

DEFINITION

β-D-Fructofuranosyl-α-D-glucopyranoside octakis(dihydroxyaluminium sulfate) with 8-10 molecules of aluminium hydroxide and 22-31 molecules of water.

Content

— *β-D-fructofuranosyl-α-D-glucopyranoside octakis(sulfate)* (*sucrose octasulfate*) ($C_{12}H_{14}O_{35}S_8^{8-}$; M_r 975): 30.0 per cent to 38.0 per cent;

— *aluminium* (Al; A_r 26.98): 15.5 per cent to 18.5 per cent.

CHARACTERS

Appearance

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White or almost white, amorphous powder.

Solubility

Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sucralfate CRS*.

B. To 2 g add 10 mL of a 10.3 g/L solution of *hydrochloric acid R* and boil. Cool and neutralise with a 4 g/L solution of *sodium hydroxide R*. To 5 mL of the solution add 0.15 mL of freshly prepared *copper sulfate solution R* and 2 mL of freshly prepared *dilute sodium hydroxide solution R*. The solution is blue and clear and remains so after boiling. To the hot solution add 4 mL of *dilute hydrochloric acid R* and boil for 1 min. Add 4 mL of *dilute sodium hydroxide solution R*; an orange precipitate is formed immediately.

C. Dissolve about 15 mg in a mixture of 0.5 mL of *dilute hydrochloric acid R* and 2 mL of *water R*. The solution gives the reaction of aluminium (2.3.1).

TESTS

Impurity A

Liquid chromatography (2.2.29).

Test solution Dissolve 450.0 mg of the substance to be examined in a mixture of equal volumes of an 88 g/L solution of *sodium hydroxide R* and a 196.2 g/L solution of *sulfuric acid R* and dilute to 10.0 mL with the same mixture of solvents. Without delay, while shaking at a moderate rate, add a volume (*V*), accurately measured in millilitres, of a 4 g/L solution of *sodium hydroxide R* to adjust the solution to approximately pH 2.3. Dilute the solution with (15.0 - *V*) mL of *water R*. Shake for 1 min. If the pH is not between 2.3 and 3.5, repeat the test using a different volume of a 4 g/L solution of *sodium hydroxide R*.

Reference solution (a) Dissolve 40.0 mg of *potassium sucrose octasulfate CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 70 g/L solution of *ammonium sulfate R*, adjusted to pH 3.5 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Differential refractometer.

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Injection 50 µL of the test solution and reference solution (b).

Relative retention With reference to sucrose octasulfate (retention time = about 6 min): impurity A = about 0.6.

System suitability Reference solution (b):

— *number of theoretical plates*: minimum 400;

— *symmetry factor*: maximum 4.0.

Limit:

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5.0 per cent).

Neutralising capacity

Disperse 0.25 g in 100.0 mL of *0.1 M hydrochloric acid*, previously heated at 37 °C, stir continuously for 1 h in a water-bath at 37 °C and cool. Titrate 20.0 mL of this solution with *0.1 M sodium hydroxide* to pH 3.5; not more than 14.0 mL of *0.1 M sodium hydroxide* is required.

Chlorides (*2.4.4*)

Maximum 0.50 per cent.

Dissolve 0.10 g in 5 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Dilute 5 mL of this solution to 15 mL with *water R*.

ASSAY

Aluminium

Disperse 1.0 g in 10 mL of *6 M hydrochloric acid R*. Heat with continuous stirring in a water-bath at 70 °C for 5 min. Cool to room temperature, transfer quantitatively to a volumetric flask, dilute to 250.0 mL with *water R*, and mix. Filter the solution, discarding the 1st portion of the filtrate. To 10.0 mL of the solution, add 10.0 mL of *0.1 M sodium edetate* and 30 mL of a mixture of equal volumes of *ammonium acetate solution R* and *dilute acetic acid R*. Heat in a water-bath at 70 °C for 5 min, then cool. Add 25 mL of *ethanol (96 per cent) R* and 1 mL of a freshly prepared 0.25 g/L solution of *dithizone R* in *ethanol (96 per cent) R*. Titrate the excess of sodium edetate with *0.1 M zinc sulfate* until the colour changes to pink.

1 mL of *0.1 M sodium edetate* is equivalent to 2.698 mg of Al.

Sucrose octasulfate

Liquid chromatography (*2.2.29*) as described in the test for impurity A with the following modifications.

Mobile phase 132 g/L solution of *ammonium sulfate R*, adjusted to pH 3.5 with *phosphoric acid R*.

Injection Test solution and reference solution (a).

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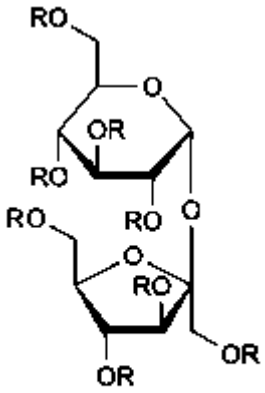
Calculate the percentage content of $C_{12}H_{14}O_{35}S_8$ taking into account the assigned content of *potassium sucrose octasulfate CRS* and by multiplying the potassium sucrose octasulfate content by 0.757.

IMPURITIES

Specified impurities A.



R = SO_3H
and H in a 7 to 1 ratio

A. β-D-fructofuranosyl-α-D-glucopyranoside heptakis(hydrogen sulfate).

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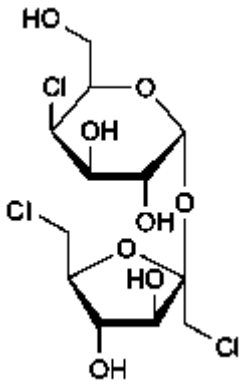
Sucralose

General Notices

(Ph. Eur. monograph 2368)



$C_{12}H_{19}Cl_3O_8$ 397.6 *56038-13-2*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in anhydrous ethanol, slightly soluble in ethyl acetate.

IDENTIFICATION

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *sucralose CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 84.0 to + 87.5 (anhydrous substance).

Dissolve 2.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Impurities H and I

Test solution Dissolve 2.5 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 1.0 g of *mannitol R* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dissolve 1.0 g of *mannitol R* and 4.0 mg of *fructose R* in *water R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel plate R*.

Application 5 µL by applying the solution slowly in 1 µL aliquots and allowing the plate to dry between applications; the 3 spots must be of a similar size.

Detection Spray with a solution prepared as follows: dissolve 1.23 g of *p-anisidine R* and 1.66 g of *phthalic acid R* in 100 mL of *methanol R*; store the solution in darkness and in a refrigerator to prevent it becoming discoloured; discard if the solution becomes discoloured; heat the plate at 100 ± 2 °C for 15 min and examine immediately against a dark background.

System suitability The spot due to mannitol obtained with reference solution (a) is colourless; darkening of the mannitol spot indicates that the plate has been held for too long in the oven and a 2nd plate has to be prepared.

Limit:

— *sum of impurities H and I*: any spot is not more intense than the spot due to fructose obtained with reference solution (b) (0.1 per cent).

Related substances

Thin-layer chromatography (2.2.27).

Test solution Dissolve 1.0 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 0.5 mL of the test solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve the contents of a vial of *sucralose impurity B CRS* in 1.0 mL of the test solution.

Plate *TLC octadecylsilyl silica gel plate R*.

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Mobile phase *acetonitrile R*, 50 g/L solution of *sodium chloride R* (30:70 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a 15 per cent *V/V* solution of *sulfuric acid R* in *methanol R* and heat at 125 °C for 10 min.

Retardation factors Impurity A = about 0.3; impurity B = about 0.35; sucralose = about 0.45; impurity F = about 0.67; impurity G = about 0.70; impurity E = about 0.72; impurity D = about 0.8.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots due to impurity B and sucralose.

Limits:

— *impurities A, B, D, E, F, G*: any spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent).

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.7 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.25 g of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution Dissolve 0.25 g of *sucralose CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *water R* (15:85 *V/V*).

Flow rate 1.5 mL/min.

Detection Refractometer maintained at a constant temperature.

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Injection 20 µL.

Retention time Sucralose = about 3 min.

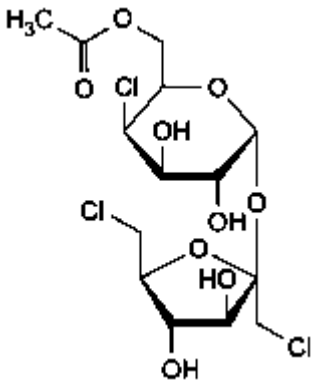
System suitability Reference solution:

— *symmetry factor*: maximum 2.0 for the peak due to sucralose.

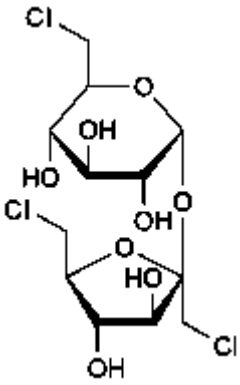
Calculate the percentage content of $C_{12}H_{19}Cl_3O_8$ taking into account the assigned content of *sucralose CRS*.

IMPURITIES

Specified impurities *A, B, D, E, F, G, H, I.*



A. 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 6-*O*-acetyl-4-chloro-4-deoxy-α-D-galactopyranoside (6-*O*-acetylsucralose),



B. 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl 6-chloro-6-deoxy-α-D-glucopyranoside (1′,6,6′-trichloro-1′,6,6′-trideoxysucrose),

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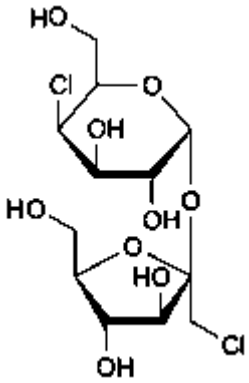
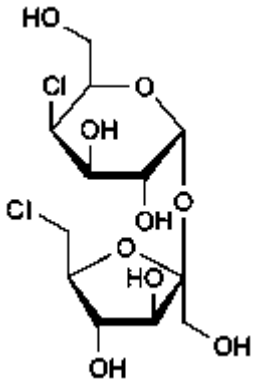
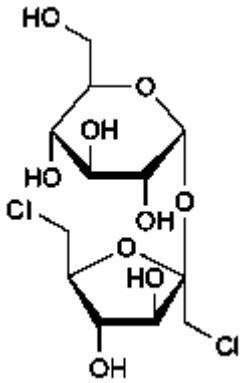


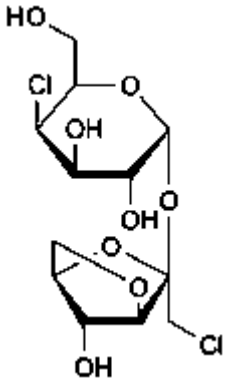
D. 1-chloro-1-deoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside (1′,4-dichloro-1′,4-dideoxygalactosucrose),



E. 6-chloro-6-deoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside (4,6′-dichloro-4,6′-dideoxygalactosucrose),



F. 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl α-D-glucopyranoside (1′,6′-dichloro-1′,6′-dideoxysucrose),



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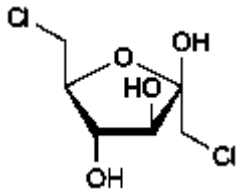
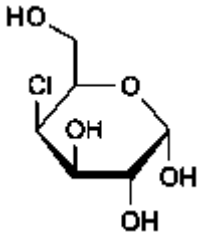
G. 3,6-anhydro-1-chloro-1-deoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside (3′,6′-anhydro-1′,4-dichloro-1′,4-dideoxygalactosucrose),



H. 1,6-dichloro-1,6-dideoxy-β-D-fructofuranose,



I. 4-chloro-4-deoxy-α-D-galactopyranose.

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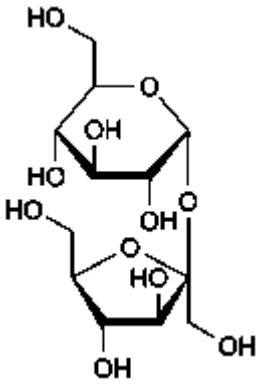
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Sucrose[1]

General Notices

Refined Sugar

(Ph. Eur. monograph 0204)



$C_{12}H_{22}O_{11}$ 342.3 *57-50-1*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

β-D-Fructofuranosyl α-D-glucopyranoside.

It contains no additives.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder, or lustrous, colourless or white or almost white crystals.

Solubility

Very soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in anhydrous ethanol.

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IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sucrose CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 mL with the same mixture of solvents.

Reference solution (a) Dissolve 10 mg of *sucrose CRS* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 mL with the same mixture of solvents.

Reference solution (b) Dissolve 10 mg of *fructose R*, 10 mg of *glucose R*, 10 mg of *lactose monohydrate R* and 10 mg of *sucrose R* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 mL with the same mixture of solvents.

Plate *TLC silica gel G plate R*.

Mobile phase *cold saturated boric acid solution R*, 60 per cent *V/V* solution of *glacial acetic acid R*, *anhydrous ethanol R*, *acetone R*, *ethyl acetate R* (10:15:20:60:60 *V/V/V/V/V*).

Application 2 µL.

Development In an unsaturated tank, over 3/4 of the plate.

Drying In a current of warm air.

Detection Spray with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*. Heat the plate at 130 °C for 10 min.

System suitability The chromatogram obtained with reference solution (b) shows 4 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dilute 1 mL of solution S (see Tests) to 100 mL with *water R*. To 5 mL of the solution add 0.15 mL of freshly prepared *copper sulfate solution R* and 2 mL of freshly prepared *dilute sodium hydroxide solution R*. The solution is blue and clear and remains so after boiling. To the hot solution add 4 mL of *dilute hydrochloric acid R* and boil for 1 min. Add 4 mL of *dilute sodium hydroxide solution R*. An orange precipitate is formed immediately.♦

TESTS

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Solution S

Dissolve 50.0 g in *water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

Conductivity (*2.2.38*)

Maximum 35 μS·cm^{-1} at 20 °C.

Dissolve 31.3 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent. Measure the conductivity of the solution (C_1), while gently stirring with a magnetic stirrer, and that of the water used for preparing the solution (C_2). The readings must be stable within 1 per cent over a period of 30 s. Calculate the conductivity of the solution of the substance to be examined using the following expression:

$$C_1 - 0.35\,C_2$$

Specific optical rotation (*2.2.7*)

+ 66.3 to + 67.0.

Dissolve 26.0 g in *water R* and dilute to 100.0 mL with the same solvent.

♦ Colour value

Maximum 45.

Dissolve 50.0 g in 50.0 mL of *water R*. Mix, filter (diameter of pores 0.45 μm) and degas. Measure the absorbance (*2.2.25*) at 420 nm, using a minimum path length of 4 cm (a path length of 10 cm or more is preferred).

Calculate the colour value using the following expression:

$$\frac{A \times 1000}{b \times c}$$

A	=	absorbance measured at 420 nm;
b	=	path length in centimetres;
c	=	concentration of the solution, in grams per millilitre, calculated from the refractive index (*2.2.6*) of the solution; use Table 0204.-1 and interpolate the values if necessary.

Table 0204.-1

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n_D^{20}	*c* (g/mL)
1.4138	0.570
1.4159	0.585
1.4179	0.600
1.4200	0.615
1.4221	0.630
1.4243	0.645
1.4264	0.661

System suitability:

— *repeatability*: the absolute difference between 2 results is not greater than 3.♦

Dextrins

If intended for use in the manufacture of large-volume parenteral preparations, it complies with the test for dextrins. To 2 mL of solution S add 8 mL of *water R*, 0.05 mL of *dilute hydrochloric acid R* and 0.05 mL of *0.05 M iodine*. The solution remains yellow.

Reducing sugars

To 5 mL of solution S in a test-tube about 150 mm long and 16 mm in diameter add 5 mL of *water R*, 1.0 mL of *1 M sodium hydroxide* and 1.0 mL of a 1 g/L solution of *methylene blue R*. Mix and place in a water-bath. After exactly 2 min, take the tube out of the bath and examine the solution immediately. The blue colour does not disappear completely. Ignore any blue colour at the air/solution interface.

Sulfites

Maximum 10 ppm, calculated as SO_2.

Determine the sulfites content by a suitable enzymatic method based on the following reactions. Sulfite is oxidised by sulfite oxidase to sulfate and hydrogen peroxide which in turn is reduced by nicotinamide-adenine dinucleotide-peroxidase in the presence of reduced nicotinamide-adenine dinucleotide (NADH). The amount of NADH oxidised is proportional to the amount of sulfite.

Test solution Dissolve 4.0 g of the substance to be examined in freshly prepared *distilled water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 4.0 g of the substance to be examined in freshly prepared *distilled water R*, add 0.5 mL of *sulfite standard solution (80 ppm SO_2) R* and dilute to 10.0 mL with freshly prepared *distilled water R*.

Blank solution Freshly prepared *distilled water R*.

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Separately introduce 2.0 mL each of the test solution, the reference solution and the blank in 10 mm cuvettes and add the reagents as described in the instructions in the kit for sulfite determination. Measure the absorbance (2.2.25) at the absorption maximum at about 340 nm before and at the end of the reaction time and subtract the value obtained with the blank.

The absorbance difference of the test solution is not greater than half the absorbance difference of the reference solution.

Loss on drying (2.2.32)

Maximum 0.1 per cent, determined on 2.000 g by drying in an oven at 105 °C for 3 h.

Bacterial endotoxins (2.6.14)

Less than 0.25 IU/mg, if intended for use in the manufacture of large-volume parenteral preparations.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of large-volume parenteral preparations.

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sucrose used as filler/diluent in solid dosage forms.

Particle-size distribution (2.9.31 or 2.9.38)

Bulk and tapped density (2.9.34).◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter 5.8 Pharmacopoeial harmonisation.

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Sucrose Monopalmitate

General Notices

(Ph. Eur. monograph 2319)

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DEFINITION

Mixture of sucrose monoesters, mainly sucrose monopalmitate, obtained by transesterification of palmitic (hexadecanoic) acid methyl esters of vegetable origin with *Sucrose (0204)*. The manufacture of the fatty acid methyl esters includes a distillation step.

It contains variable quantities of mono-, di-, tri- and polyesters.

Content

— *monoesters*: minimum 55.0 per cent;

— *diesters*: maximum 40.0 per cent;

— *sum of triesters and polyesters*: maximum 20.0 per cent.

CHARACTERS

Appearance

White or almost white, unctuous powder.

Solubility

Very slightly soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Composition of fatty acids (see Tests).

B. It complies with the limits of the assay.

TESTS

Acid value (*2.5.1*)

Maximum 6.0, determined on 3.00 g.

Use a freshly neutralised mixture of 1 volume of *water R* and 2 volumes of *2-propanol R* as solvent and heat gently.

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Composition of fatty acids (*2.4.22, Method C*)

Use the mixture of calibrating substances in Table 2.4.22.-1.

Composition of the fatty-acid fraction of the substance:

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 3.0 per cent;

— *palmitic acid*: 70.0 per cent to 85.0 per cent;

— *stearic acid*: 10.0 per cent to 25.0 per cent;

— *sum of the contents of palmitic acid and stearic acid*: minimum 90.0 per cent.

Free sucrose

Liquid chromatography (*2.2.29*).

Solvent mixture *water for chromatography R*, *tetrahydrofuran for chromatography R* (12.5:87.5 *V/V*).

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 4.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of *sucrose CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) In 4 volumetric flasks, introduce respectively 5.0 mg, 10.0 mg, 20.0 mg and 25.0 mg of *sucrose CRS*, dissolve in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *aminopropylsilyl silica gel for chromatography R* (4 µm).

Mobile phase:

— *mobile phase A*: 0.01 g/L solution of *ammonium acetate R* in *acetonitrile for chromatography R*;

— *mobile phase B*: 0.01 g/L solution of *ammonium acetate R* in a mixture of 10 volumes of *water for chromatography R* and 90 volumes of *tetrahydrofuran for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 1	100	0	1.0
1 - 9	100 → 0	0 → 100	1.0

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
9 - 16	0	100	1.0
16 - 16.01	0	100	1.0 → 2.5
16.01 - 32	0	100	2.5

Detection Evaporative light-scattering detector; the following settings have been found to be suitable; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criterion:

— *carrier gas*: *nitrogen R*;

— *flow rate*: 1.0 mL/min;

— *evaporator temperature*: 45 °C;

— *nebuliser temperature*: 40 °C.

Injection 20 µL.

Retention time About 26 min.

System suitability Reference solution (a):

— *signal-to-noise ratio*: minimum 10.

Limit Maximum 4.0 per cent.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.20 g.

Total ash (*2.4.16*)

Maximum 1.5 per cent.

ASSAY

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Dissolve 60.0 mg of the substance to be examined in *tetrahydrofuran R* and dilute to 4.0 mL with the same solvent.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

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Mobile phase: *tetrahydrofuran R*.

Flow rate 1.2 mL/min.

Detection Differential refractometer.

Injection 20 µL.

Relative retention With reference to monoesters (retention time = about 13 min): diesters = about 0.93; triesters and polyesters = about 0.91.

Calculations:

— *disregard limit*: disregard the peaks having a signal-to-noise ratio less than 10;

— *free fatty acids*: calculate the percentage content of free fatty acids (*C*), using the following expression:

$$\frac{I_A \times 256}{56.11 \times 10}$$

I_A = acid value (see Tests);

256 = rounded molar mass of palmitic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoesters*: calculate the percentage content of monoesters using the following expression:

$$\left[\frac{X}{X+Y+Z}\ (100 - A - B)\right] - C$$

A = percentage content of free sucrose (see Tests);

B = percentage content of water (see Tests);

C = percentage content of free fatty acids;

X = area of the peak due to monoesters and free fatty acids;

Y = area of the peak due to diesters;

Z = area of the peak due to triesters and polyesters.

— *diesters*: calculate the percentage content of diesters using the following expression:

$$\frac{Y}{X+Y+Z}\ (100 - A - B)$$

— *sum of triesters and polyesters*: calculate the sum of the percentage contents of triesters and polyesters using the following expression:

$$\frac{Z}{X+Y+Z}\ (100 - A - B)$$

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Sucrose Stearate

General Notices

(Ph. Eur. monograph 2318)

Ph Eur

DEFINITION

Mixture of sucrose esters, mainly sucrose stearate, obtained by transesterification of stearic (octadecanoic) acid methyl esters of vegetable origin with *sucrose (0204)*. The manufacture of the fatty acid methyl esters includes a distillation step.

It contains variable quantities of mono-, di-, tri- and polyesters.

Content

Sucrose stearate type I:

— *monoesters*: minimum 50.0 per cent;

— *diesters*: maximum 40.0 per cent;

— *sum of triesters and polyesters*: maximum 25.0 per cent;

Sucrose stearate type II:

— *monoesters*: 20.0 per cent to 45.0 per cent;

— *diesters*: 30.0 per cent to 40.0 per cent;

— *sum of triesters and polyesters*: maximum 30.0 per cent;

Sucrose stearate type III:

— *monoesters*: 15.0 per cent to 25.0 per cent;

— *diesters*: 30.0 per cent to 45.0 per cent;

— *sum of triesters and polyesters*: 35.0 per cent to 50.0 per cent.

CHARACTERS

Appearance

White or almost white, unctuous powder.

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Solubility

Very slightly soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Composition of fatty acids (see Tests).

B. It complies with the limits of the assay.

TESTS

Acid value (2.5.1)

Maximum 6.0, determined on 3.00 g.

Use a freshly neutralised mixture of 1 volume of *water R* and 2 volumes of *2-propanol R* as solvent and heat gently.

Composition of fatty acids (2.4.22, Method C)

Use the mixture of calibrating substances in Table 2.4.22.-1.

Composition of the fatty-acid fraction of the substance:

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 3.0 per cent;

— *palmitic acid*: 25.0 per cent to 40.0 per cent;

— *stearic acid*: 55.0 per cent to 75.0 per cent;

— *sum of the contents of palmitic acid and stearic acid*: minimum 90.0 per cent.

Free sucrose

Liquid chromatography (2.2.29).

Solvent mixture *water for chromatography R*, *tetrahydrofuran for chromatography R* (12.5:87.5 *V/V*).

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 4.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of *sucrose CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) In 4 volumetric flasks, introduce respectively 5.0 mg, 10.0 mg, 20.0 mg and 25.0 mg of *sucrose CRS*, dissolve in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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— *stationary phase*: spherical *aminopropylsilyl silica gel for chromatography R* (4 µm).

Mobile phase:

— *mobile phase A*: 0.01 g/L solution of *ammonium acetate R* in *acetonitrile for chromatography R*;

— *mobile phase B*: 0.01 g/L solution of *ammonium acetate R* in a mixture of 10 volumes of *water for chromatography R* and 90 volumes of *tetrahydrofuran for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 1	100	0	1.0
1 - 9	100 → 0	0 → 100	1.0
9 - 16	0	100	1.0
16 - 16.01	0	100	1.0 → 2.5
16.01 - 32	0	100	2.5

Detection Evaporative light-scattering detector; the following settings have been found to be suitable; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criterion:

— *carrier gas*: *nitrogen R*;

— *flow rate*: 1.0 mL/min;

— *evaporator temperature*: 45 °C;

— *nebuliser temperature*: 40 °C.

Injection 20 µL.

Retention time About 26 min.

System suitability Reference solution (a):

— *signal-to-noise ratio*: minimum 10.

Limit:

— *sucrose*: maximum 4.0 per cent.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.20 g.

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Total ash (*2.4.16*)

Maximum 1.5 per cent.

ASSAY

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Dissolve 60.0 mg of the substance to be examined in *tetrahydrofuran R* and dilute to 4.0 mL with the same solvent.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1.2 mL/min.

Detection Differential refractometer.

Injection 20 µL.

Relative retention With reference to monoesters (retention time = about 13 min): diesters = about 0.94; triesters and polyesters = about 0.92.

Calculations:

— *disregard limit*: disregard the peaks having a signal-to-noise ratio less than 10;

— *free fatty acids*: calculate the percentage content of free fatty acids (*C*) using the following expression:

$$\frac{I_A \times 284}{56.11 \times 10}$$

I_A = acid value (see Tests);

284 = rounded molar mass of stearic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoesters*: calculate the percentage content of monoesters using the following expression:

$$\left[\frac{X}{X+Y+Z}\ (100 - A - B)\right] - C$$

A = percentage content of free sucrose (see Tests);

B = percentage content of water (see Tests);

C = percentage content of free fatty acids;

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X = area of the peak due to monoesters and free fatty acids;

Y = area of the peak due to diesters;

Z = area of the peak due to triesters and polyesters.

— *diesters*: calculate the percentage content of diesters using the following expression:

$$\frac{Y}{X+Y+Z}(100 - A - B)$$

— *sum of triesters and polyesters*: calculate the sum of the percentage contents of triesters and polyesters using the following expression:

$$\frac{Z}{X+Y+Z}(100 - A - B)$$

LABELLING

The label states the type of sucrose stearate (type I, II or III).

STORAGE

Protected from humidity.

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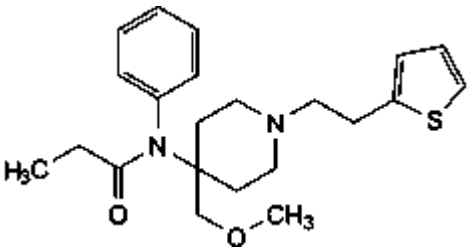
Sufentanil

General Notices

(Ph. Eur. monograph 1569)



$C_{22}H_{30}N_2O_2S$ 386.6 *56030-54-7*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

N-[4-(Methoxymethyl)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]-*N*-phenylpropanamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methanol.

mp

About 98 °C.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of sufentanil*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.10 g in *methanol R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) In order to produce impurity E *in situ*, dissolve 10 mg of the substance to be examined in 10.0 mL of *dilute hydrochloric acid R*. Heat on a water-bath under a reflux condenser for 4 h. Add 10.0 mL of *dilute sodium hydroxide solution R*. Evaporate to dryness on a water-bath. Cool and take up the residue in 10 mL of *methanol R*. Filter.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 20.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 5 g/L solution of *ammonium carbonate R* in a mixture of 10 volumes of *tetrahydrofuran R* and 90 volumes of *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 40	10 → 60
15 - 20	40	60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

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Injection 10 µL.

Relative retention With reference to sufentanil (retention time = about 13 min): impurity D = about 0.85; impurity E = about 0.9; impurity F = about 0.95; impurity H = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity E and sufentanil.

Limits:

— *impurities D, F, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 2 h.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R* and titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 38.66 mg of $C_{22}H_{30}N_2O_2S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *D, F, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, G, I.*

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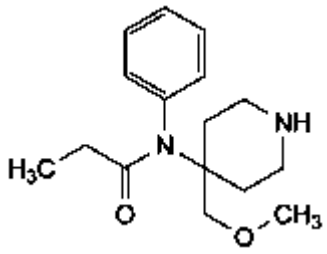
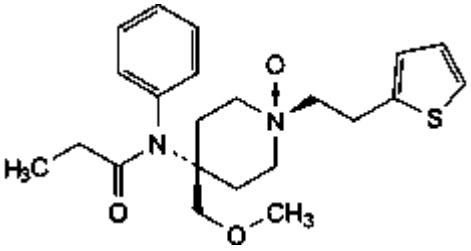
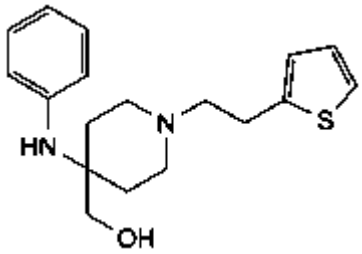


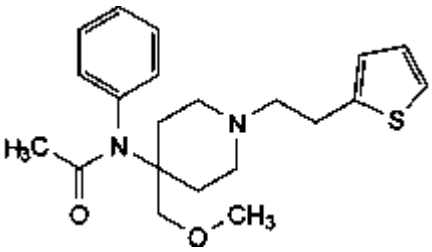
A. *N*-[4-(methoxymethyl)piperidin-4-yl]-*N*-phenylpropanamide,



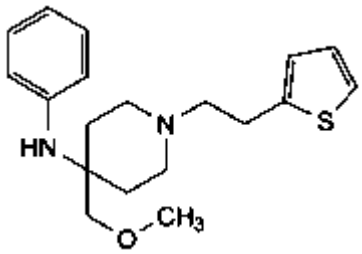
B. *cis*-4-(methoxymethyl)-4-(phenylpropanoylamino)-1-[2-(thiophen-2-yl)ethyl]piperidine 1-oxide,



C. [4-(phenylamino)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]methanol,



D. *N*-[4-(methoxymethyl)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]-*N*-phenylacetamide,



E. 4-(methoxymethyl)-*N*-phenyl-1-[2-(thiophen-2-yl)ethyl]piperidin-4-amine,

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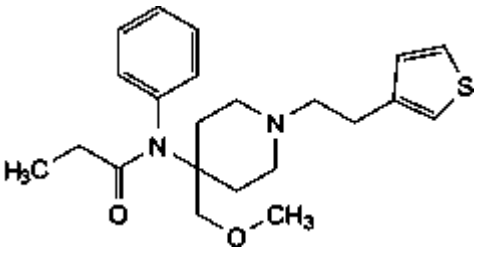
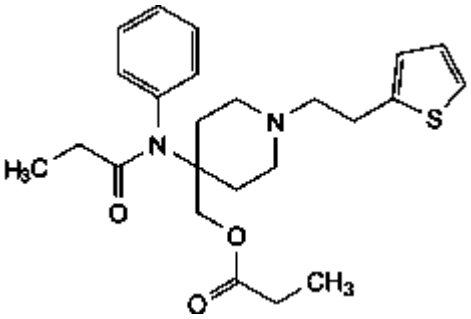
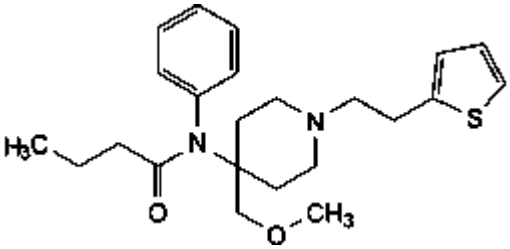


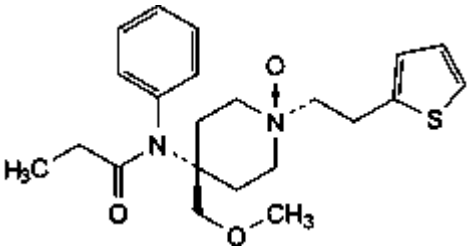
F. *N*-[4-(methoxymethyl)-1-[2-(thiophen-3-yl)ethyl]piperidin-4-yl]-*N*-phenylpropanamide,



G. [4-(phenylpropanoylamino)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]methyl propanoate,



H. *N*-[4-(methoxymethyl)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]-*N*-phenylbutanamide,



I. *trans*-4-(methoxymethyl)-4-(phenylpropanoylamino)-1-[2-(thiophen-2-yl)ethyl]piperidine 1-oxide.

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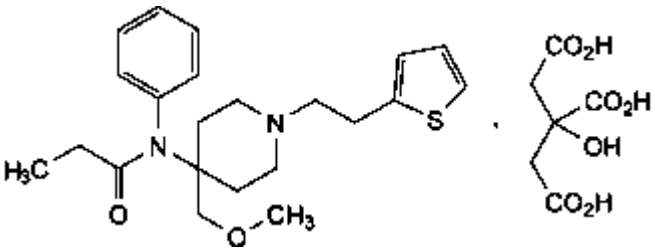
Sufentanil Citrate

General Notices

(Ph. Eur. monograph 1269)



$C_{28}H_{38}N_2O_9S$ 578.7 *60561-17-3*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

N-[4-(Methoxymethyl)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]-*N*-phenylpropanamide citrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent).

mp

About 140 °C, with decomposition.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of sufentanil citrate*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.2 g in *water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) In order to produce impurity E *in situ*, dissolve 10 mg of the substance to be examined in 10.0 mL of *dilute hydrochloric acid R*. Heat on a water-bath under a reflux condenser for 4 h. Add 10.0 mL of *dilute sodium hydroxide solution R*. Evaporate to dryness on a water-bath. Cool and take up the residue in 10 mL of *methanol R*. Filter.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 5 g/L solution of *ammonium carbonate R* in a mixture of 10 volumes of *tetrahydrofuran R* and 90 volumes of *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 40	10 → 60
15 - 20	40	60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

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Injection 10 µL.

Relative retention With reference to sufentanil (retention time = about 13 min): impurity A = about 0.3; impurity B = about 0.4; impurity I = about 0.45; impurity C = about 0.7; impurity D = about 0.85; impurity E = about 0.9; impurity F = about 0.95; impurity G = about 1.05; impurity H = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity E and sufentanil.

Limits:

— *impurities A, B, C, D, E, F, G, H, I*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak with a relative retention with reference to sufentanil of 0.05 or less.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

ASSAY

Dissolve 0.400 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R* and titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 57.87 mg of $C_{28}H_{38}N_2O_9S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I.*

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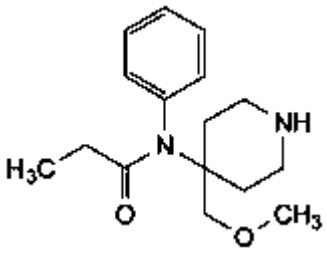
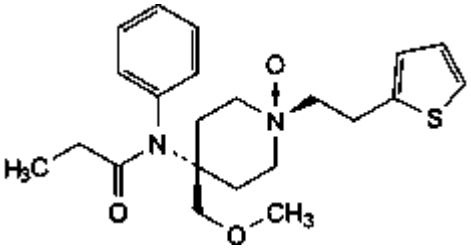
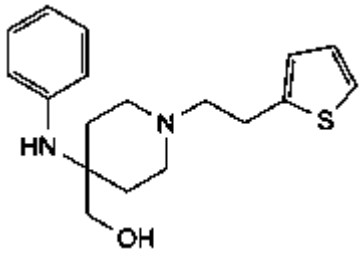


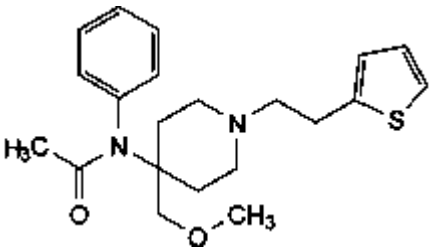
A. *N*-[4-(methoxymethyl)piperidin-4-yl]-*N*-phenylpropanamide,



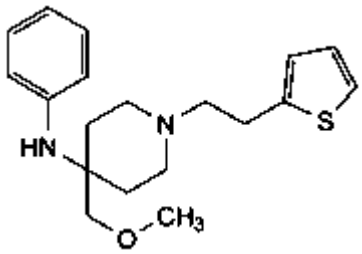
B. *cis*-4-(methoxymethyl)-4-(phenylpropanoylamino)-1-[2-(thiophen-2-yl)ethyl]piperidine 1-oxide,



C. [4-(phenylamino)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]methanol,



D. *N*-[4-(methoxymethyl)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]-*N*-phenylacetamide,



E. 4-(methoxymethyl)-*N*-phenyl-1-[2-(thiophen-2-yl)ethyl] piperidin-4-amine,

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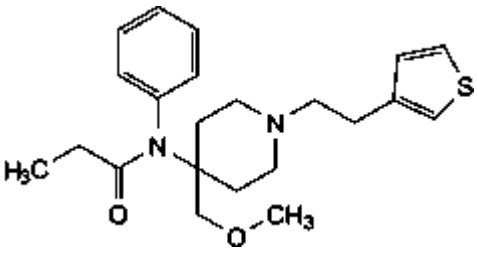
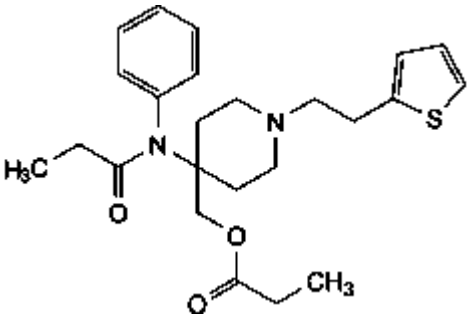
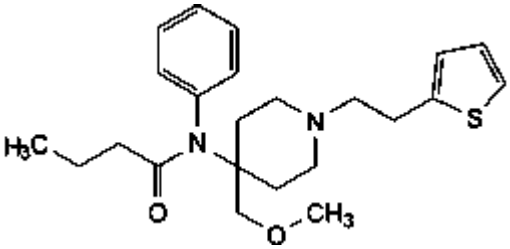


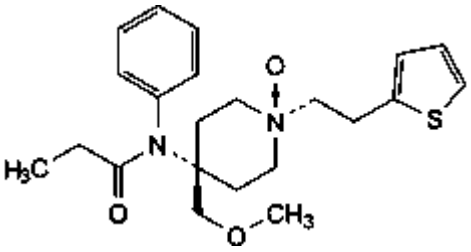
F. *N*-[4-(methoxymethyl)-1-[2-(thiophen-3-yl)ethyl]piperidin-4-yl]-*N*-phenylpropanamide,



G. [4-(phenylpropanoylamino)-1-[2-(thiophen-2-yl)ethyl] piperidin-4-yl]methyl propanoate,



H. *N*-[4-(methoxymethyl)-1-[2-(thiophen-2-yl)ethyl]piperidin-4-yl]-*N*-phenylbutanamide,



I. *trans*-4-(methoxymethyl)-4-(phenylpropanoylamino)-1-[2-(thiophen-2-yl)ethyl]piperidine 1-oxide.

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Sugar Spheres

General Notices

(Ph. Eur. monograph 1570)

Action and use

Excipient.

Ph Eur

DEFINITION

Sugar spheres contain not more than 92 per cent of sucrose, calculated on the dried basis. The remainder consists of maize starch and may also contain starch hydrolysates and colour additives. The diameter of sugar spheres varies usually from 200 µm to 2000 µm and the upper and lower limits of the size of the sugar spheres are stated on the label.

IDENTIFICATION

A. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel G plate R*.

Solvent mixture *water R*, *methanol R* (2:3 *V/V*).

Test solution Mix 2 mL of solution S (see Tests) with 3 mL of *methanol R* and dilute to 20 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *sucrose CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *fructose R*, 10 mg of *glucose R*, 10 mg of *lactose monohydrate R* and 10 mg of *sucrose R* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Apply to the plate 2 µL of each solution and thoroughly dry the points of application. Develop over a path of 15 cm using a mixture of 10 volumes of *water R*, 15 volumes of *methanol R*, 25 volumes of *anhydrous acetic acid R* and 50 volumes of *ethylene chloride R*, measured accurately as a slight excess of water causes cloudiness of the solution. Dry the plate in a current of warm air. Repeat the development immediately after renewing the mobile phase. Dry the plate in a current of warm air and spray evenly with a 5 g/L solution of *thymol R* in a mixture of 5 volumes of *sulfuric acid R* and 95 volumes of *ethanol (96 per cent) R*. Heat at 130 °C for 10 min. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows 4 clearly separated spots.

B. To a water slurry of the insoluble portion obtained in the assay, add 0.05 mL of *iodine solution R1*. A dark-blue colour is produced, which disappears on heating.

C. To 5 mL of solution S add 0.15 mL of freshly prepared *copper sulfate solution R* and 2 mL of freshly prepared *dilute sodium hydroxide solution R*. The solution is blue and clear and remains so after boiling. To the hot solution add 4 mL of *dilute hydrochloric acid R* and boil for

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1 min. Add 4 mL of *dilute sodium hydroxide solution R*. An orange precipitate is formed immediately.

TESTS

Solution S

To 0.5 g in a 100 mL volumetric flask add 80 mL of *water R* and shake until the sucrose is dissolved. Dilute to 100.0 mL with *water R*. Filter under vacuum to obtain a clear solution.

Fineness (*2.9.35*)

Not less than 90 per cent *m/m* of the sugar spheres are between the lower and the upper limits of the size of the sugar spheres stated on the label.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 2 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

ASSAY

Sucrose content

Weigh 10.000 g of ground sugar spheres in a 100 mL flask and make up to 100.0 mL with *water R*. Stir and decant. Filter under vacuum to obtain a clear solution (the insoluble portion is used for identification test B). Measure the angle of optical rotation (*2.2.7*) and calculate the sucrose percentage content using the following expression:

$$\frac{10^6 \times \alpha}{66.5 \times l \times m \times (100 - H)}$$

α	=	angle of rotation;
l	=	length of the polarimeter tube, in decimetres;
m	=	exact mass of the sample, in grams;

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H = loss on drying.

LABELLING

The label states the upper and the lower limits of the size of the sugar spheres.

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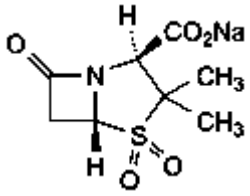
Sulbactam Sodium

General Notices

(Ph. Eur. monograph 2209)



$C_8H_{10}NNaO_5S$ 255.2 *69388-84-7*

Action and use

Beta-lactam antibacterial.

Ph Eur

DEFINITION

Sodium (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide.

Semi-synthetic product derived from a fermentation product.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in ethyl acetate, very slightly soluble in ethanol (96 per cent). It is freely soluble in dilute acids.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *sulbactam sodium CRS*.

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B. It gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent.

Absorbance (2.2.25)

Maximum 0.10 at 430 nm.

Dissolve 1.0 g in *water R* and dilute to 100.0 mL with the same solvent.

pH (2.2.3)

4.5 to 7.2; if the substance is sterile: 5.2 to 7.2.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 219 to + 233 (anhydrous substance).

Dissolve 0.500 g in *water R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solution A 2.72 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 4.0 with *dilute phosphoric acid R*.

Solution B Dilute 2 mL of *acetonitrile R1* to 100.0 mL with solution A.

Test solution Suspend 77.0 mg of the substance to be examined in 2 mL of *acetonitrile R1*, sonicate for about 5 min and dilute to 100.0 mL with solution A.

Reference solution (a) Suspend 70.0 mg of *sulbactam CRS* in 2 mL of *acetonitrile R1*, sonicate for about 5 min and dilute to 100.0 mL with solution A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with solution B. Dilute 1.0 mL of this solution to 10.0 mL with solution B.

Reference solution (c) Dissolve 15.0 mg of *6-aminopenicillanic acid R* (impurity B) in solution A and dilute to 50.0 mL with solution A.

Reference solution (d) Mix 1 mL of reference solution (a) and 1 mL of reference solution (c) and dilute to 25.0 mL with solution B.

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Reference solution (e) Dissolve 8 mg of *sulbactam for peak identification CRS* (containing impurities A, C, D, E and F) in 1 mL of *acetonitrile R1*, sonicate for about 5 min and dilute to 10 mL with solution B.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.0 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 5.44 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 4.0 with *dilute phosphoric acid R*;

— *mobile phase B*: mobile phase A, *acetonitrile R1* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.0	98	2
2.0 - 9.5	98 → 50	2 → 50
9.5 - 12.0	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL of the test solution, solution B and reference solutions (b), (d) and (e).

Identification of impurities Use the chromatogram supplied with *sulbactam for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, C, D, E and F; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity B.

Relative retention With reference to sulbactam (retention time = about 3 min): impurity A = about 0.4; impurity B = about 0.7; impurity C = about 2.3; impurity D = about 3.1; impurity E = about 3.3; impurity F = about 3.9.

System suitability Reference solution (d):

— *resolution*: minimum 5.0 between the peaks due to impurity B and sulbactam.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity B = 0.5; impurity D = 0.5; impurity F = 0.6;

— for each impurity, use the concentration of sulbactam in reference solution (b).

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Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurities C, E*: for each impurity, maximum 0.2 per cent;

— *impurities B, D, F*: for each impurity, maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

2-Ethylhexanoic acid (2.4.28)

Maximum 0.5 per cent *m/m*.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g.

Bacterial endotoxins (2.6.14, Method A)

Less than 0.17 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_8H_{10}NNaO_5S$ taking into account the assigned content of *sulbactam CRS* and a conversion factor of 1.094.

STORAGE

In an airtight container. If the substance is sterile, store in a sterile, the container is also sterile and tamper-evident.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*

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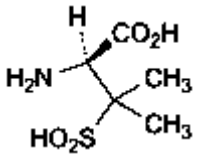
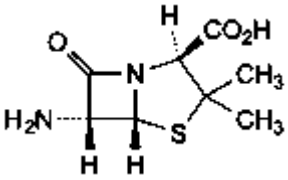
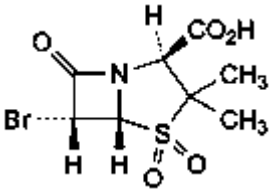


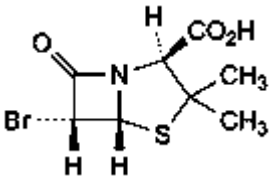
A. (2*S*)-2-amino-3-methyl-3-sulfinobutanoic acid,



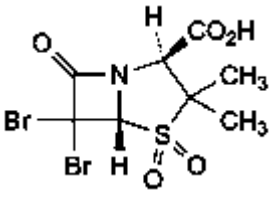
B. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



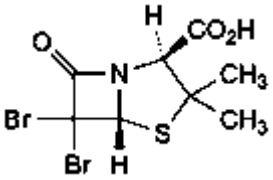
C. (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6-bromopenicillanic acid sulfone),



D. (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-bromopenicillanic acid),



E. (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6,6-dibromopenicillanic acid sulfone),



F. (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6,6-dibromopenicillanic acid),

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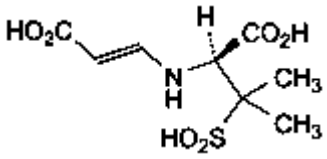

G. (2*S*)-2-[[(2*E*)-2-carboxyethenyl]amino]-3-methyl-3-sulfinobutanoic acid.

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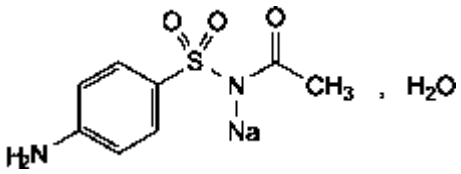
Sulfacetamide Sodium

General Notices

Soluble Sulfacetamide

(Ph. Eur. monograph 0107)



$C_8H_9N_2NaO_3S,H_2O$ 254.2

Action and use

Sulfonamide antibacterial.

Ph Eur

DEFINITION

Sodium acetyl[(4-aminophenyl)sulfonyl]azanide monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: B, F.

Second identification: A, C, E, F.

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A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.1 g in *phosphate buffer solution pH 7.0 R* and dilute to 100.0 mL with the same buffer solution. Dilute 1.0 mL of this solution to 100.0 mL with *phosphate buffer solution pH 7.0 R*.

Spectral range 230-350 nm.

Absorption maximum At 255 nm.

Specific absorbance at the absorption maximum 660 to 720 (anhydrous substance).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *sulfacetamide sodium CRS*.

C. Melting point (2.2.14): 181 °C to 185 °C.
Dissolve 1 g in 10 mL of *water R*, add 6 mL of *dilute acetic acid R* and filter. Wash the precipitate with a small quantity of *water R* and dry at 100-105 °C for 4 h.

E. Dissolve about 1 mg of the precipitate obtained in identification C, with heating, in 1 mL of *water R*. The solution gives the reaction of primary aromatic amines (2.3.1) with formation of an orange-red precipitate.
F. Solution S (see Tests) gives the reactions of sodium (2.3.1).

TESTS

Solution S

Dissolve 1.25 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution GY_4 (2.2.2, *Method II*).

pH (2.2.3)

8.0 to 9.5 for solution S.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and carry out the test protected from light.*

Test solution Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *sulfacetamide sodium CRS* and 5 mg of *sulfanilamide R* (impurity A) in 1.0 mL of the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

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Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R*, *methanol R*, *water for chromatography R* (1:10:89 *V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 7 times the retention time of sulfacetamide.

Relative retention With reference to sulfacetamide (retention time = about 5 min): impurity A = about 0.5.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity A and sulfacetamide.

Limits:

— *correction factor*: for the calculation of the content, multiply the peak area of impurity A by 0.5;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Sulfates (2.4.13)

Maximum 200 ppm.

Dissolve 2.5 g in *distilled water R* and dilute to 25 mL with the same solvent. Add 25 mL of *dilute acetic acid R*, shake for 30 min and filter. 15 mL of the filtrate complies with the limit test for sulfates.

Water (2.5.12)

6.0 per cent to 8.0 per cent, determined on 0.200 g.

ASSAY

Dissolve 0.500 g in a mixture of 50 mL of *water R* and 20 mL of *dilute hydrochloric acid R*. Cool the solution in a bath of iced water and carry out the determination of primary aromatic amino-nitrogen (2.5.8), determining the end-point electrometrically.

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1 mL of *0.1 M sodium nitrite* is equivalent to 23.62 mg of $C_8H_9N_2NaO_3S$.

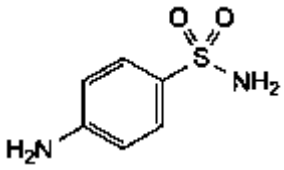
STORAGE

Protected from light.

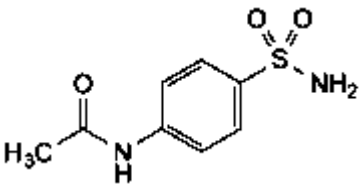
IMPURITIES

Specified impurities A.

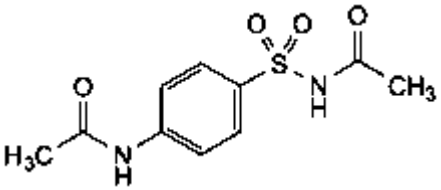
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D.



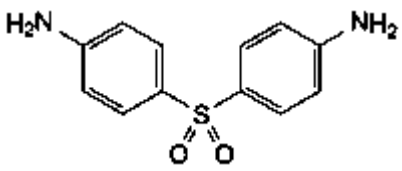
A. 4-aminobenzenesulfonamide (sulfanilamide),



B. *N*-(4-sulfamoylphenyl)acetamide,



C. *N*-[[4-(acetylamino)phenyl]sulfonyl]acetamide,



D. 4,4′-sulfonyldianiline (dapsone).

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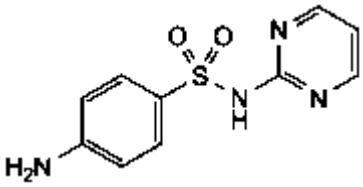
Sulfadiazine

General Notices

(Ph. Eur. monograph 0294)



$C_{10}H_{10}N_4O_2S$ 250.3 *68-35-9*

Action and use

Sulfonamide antibacterial.

Preparation

Sulfadiazine Injection

Ph Eur

DEFINITION

4-Amino-*N*-(pyrimidin-2-yl)benzenesulfonamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White, yellowish-white or pinkish-white, crystalline powder or crystals.

Solubility

Practically insoluble in water, slightly soluble in acetone, very slightly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides and in dilute mineral acids.

IDENTIFICATION

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First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sulfadiazine CRS*.

B. Thin-layer chromatography (2.2.27).

Solvent mixture *concentrated ammonia R*, *methanol R* (4:96 *V/V*)

Test solution Dissolve 20 mg of the substance to be examined in 3 mL of the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution Dissolve 20 mg of *sulfadiazine CRS* in 3 mL of the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *dilute ammonia R1*, *water R*, *nitromethane R*, *dioxan R* (3:5:40:50 *V/V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying At 105 °C.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Place 3 g in a dry tube. Immerse the lower part of the tube, inclined at 45°, in a silicone oil bath and heat to about 270 °C. The substance to be examined decomposes and a white or yellowish-white sublimate is formed, which, after recrystallisation from *toluene R* and drying at 100 °C, melts (2.2.14) at 123 °C to 127 °C.

D. Dissolve about 5 mg in 10 mL of a 103 g/L solution of *hydrochloric acid R*. Dilute 1 mL of the solution to 10 mL with *water R*. The solution, without further acidification, gives the reaction of primary aromatic amines (2.3.1).

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution Y_5, BY_5 or GY_5 (*2.2.2. Method II*).

Dissolve 0.8 g in a mixture of 5 mL of *dilute sodium hydroxide solution R* and 5 mL of *water R*.

Acidity

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To 1.25 g, finely powdered, add 25 mL of *carbon dioxide-free water R*. Heat at about 70 °C for 5 min. Cool in iced water for about 15 min and filter. To 20 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture 40 g/L solution of *sodium hydroxide R*, *acetonitrile R*, *water R* (2:20:60 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with *water R*.

Reference solution (a) Dissolve 5.0 mg of *sulfadiazine impurity A CRS* and 5.0 mg of *sulfanilic acid RV* (impurity B) in the solvent mixture and dilute to 10.0 mL with *water R*. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 3.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *acetylsulfadiazine CRS* (impurity E) in 1 mL of the mobile phase.

Reference solution (d) Dissolve 5 mg of *sulfadiazine for identification of impurity F CRS* in the solvent mixture and dilute to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, 2.8 g/L solution of *phosphoric acid R* (10:90 *V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time 7 times the retention time of sulfadiazine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to sulfadiazine (retention time = about 8.5 min): impurity A = about 0.26; impurity B = about 0.30; impurity E = about 2.1; impurity F = about 6.0.

System suitability Reference solution (a):

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— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.7;

— *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity E*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity F*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: maximum 0.5 per cent;

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 20 mL of *dilute hydrochloric acid R* and 50 mL of *water R*. Cool the solution in iced water. Carry out the determination of primary aromatic amino-nitrogen (*2.5.8*), determining the end-point electrometrically.

1 mL of *0.1 M sodium nitrite* is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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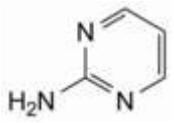
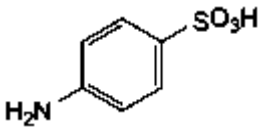
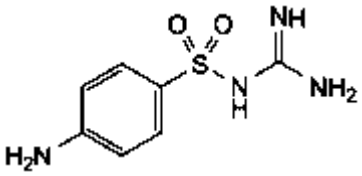
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D.



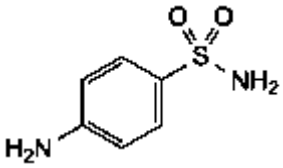
A. pyrimidin-2-amine,



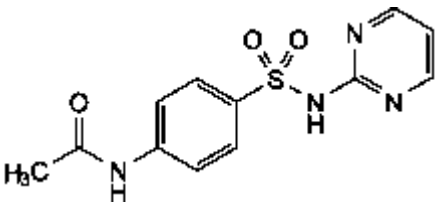
B. 4-aminobenzenesulfonic acid (sulfanilic acid),



C. [(4-aminophenyl)sulfonyl]guanidine (sulfaguanidine),



D. 4-aminobenzenesulfonamide (sulfanilamide),



E. *N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]acetamide (acetylsulfadiazine),

F. unknown structure.

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Sulfadiazine Injection

General Notices

Action and use

Sulfonamide antibacterial.

DEFINITION

Sulfadiazine Injection is a sterile solution of the sodium derivative of Sulfadiazine in Water for Injections free from dissolved air.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sulfadiazine, $C_{10}H_{10}N_4O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Acidify a volume of the injection containing the equivalent of 0.5 g of Sulfadiazine with 6M *acetic acid* and filter. The *infrared absorption spectrum*, Appendix II A, of the residue, after washing with *water* and drying at 105°, is concordant with the *reference spectrum* of sulfadiazine (*RS 325*).

TESTS

Alkalinity

pH, 10.0 to 11.0, Appendix V L.

Colour of solution

An injection containing the equivalent of 1 g of Sulfadiazine in 4 mL of *water* is not more intensely coloured than *reference solution BY_5*, Appendix IV B, Method II.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the injection containing the equivalent of 0.5 g of Sulfadiazine with sufficient of a mixture of 1 volume of 13.5M *ammonia* and 9 volumes of *methanol* to produce 25 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes with a mixture of 1 volume of 13.5M *ammonia* and 24 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

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(a) Using as the coating *silica gel GF_{254}*.

(b) The mobile phase is a mixture of 3 volumes of 6M *ammonia*, 5 volumes of *water*, 40 volumes of *nitromethane* and 50 volumes of *1,4-dioxan*.

(c) Develop to 15 cm.

(d) Application volume of 5 µL for each solution.

(e) Remove the plate, dry it at 100° to 105° and examine under *ultraviolet light (254 nm)*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

To a volume containing the equivalent of 0.5 g of Sulfadiazine add a mixture of 75 mL of *water* and 10 mL of *hydrochloric acid*, add 3 g of *potassium bromide*, cool in ice and titrate slowly with 0.1M *sodium nitrite VS*, stirring constantly and determining the end point electrometrically. Each mL of 0.1M *sodium nitrite VS* is equivalent to 25.03 mg of $C_{10}H_{10}N_4O_2S$.

STORAGE

Sulfadiazine Injection should be protected from light.

LABELLING

The strength is stated in terms of the equivalent amount of Sulfadiazine in a suitable dose-volume.

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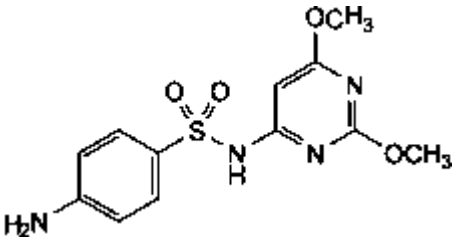
Sulfadimethoxin

General Notices

(Ph. Eur. monograph 2741)



$C_{12}H_{14}N_4O_4S$ 310.3 *122-11-2*

Action and use

Sulfonamide antibacterial.

Ph Eur

DEFINITION

4-Amino-*N*-(2,6-dimethoxypyrimidin-4-yl)benzene-1-sulfonamide.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in methylene chloride, very slightly soluble in ethanol (96 per cent).

It is freely soluble in dilute sodium hydroxide and sparingly soluble in dilute hydrochloric acid.

mp

197 °C to 202 °C.

IDENTIFICATION

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison sulfadimethoxine CRS.

TESTS

Acidity

Suspend 0.5 g in 25 mL of carbon dioxide-free water R. Heat the suspension at 70 °C for 5 min, cool quickly to room temperature and filter. Not more than 0.1 mL of 0.1 M sodium hydroxide is required to reach pH 7.0.

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 6.0 g of sodium dihydrogen phosphate R in 950 mL of water for chromatography R, adjust to pH 7.0 with dilute sodium hydroxide solution R and dilute to 1000 mL with water for chromatography R.

Test solution Dissolve 20.0 mg of the substance to be examined in 25 mL of methanol R and dilute to 100.0 mL with solution A.

Reference solution (a) Dissolve 20.0 mg of sulfadimethoxine CRS in 25 mL of methanol R and dilute to 100.0 mL with solution A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 4 mg of sulfadimethoxine for peak identification CRS (containing impurities A and F) in 5 mL of methanol R and dilute to 20 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: methanol R, solution A (25:75 *V/V*);

— *mobile phase B*: methanol R, acetonitrile R, solution A (25:35:40 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 30	100 → 0	0 → 100

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
30 - 35	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *sulfadimethoxine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and F.

Relative retention With reference to sulfadimethoxine (retention time = about 11 min): impurity F = about 0.4; impurity A = about 1.2.

System suitability:

— *resolution*: minimum 2.5 between the peaks due to sulfadimethoxine and impurity A in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.4; impurity F = 1.7;

— for each impurity, use the concentration of sulfadimethoxine in reference solution (b).

Limits:

— *impurities A, F*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{12}H_{14}N_4O_4S$ taking into account the assigned content of *sulfadimethoxine CRS*.

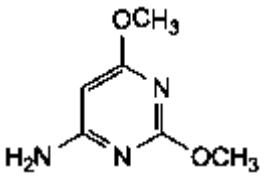
STORAGE

Protected from light.

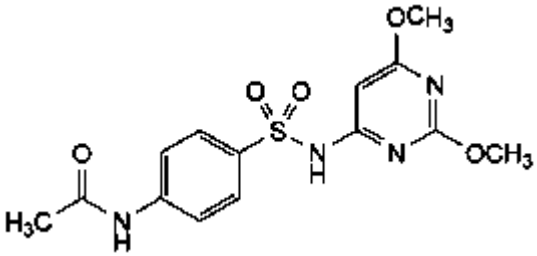
IMPURITIES

Specified impurities *A, F.*

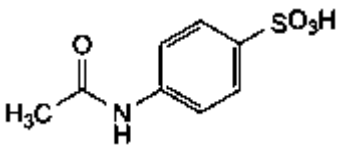
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*



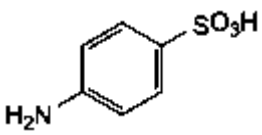
A. 2,6-dimethoxypyrimidin-4-amine,



B. *N*-[4-[(2,6-dimethoxypyrimidin-4-yl)sulfamoyl]phenyl]acetamide,



C. 4-(acetylamino)benzene-1-sulfonic acid,



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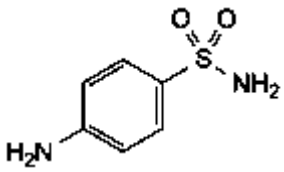
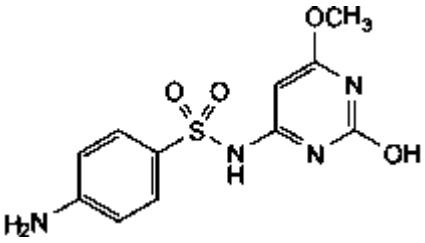
D. 4-aminobenzene-1-sulfonic acid (sulfanilic acid),



E. 4-aminobenzene-1-sulfonamide (sulfanilamide),



F. 4-amino-*N*-(2-hydroxy-6-methoxypyrimidin-4-yl)benzene-1-sulfonamide.

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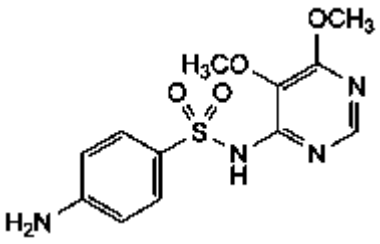
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Sulfadoxine

General Notices

(Ph. Eur. monograph 0740)



$C_{12}H_{14}N_4O_4S$ 310.3 *2447-57-6*

Action and use

Sulfonamide antibacterial.

Ph Eur

DEFINITION

Sulfadoxine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 4-amino-*N*-(5,6-dimethoxypyrimidin-4-yl)benzenesulfonamide, calculated with reference to the dried substance.

CHARACTERS

White or yellowish-white crystalline powder or crystals, very slightly soluble in water, slightly soluble in ethanol (96 per cent) and in methanol. It dissolves in solutions of alkali hydroxides and in dilute mineral acids.

It melts at about 198 °C, with decomposition.

IDENTIFICATION

First identification: A, C.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *sulfadoxine CRS*. Examine the substances prepared as discs.

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B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.5 g in 1 mL of a 40 per cent *V/V* solution of *sulfuric acid R*, heating gently. Continue heating until a crystalline precipitate appears (about 2 min). Allow to cool and add 10 mL of *dilute sodium hydroxide solution R*. Cool again. Add 25 mL of *ether R* and shake for 5 min. Separate the ether layer, dry over *anhydrous sodium sulfate R* and filter. Evaporate the solvent by heating in a water-bath. The residue melts (*2.2.14*) at 80 °C to 82 °C or at 90 °C to 92 °C.

D. Dissolve about 5 mg in 10 mL of *1 M hydrochloric acid*. Dilute 1 mL of the solution to 10 mL with *water R*. The solution, without further acidification, gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Appearance of solution

Dissolve 1.0 g in a mixture of 5 mL of *dilute sodium hydroxide solution R* and 5 mL of *water R*. The solution is not more intensely coloured than reference solution Y_5, BY_5 or GY_5 (*2.2.2, Method II*).

Acidity

To 1.25 g, finely powdered, add 25 mL of *carbon dioxide-free water R*. Heat at 70 °C for 5 min. Cool in a bath of iced water for about 15 min and filter. To 20 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in 3 mL of a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Test solution (b) Dilute 1 mL of test solution (a) to 5 mL with a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R*.

Reference solution (a) Dissolve 20 mg of *sulfadoxine CRS* in 3 mL of a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Reference solution (b) Dilute 2.5 mL of test solution (b) to 100 mL with a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R*.

Apply to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 3 volumes of *dilute ammonia R1*, 5 volumes of *water R*, 40 volumes of *nitromethane R* and 50 volumes of *dioxan R*. Dry the plate at 100 °C to 105 °C and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Loss on drying (*2.2.32*)

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Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the determination of primary aromatic amino- nitrogen (*2.5.8*), using 0.250 g and determining the end-point electrometrically.

1 mL of *0.1 M sodium nitrite* is equivalent to 31.03 mg of $C_{12}H_{14}N_4O_4S$.

STORAGE

Store protected from light.

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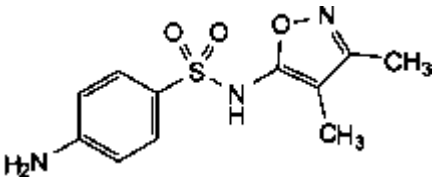
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Sulfafurazole

General Notices

(Ph. Eur. monograph 0741)



$C_{11}H_{13}N_3O_3S$ 267.3 *127-69-5*

Action and use

Sulfonamide antibacterial.

Ph Eur

DEFINITION

Sulfafurazole contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 4-amino-*N*-(3,4-dimethylisoxazol-5-yl)benzenesulfonamide, calculated with reference to the dried substance.

CHARACTERS

White or yellowish-white, crystalline powder or crystals, practically insoluble in water, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride. It dissolves in solutions of alkali hydroxides and in dilute mineral acids.

It melts at about 197 °C, with decomposition.

IDENTIFICATION

First identification: A, C.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *sulfafurazole CRS*. Examine the substances prepared as discs.

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B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 0.5 g add 1 mL of a 40 per cent *V/V* solution of *sulfuric acid R* and heat over a low flame to dissolve. Continue heating until a crystalline precipitate appears (about 2 min). Allow to cool and add 10 mL of *dilute sodium hydroxide solution R*. Cool. Shake the solution for 5 min with 25 mL of *ether R*. Separate the ether layer, dry over *anhydrous sodium sulfate R* and filter. Evaporate the solvent by heating on a water-bath. The residue melts (*2.2.14*) at 119 °C to 123 °C.

D. Dissolve about 5 mg in 10 mL of *1 M hydrochloric acid*. Dilute 1 mL of the solution to 10 mL with *water R*. The solution, without further acidification, gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Appearance of solution

Dissolve 0.4 g in a mixture of 5 mL of *dilute sodium hydroxide solution R* and 5 mL of *water R*, with gently warming if necessary. The solution is not more intensely coloured than reference solution Y_6, BY_6 or GY_6 (*2.2.2, Method II*).

Acidity

To 1.25 g, finely powdered, add 25 mL of *carbon dioxide-free water R*. Heat at 70 °C for 5 min. Cool in iced water for about 15 min and filter. To 20 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in 3 mL of a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Test solution (b) Dilute 1 mL of test solution (a) to 5 mL with a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R*.

Reference solution (a) Dissolve 20 mg of *sulfafurazole CRS* in 3 mL of a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.25 mL of test solution (b) to 50 mL with a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R*.

Apply to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *concentrated ammonia R*, 25 volumes of *methanol R* and 75 volumes of *methylene chloride R*. Dry the plate at 100 °C to 105 °C and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Loss on drying (*2.2.32*)

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Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *acetone R*. Titrate with *0.1 M tetrabutylammonium hydroxide* using a 4 g/L solution of *thymol blue R* in *methanol R* as indicator.

1 mL of *0.1 M tetrabutylammonium hydroxide* is equivalent to 26.73 mg of $C_{11}H_{13}N_3O_3S$.

STORAGE

Store protected from light.

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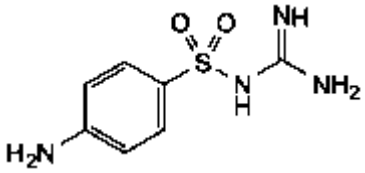
Sulfaguanidine

General Notices

(Ph. Eur. monograph 1476)



$C_7H_{10}N_4O_2S$ 214.3 *57-67-0*

Action and use

Sulfonamide antibacterial.

Ph Eur

DEFINITION

Sulfaguanidine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (4-aminophenylsulfonyl)guanidine, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, fine crystalline powder, very slightly soluble in water, slightly soluble in acetone, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of mineral acids.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 189 °C to 193 °C, determined on the dried substance.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *sulfaguanidine CRS*.

C. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 5 mg in 10 mL of *1 M hydrochloric acid*. Dilute 1 mL of the solution to 10 mL with *water R*. The solution, without further acidification, gives the reaction of primary aromatic amines (*2.3.1*).

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E. Suspend 0.1 g in 2 mL of *water R*, add 1 mL of *α-naphthol solution R* and 2 mL of a mixture of equal volumes of *water R* and *strong sodium hypochlorite solution R*. A red colour develops.

TESTS

Solution S

To 2.5 g, add 40 mL of *carbon dioxide-free water R*. Heat at about 70 °C for 5 min. Cool while stirring in iced water for about 15 min, filter and dilute to 50 mL with *carbon dioxide-free water R*.

Acidity

To 20 mL of solution S, add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Examine by thin layer chromatography (*2.2.27*), using a *TLC silica gel GF_{254} plate R*.

Test solution (a) Dissolve 50 mg of the substance to be examined in *acetone R* and dilute to 5 mL with the same solvent.

Test solution (b) Dilute 2 mL of test solution (a) to 10 mL with *acetone R*.

Reference solution (a) Dissolve 10 mg of *sulfaguanidine CRS* in *acetone R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dilute 5 mL of test solution (b) to 200 mL with *acetone R*.

Reference solution (c) Dilute 5 mL of reference solution (b) to 10 mL with *acetone R*.

Reference solution (d) Dissolve 10 mg of *sulfanilamide R* in test solution (b) and dilute to 5 mL with the same solution.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *anhydrous formic acid R*, 20 volumes of *methanol R* and 70 volumes of *methylene chloride R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent) and at most one such spot is more intense than the spot in the chromatogram obtained with reference solution (c) (0.25 per cent). The test is not valid unless the chromatogram obtained with reference solution (d) shows two clearly separated principal spots.

Loss on drying (*2.2.32*)

Not more than 8.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

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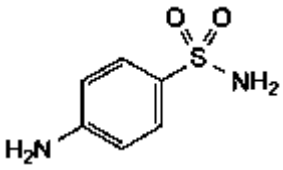
Dissolve 0.175 g in 50 mL of *dilute hydrochloric acid R*. Cool the solution in iced water. Carry out the determination of primary aromatic amino-nitrogen (2.5.8), determining the end-point electrometrically.

1 mL of *0.1 M sodium nitrite* is equivalent to 21.42 mg of $C_7H_{10}N_4O_2S$.

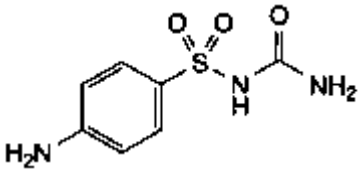
STORAGE

Store protected from light.

IMPURITIES



A. 4-aminobenzenesulfonamide (sulfanilamide),



B. *N*-[(4-aminophenyl)sulfonyl]urea (sulfacarbamide).

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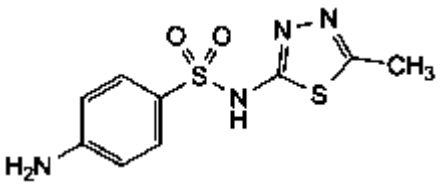
Sulfamethizole

General Notices

(Ph. Eur. monograph 0637)



$C_9H_{10}N_4O_2S_2$ 270.3 *144-82-1*

Action and use

Sulfonamide antibacterial.

Ph Eur

DEFINITION

4-Amino-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzene-1-sulfonamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder or crystals.

Solubility

Very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids.

mp

About 210 °C.

IDENTIFICATION

https://thuocngocanh.com/

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sulfamethizole CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in *acetone R* and dilute to 3 mL with the same solvent.

Reference solution Dissolve 30 mg of *sulfamethizole CRS* in *acetone R* and dilute to 3 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (15:85 *V/V*).

Application 2 µL; the volume may be adapted based on the type of plate used.

Development Over 3/4 of the plate.

Drying At 100-105 °C.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

Detection B Spray with a 40 g/L solution of *copper acetate R* and examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in colour to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution Y_5, BY_5 or GY_5 (2.2.2. *Method II*).

Dissolve 1.0 g in a mixture of 5 mL of *dilute sodium hydroxide solution R* and 5 mL of *water R*.

Acidity

To 1.25 g add 25 mL of *carbon dioxide-free water R* and heat at 70 °C for 5 min. Cool for about 15 min in iced water and filter. To 20 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

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Liquid chromatography (2.2.29).

Solvent mixture methanol R, water R (15:85 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 1 mL of methanol R, sonicate if necessary and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of sulfamethizole for system suitability CRS (containing impurities B, C and D) in 0.1 mL of methanol R, sonicate if necessary and dilute to 2 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: acetic acid R, methanol R, water for chromatography R (1:14:85 *V/V/V*);

— *mobile phase B*: acetic acid R, methanol R (1:99 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 40	100 → 30	0 → 70
40 - 45	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with sulfamethizole for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C and D.

Relative retention With reference to sulfamethizole (retention time = about 17 min): impurity B = about 0.23; impurity C = about 0.24; impurity D = about 1.9.

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System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and C.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 1.4;

— for each impurity, use the concentration of sulfamethizole in reference solution (a).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the determination of primary aromatic amino-nitrogen (2.5.8), using 0.2500 g and determining the end-point electrometrically.

1 mL of *0.1 M sodium nitrite* is equivalent to 27.03 mg of $C_9H_{10}N_4O_2S_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *D*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C*.

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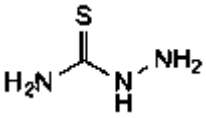
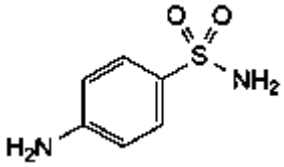
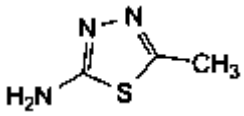


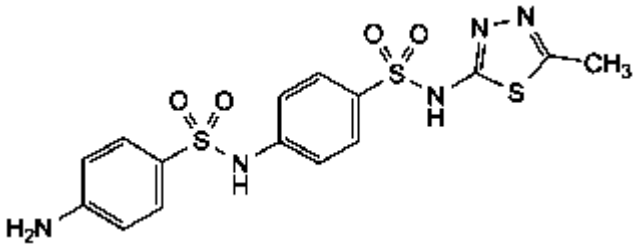
A. hydrazinecarbothioamide (thiosemicarbazide),



B. 4-aminobenzene-1-sulfonamide (sulfanilamide),



C. 5-methyl-1,3,4-thiadiazol-2-amine,



D. 4-(4-aminobenzene-1-sulfonamido)-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzene-1-sulfonamide.

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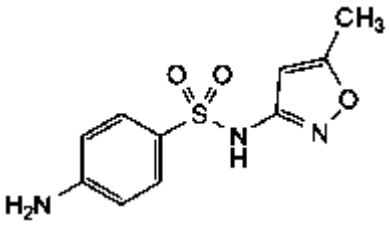
Sulfamethoxazole

General Notices

(Ph. Eur. monograph 0108)



$C_{10}H_{11}N_3O_3S$ 253.3 *723-46-6*

Action and use

Sulfonamide antibacterial.

Preparations

Co-trimoxazole Infusion

Co-trimoxazole Oral Suspension

Paediatric Co-trimoxazole Oral Suspension

Co-trimoxazole Tablets

Co-trimoxazole Dispersible Tablets

Paediatric Co-trimoxazole Tablets

Ph Eur

DEFINITION

4-Amino-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of sodium hydroxide and in dilute acids.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Melting point (2.2.14): 169 °C to 172 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *sulfamethoxazole CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 3 mL of a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Reference solution Dissolve 20 mg of *sulfamethoxazole CRS* in 3 mL of a mixture of 2 volumes of *concentrated ammonia R* and 48 volumes of *methanol R* and dilute to 5 mL with the same mixture of solvents.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *dilute ammonia R1*, *water R*, *nitromethane R*, *dioxan R* (3:5:41:51 *V/V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying At 100-105 °C.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 5 mg in 10 mL of *1 M hydrochloric acid*. Dilute 1 mL of the solution to 10 mL with *water R*. The solution, without further acidification, gives the reaction of primary aromatic amines (2.3.1).

TESTS

Appearance of solution

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The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5, BY_5 or GY_5 (2.2.2, Method II).

Dissolve 1.0 g in a mixture of 5 mL of *dilute sodium hydroxide solution R* and 5 mL of *water R*.

Acidity

To 1.25 g, finely powdered, add 25 mL of *water R*. Heat at 70 °C for 5 min. Cool in iced water for about 15 min and filter. To 20 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.3 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 45 mL of the mobile phase, sonicate at about 45 °C for 10 min, cool and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 1 mg of the substance to be examined and 1 mg of *sulfamethoxazole impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 1.0 mg of *sulfamethoxazole impurity F CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm,

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 30 °C.

Mobile phase Mix 35 volumes of *methanol R2* and 65 volumes of a 13.6 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.3 with a 20 g/L solution of *potassium hydroxide R*.

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time 3 times the retention time of sulfamethoxazole.

Relative retention With reference to sulfamethoxazole (retention time = about 10 min): impurity D = about 0.3; impurity E = about 0.35; impurity F = about 0.45; impurity C = about 0.5; impurity A = about 1.2; impurity B = about 2.0.

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System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to sulfamethoxazole and impurity A.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.025 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the assay of primary aromatic amino-nitrogen (2.5.8), using 0.200 g and determining the end-point electrometrically.

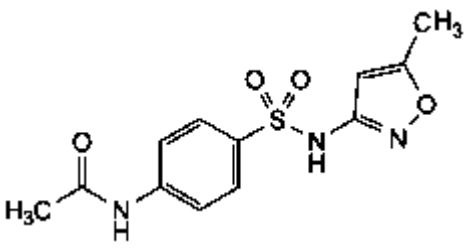
1 mL of *0.1 M sodium nitrite* is equivalent to 25.33 mg of $C_{10}H_{11}N_3O_3S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*



A. *N*-[4-[(5-methylisoxazol-3-yl)sulfamoyl]phenyl]acetamide,

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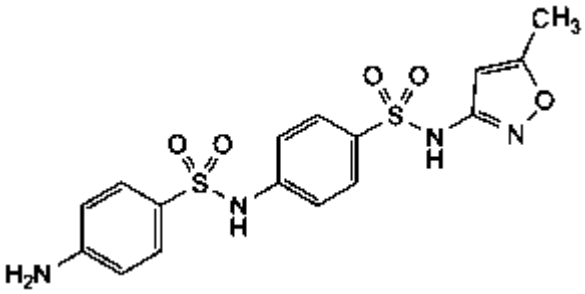
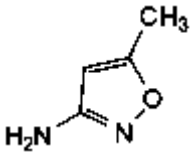
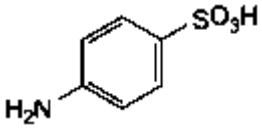


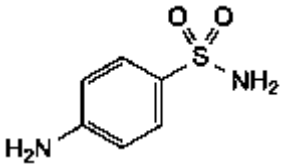
B. 4-[[(4-aminophenyl)sulfonyl]amino]-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide,



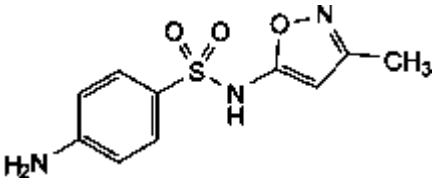
C. 5-methylisoxazol-3-amine,



D. 4-aminobenzenesulfonic acid (sulfanilic acid),



E. 4-aminobenzenesulfonamide (sulfanilamide),



F. 4-amino-*N*-(3-methylisoxazol-5-yl)benzenesulfonamide.

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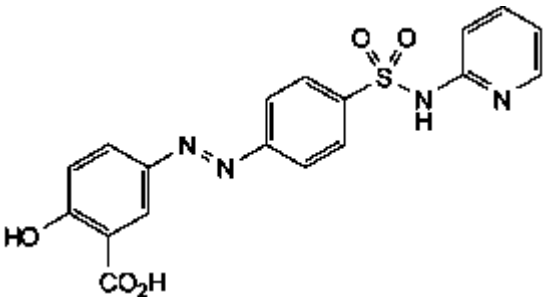
Sulfasalazine

General Notices

(Ph. Eur. monograph 0863)



$C_{18}H_{14}N_4O_5S$ 398.4 *599-79-1*

Action and use

Sulfonamide aminosalicylate; treatment of ulcerative colitis.

Preparations

Sulfasalazine Gastro-resistant Tablets

Sulfasalazine Tablets

Ph Eur

DEFINITION

2-Hydroxy-5-[2-[4-(pyridin-2-ylsulfamoyl)phenyl]diazenyl]benzoic acid.

Content

97.0 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Bright yellow or brownish-yellow, fine powder.

Solubility

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Practically insoluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *sulfasalazine CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in *dilute ammonia R3* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *dilute ammonia R3*.

Reference solution (b) Dissolve 1.0 mg of *sulfasalazine derivative for resolution CRS* in 10.0 mL of reference solution (a). Dilute 1.0 mL of this solution to 10.0 mL with reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: in a 1000 mL volumetric flask dissolve 1.13 g of *sodium dihydrogen phosphate R* and 2.5 g of *sodium acetate R* in 900 mL of *water R*; adjust to pH 4.8 with *glacial acetic acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: mobile phase A, *methanol R* (10:40 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	60 → 45	40 → 55
15 - 25	45	55
25 - 60	45 → 0	55 → 100
60 - 65	0	100

Flow rate 1 mL/min.

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Detection Spectrophotometer at 320 nm.

Injection 20 µL.

Relative retention With reference to sulfasalazine: impurity H = about 0.16; impurity I = about 0.28; impurity C = about 0.80; impurity F = about 0.85; impurity G = about 1.39; impurity E = about 1.63; impurity B = about 1.85; impurity D = about 1.90; impurity A = about 2.00.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to sulfasalazine and sulfasalazine derivative for resolution.

Limits:

— *impurities A, B, C, D, E, F, G, I*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (4 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak with a retention time less than 6 min (due to impurities H and J).

Impurities H and J

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in *dilute ammonia R3* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *salicylic acid R* (impurity H) and 5.0 mg of *sulfapyridine CRS* (impurity J) in *dilute ammonia R3* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 2.0 mL of reference solution (a) to 100.0 mL with *dilute ammonia R3*.

Column:

— *size*: *l* = 0.25, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mobile phase B (described in the test for related substances), mobile phase A (described in the test for related substances) (30:70 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 300 nm.

Injection 20 µL of the test solution and reference solution (b).

Run time 10 min.

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Retention time Impurity H = about 6 min; impurity J = about 7 min.

System suitability Reference solution (b):

— *resolution*: minimum 2 between the peaks due to impurities H and J.

Limits:

— *impurities H, J*: for each impurity, not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (2.4.4)

Maximum 140 ppm.

To 1.25 g add 50 mL of *distilled water R*. Heat at about 70 °C for 5 min. Cool and filter. To 20 mL of the filtrate add 1 mL of *nitric acid R*, allow to stand for 5 min and filter to obtain a clear solution.

Sulfates (2.4.13)

Maximum 400 ppm.

To 20 mL of the filtrate prepared for the test for chlorides add 1 mL of *dilute hydrochloric acid R*, allow to stand for 5 min and filter.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in *0.1 M sodium hydroxide* and dilute to 100.0 mL with the same solvent. Transfer 5.0 mL of this solution to a 1000 mL volumetric flask containing about 750 mL of *water R*. Add 20.0 mL of a 6 g/L solution of *glacial acetic acid R* and dilute to 1000.0 mL with *water R*. Prepare a standard solution at the same time and in the same manner using 0.150 g of *sulfasalazine CRS*. Measure the absorbance (2.2.25) of the 2 solutions at the absorption maximum at 359 nm.

Calculate the content of $C_{18}H_{14}N_4O_5S$ from the absorbances measured and the concentration of the solutions.

STORAGE

Protected from light.

IMPURITIES

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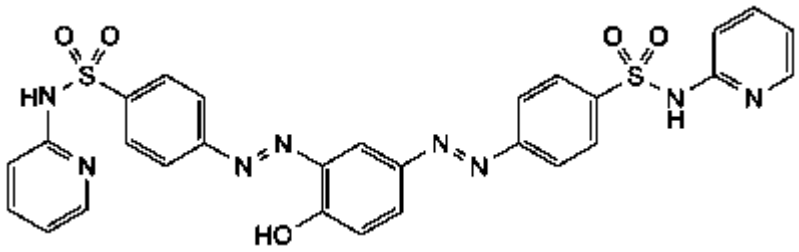
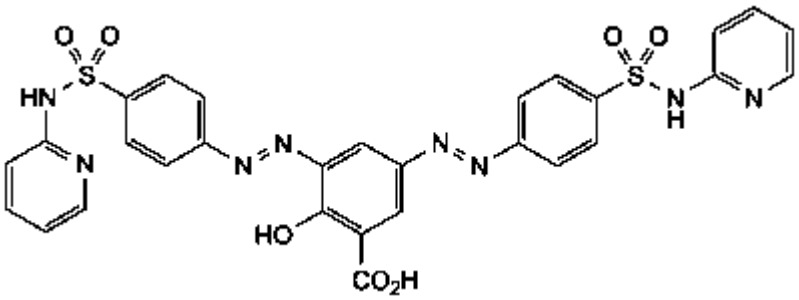
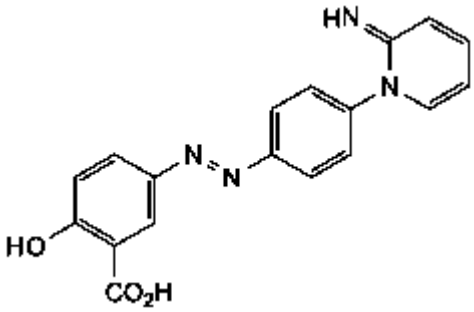
Specified impurities *A, B, C, D, E, F, G, H, I, J.*



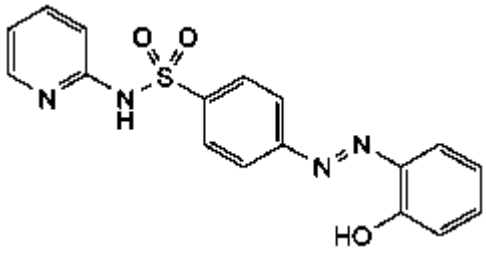
A. 4,4′-[(4-hydroxy-1,3-phenylene)bis(diazenediyl)]bis[*N*-(pyridin-2-yl)benzenesulfonamide],



B. 2-hydroxy-3,5-bis[2-[4-(pyridin-2-ylsulfamoyl)phenyl]diazenyl]benzoic acid,



C. 2-hydroxy-5-[2-[4-(2-iminopyridin-1(2*H*)-yl)phenyl]diazenyl]benzoic acid,



D. 4-[2-(2-hydroxyphenyl)diazenyl]-*N*-(pyridin-2-yl)benzenesulfonamide,

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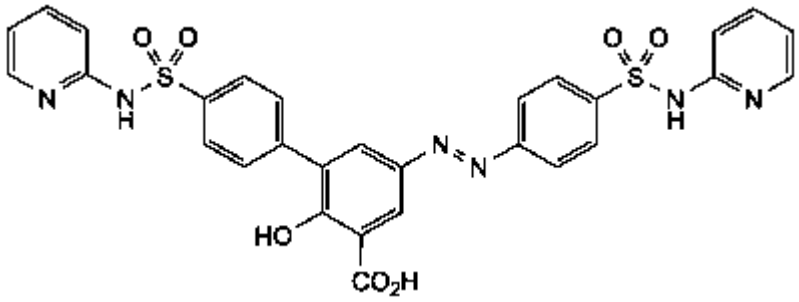
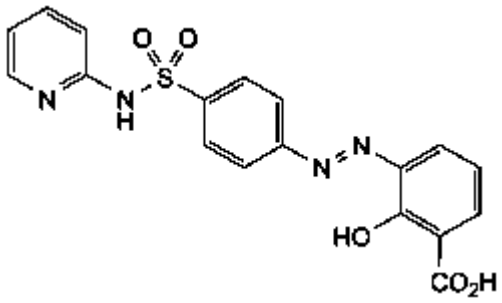
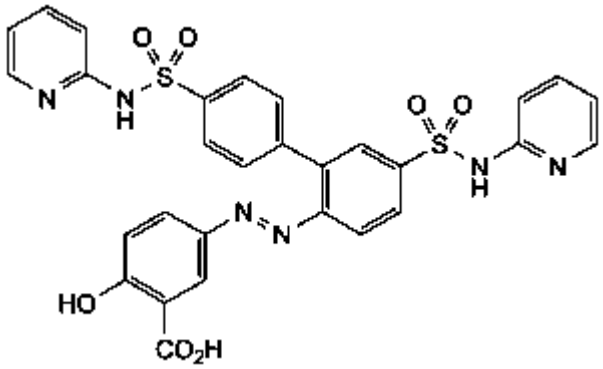


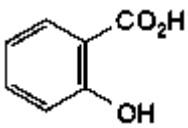
E. 2-hydroxy-4′-(pyridin-2-ylsulfamoyl)-5-[2-[4-(pyridin-2-ylsulfamoyl)phenyl]diazenyl]biphenyl-3-carboxylic acid,



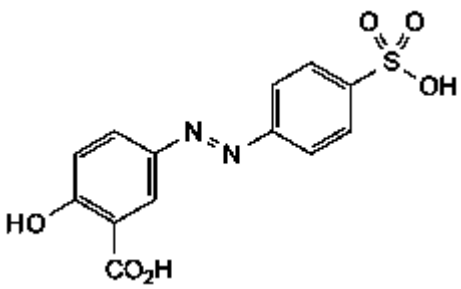
F. 2-hydroxy-3-[2-[4-(pyridin-2-ylsulfamoyl)phenyl]diazenyl]benzoic acid,



G. 5-[2-[4′,5-bis(pyridin-2-ylsulfamoyl)biphenyl-2-yl]diazenyl]-2-hydroxybenzoic acid,



H. 2-hydroxybenzenecarboxylic acid (salicylic acid),



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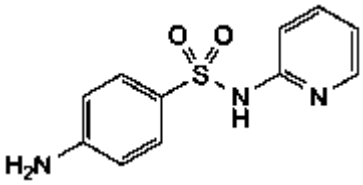
I. 2-hydroxy-5-[2-(4-sulfophenyl)diazenyl]benzoic acid,



J. 4-amino-*N*-(pyridin-2-yl)benzenesulfonamide (sulfapyridine).

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Sulfasalazine Gastro-resistant Tablets

General Notices

Gastro-resistant Sulfasalazine Tablets

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Sulfasalazine Gastro-resistant Tablets contain Sulfasalazine. They are covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sulfasalazine, $C_{18}H_{14}N_4O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract for 30 minutes with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Sulfasalazine with 100 mL of *methanol*, filter, evaporate the filtrate to dryness and dry at 35° at a pressure of 2 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of sulfasalazine *(RS 429)*.

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a phosphate buffer prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 1.66 g of *sodium hydroxide* in sufficient *water* to produce 1000 mL and adjusting the pH to 7.5 with 5M *sodium hydroxide*, if necessary, at a temperature of 37° as the medium.

PROCEDURE

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(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.005% w/v of Sulfasalazine, at the maximum at 406 nm, Appendix II B using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.005% w/v solution of *sulfasalazine BPCRS* in dissolution medium, using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of sulfasalazine, $C_{18}H_{14}N_4O_5S$, in the medium from the absorbances obtained and using the declared content of $C_{18}H_{14}N_4O_5S$ in *sulfasalazine BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Sulfasalazine with 100 mL of 0.1M *ammonia* for 30 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *ammonia*.

(3) 0.001% w/v of *sulfasalazine derivative for resolution EPCRS* in solution (2).

(4) 0.001% w/v of *sulfasalazine BPCRS* in 0.1M *ammonia*.

(5) Dilute 1 volume of solution (2) to 20 volumes with 0.1M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 320 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.013% w/v of *sodium dihydrogen orthophosphate* and 0.25% w/v of *sodium acetate* adjusted to pH 4.8 with *glacial acetic acid*.

Mobile phase B 1 volume of mobile phase A and 4 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	60→45	40→55	linear gradient
15-25	45	55	isocratic
25-60	45→0	55→100	linear gradient

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
60-65	0	100	isocratic
65-67	0→60	100→40	linear gradient
67-77	60	40	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retentions relative to sulfasalazine (retention time about 24 minutes) are: salicylic acid (impurity H), about 0.16; impurity I, about 0.28; impurity C, about 0.80; impurity F, about 0.85; impurity G, about 1.39; impurity E, about 1.63; impurity B, about 1.85; impurity D, about 1.90 and impurity A, about 2.00.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to sulfasalazine and sulfasalazine derivative for resolution is at least 3.

LIMITS

In the chromatogram obtained with solution (1);

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4%).

Disregard any peak with a retention time less than 6 minutes (corresponding to salicylic acid and sulfapyridine) and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

Salicylic acid and sulfapyridine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Sulfasalazine with 100 mL of 0.1M *ammonia* for 30 minutes, centrifuge and use the supernatant liquid.
(2) 0.001% w/v of *salicylic acid* and 0.001% w/v of *sulfapyridine EPCRS* in 0.1M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use ambient column temperature.
(e) Use a detection wavelength of 300 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 10 minutes.

MOBILE PHASE

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A mixture of 30 volumes of mobile phase B and 70 volumes of mobile phase A described in the test for Related substances.

When the chromatograms are recorded under the prescribed conditions the retention time of salicylic acid is about 6 minutes and that of sulfapyridine is about 7 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks corresponding to salicylic acid and sulfapyridine is at least 2.

LIMITS

In the chromatogram obtained with solution (1), the areas of any peaks corresponding to salicylic acid and sulfapyridine are not greater than half the areas of the corresponding peaks in the chromatogram obtained with solution (2) (0.5% of each).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.15 g of Sulfasalazine with about 50 mL of 0.1M *sodium hydroxide*, add sufficient of the same solvent to produce 100 mL, filter and discard the first 20 mL of filtrate. Dilute 5 mL of the filtrate with 750 mL of *water*, add 20 mL of 0.1M *acetic acid*, mix and add sufficient *water* to produce 1000 mL. Measure the *absorbance* of this solution at the maximum at 359 nm, Appendix II B. Calculate the content of $C_{18}H_{14}N_4O_5S$ in the tablets from the *absorbance* of a standard solution prepared in the same manner using 0.15 g of *sulfasalazine BPCRS* and using the declared content of $C_{18}H_{14}N_4O_5S$ in *sulfasalazine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sulfasalazine.

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Sulfasalazine Tablets

General Notices

Action and use

Sulfonamide aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Sulfasalazine Tablets contain Sulfasalazine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sulfasalazine, $C_{18}H_{14}N_4O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 16 mg of Sulfasalazine with 100 mL of 0.1M *sodium hydroxide* until dispersed and filter. Dilute 5 mL of the filtrate to 100 mL with a mixture of 7 volumes of *water* and 2 volumes of 0.1M *acetic acid*. Record the *light absorbances* in the range 220 nm to 400 nm, Appendix II B. The absorbance at all wavelengths in the range is similar to that of a solution prepared from *sulfasalazine BPCRS* prepared in the same manner.

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a phosphate buffer prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 1.66 g of *sodium hydroxide* in sufficient *water* to produce 1000 mL and adjusting the pH to 7.5 with 5M *sodium hydroxide*, if necessary, at a temperature of 37°, as the medium.

PROCEDURE

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(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.005% w/v of Sulfasalazine, at the maximum at 406 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.005% w/v solution of *sulfasalazine BPCRS* in dissolution medium, using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of sulfasalazine, $C_{18}H_{14}N_4O_5S$, in the medium from the absorbances obtained and using the declared content of $C_{18}H_{14}N_4O_5S$ in *sulfasalazine BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Sulfasalazine with 100 mL of 0.1M *ammonia* for 30 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *ammonia*.

(3) 0.001% w/v of *sulfasalazine derivative for resolution EPCRS* in solution (2).

(4) 0.001% w/v of *sulfasalazine BPCRS* in 0.1M *ammonia*.

(5) Dilute 1 volume of solution (2) to 20 volumes with 0.1M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 320 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.013% w/v of *sodium dihydrogen orthophosphate* and 0.25% w/v of *sodium acetate* adjusted to pH 4.8 with *glacial acetic acid*.

Mobile phase B 1 volume of mobile phase A and 4 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	60→45	40→55	linear gradient
15-25	45	55	isocratic
25-60	45→0	55→100	linear gradient

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
60-65	0	100	isocratic
65-67	0→60	100→40	linear gradient
67-77	60	40	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retentions relative to sulfasalazine (retention time about 24 minutes) are: salicylic acid (impurity H), about 0.16; impurity I, about 0.28; impurity C, about 0.80; impurity F, about 0.85; impurity G, about 1.39; impurity E, about 1.63; impurity B, about 1.85; impurity D, about 1.90 and impurity A, about 2.00.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sulfasalazine and sulfasalazine derivative for resolution is at least 3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peaks corresponding to impurities A, B, C, D, E, F, G and I are not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any other *secondary peak* is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (4%).

Disregard any peak with a retention time less than 6 minutes (corresponding to salicylic acid and sulfapyridine) and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

Salicylic acid and sulfapyridine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Sulfasalazine with 100 mL of 0.1M *ammonia* for 30 minutes, centrifuge and use the supernatant liquid.
(2) 0.001% w/v of *salicylic acid* and 0.001% w/v of *sulfapyridine EPCRS* in 0.1M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 300 nm.

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(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 10 minutes.

MOBILE PHASE

30 volumes of mobile phase B described in the test for Related substances and 70 volumes of mobile phase A described in the test for Related substances.

When the chromatograms are recorded under the prescribed conditions the retention time of salicylic acid is about 6 minutes and that of sulfapyridine is about 7 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to salicylic acid and sulfapyridine is at least 2.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to salicylic acid or sulfapyridine is not greater than half the area of the corresponding peaks in the chromatogram obtained with solution (2) (0.5% of each).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.15 g of Sulfasalazine with about 50 mL of 0.1M *sodium hydroxide*, add sufficient of the same solvent to produce 100 mL, filter and discard the first 20 mL of filtrate. Dilute 5 mL of the filtrate with 750 mL of *water*, add 20 mL of 0.1M *acetic acid*, mix and add sufficient *water* to produce 1000 mL. Measure the *absorbance* of this solution at the maximum at 359 nm, Appendix II B. Calculate the content of $C_{18}H_{14}N_4O_5S$ in the tablets from the *absorbance* of a standard solution prepared in the same manner using 0.15 g of *sulfasalazine BPCRS* and using the declared content of $C_{18}H_{14}N_4O_5S$ in *sulfasalazine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sulfasalazine.

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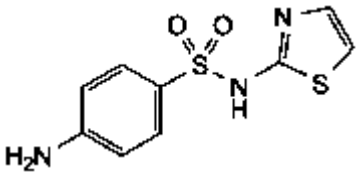
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Sulfathiazole

General Notices

(Ph. Eur. monograph 0742)



$C_9H_9N_3O_2S_2$ 255.3 *72-14-0*

Action and use

Sulfonamide antibacterial.

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DEFINITION

Sulfathiazole contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 4-amino-*N*-(thiazol-2-yl)benzenesulfonamide, calculated with reference to the dried substance.

CHARACTERS

A white or slightly yellowish, crystalline powder, practically insoluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 200 °C to 203 °C. Melting may occur at about 175 °C, followed by solidification and a second melting between 200 °C and 203 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *sulfathiazole CRS*. Examine the substances prepared as discs. If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *alcohol R*, evaporate to dryness *in vacuo* and record the spectra again using the residues.

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C. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 10 mg in a mixture of 10 mL of *water R* and 2 mL of *0.1 M sodium hydroxide* and add 0.5 mL of *copper sulfate solution R*. A greyish-blue or purple precipitate is formed.

E. Dissolve about 5 mg in 10 mL of *1 M hydrochloric acid*. Dilute 1 mL of the solution to 10 mL with *water R*. The solution, without further addition of acid, gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Appearance of solution

Dissolve 1.0 g in 10 mL of *1 M sodium hydroxide*. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution GY_4 (*2.2.2, Method II*).

Acidity

To 1.0 g add 50 mL of *carbon dioxide-free water R*. Heat to 70 °C for 5 min. Cool rapidly to 20 °C and filter. To 25 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel H R* as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in a mixture of 1 volume of *concentrated ammonia R* and 9 volumes of *alcohol R* and dilute to 10 mL with the same mixture of solvents.

Test solution (b) Dilute 1 mL of test solution (a) to 5 mL with a mixture of 1 volume of *concentrated ammonia R* and 9 volumes of *alcohol R*.

Reference solution (a) Dissolve 20 mg of *sulfathiazole CRS* in a mixture of 1 volume of *concentrated ammonia R* and 9 volumes of *alcohol R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b) Dissolve 50 mg of *sulfanilamide R* in a mixture of 1 volume of *concentrated ammonia R* and 9 volumes of *alcohol R* and dilute to 100 mL with the same mixture of solvents. Dilute 1 mL of this solution to 10 mL with the same mixture of solvents.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 18 volumes of *ammonia R* and 90 volumes of *butanol R*. Dry the plate at 100 °C to 105 °C for 10 min and spray with a 1 g/L solution of *dimethylaminobenzaldehyde R* in *alcohol R* containing 1 per cent *V/V* of *hydrochloric acid R*. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

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Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the determination of primary aromatic amino- nitrogen (*2.5.8*), using 0.200 g, determining the end-point electrometrically.

1 mL of *0.1 M sodium nitrite* is equivalent to 25.53 mg of $C_9H_9N_3O_2S_2$.

STORAGE

Store protected from light.

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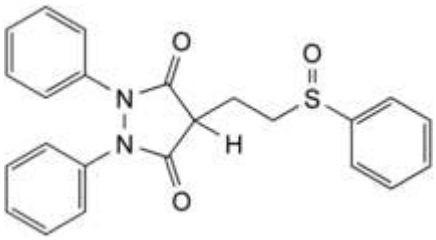
Sulfinpyrazone

General Notices

(Ph. Eur. monograph 0790)



$C_{23}H_{20}N_2O_3S$ 404.5 *57-96-5*

Action and use

Uricosuric.

Ph Eur

DEFINITION

1,2-Diphenyl-4-[2-(phenylsulfinyl)ethyl]pyrazolidine-3,5-dione.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

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A. Melting point (2.2.16): 131 °C to 135 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 30.0 mg in *0.01 M sodium hydroxide* and dilute to 100.0 mL with the same alkaline solution. Dilute 1.0 mL of this solution to 20.0 mL with *0.01 M sodium hydroxide*.

Spectral range 230-350 nm.

Absorption maximum At 260 nm.

Specific absorbance at the absorption maximum 530 to 580.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *sulfinpyrazone CRS*.

D. Dissolve about 10 mg in 3 mL of *acetone R* and add a mixture of 0.2 mL of *ferric chloride solution R2* and 3 mL of *water R*. A red to violet colour develops.

TESTS

Appearance of solution in acetone

The solution is clear (2.2.1) and its absorbance (2.2.25) at 420 nm using a path length of 4 cm is not greater than 0.10.

Dissolve 1.25 g in *acetone R* and dilute to 25 mL with the same solvent.

Appearance of solution in 1 M sodium hydroxide

The solution is clear (2.2.1) and its absorbance (2.2.25) at 420 nm using a path length of 4 cm is not greater than 0.15.

Dissolve 1.25 g, heating gently if necessary, in 25 mL of *1 M sodium hydroxide*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Solvent mixture *water R*, *acetonitrile R* (10:40 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of *sulfinpyrazone impurity A CRS* and 5.0 mg of *sulfinpyrazone impurity B CRS* in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 100.0 mL with the solvent mixture.

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Reference solution (d) Dissolve the contents of a vial of *sulfinpyrazone for system suitability CRS* (containing impurity C) in 1.0 mL of the solvent mixture.

Reference solution (e) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *tetrahydrofuran for chromatography R*, *acetonitrile R*, 0.3 per cent *V/V* solution of *phosphoric acid R* (7:35:58 *V/V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µl.

Run time 7 times the retention time of sulfinpyrazone.

Identification of impurities Use the chromatogram supplied with *sulfinpyrazone for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to sulfinpyrazone (retention time = about 3.5 min): impurity C = about 0.8; impurity A = about 1.6; impurity B = about 4.8.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to impurity C and sulfinpyrazone.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (e) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.05 per cent).

Loss on drying (*2.2.32*)

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Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 25 mL of *acetone R*. Add 0.5 mL of *bromothymol blue solution R1*. Titrate with *0.1 M sodium hydroxide* until the colour changes from yellow to blue.

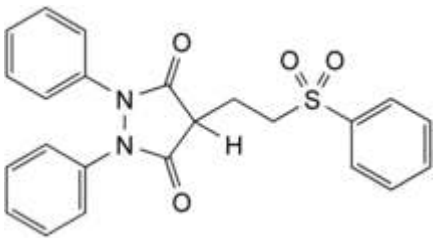
1 mL of *0.1 M sodium hydroxide* is equivalent to 40.45 mg of $C_{23}H_{20}N_2O_3S$.

STORAGE

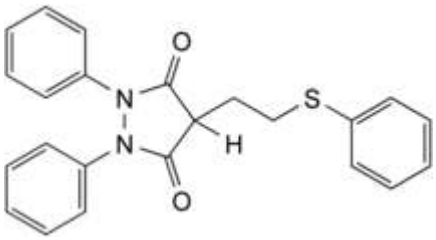
Protected from light.

IMPURITIES

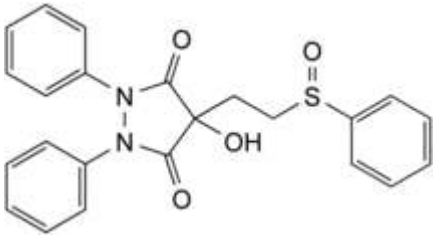
Specified impurities *A, B, C.*



A. 1,2-diphenyl-4-[2-(phenylsulfonyl)ethyl]pyrazolidine-3,5-dione,



B. 1,2-diphenyl-4-[2-(phenylsulfanyl)ethyl]pyrazolidine-3,5-dione,



C. 4-hydroxy-1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]pyrazolidine-3,5-dione.

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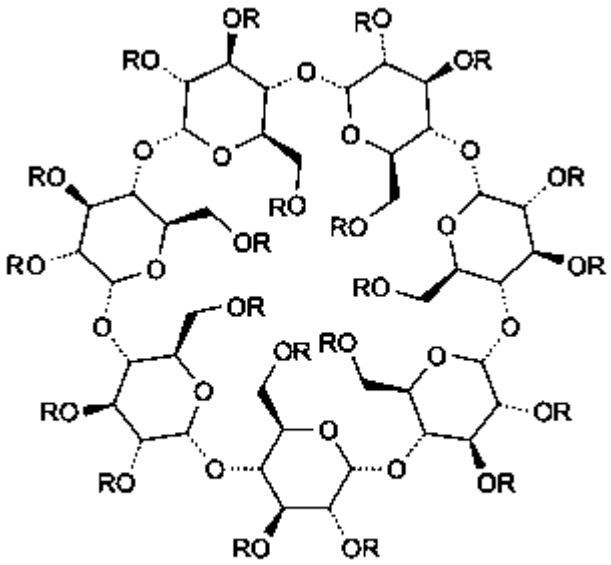
Sulfobutylbetadex Sodium

General Notices

(Ph. Eur. monograph 2804)



$C_{42}H_{70-n}O_{35}(C_4H_8SO_3Na)_n$ 2163 when *n* = 6.5 *182410-00-0*

Ph Eur

DEFINITION

Sulfobutylbetadex sodium (β-cyclodextrin, sodium 4-sulfonatobutyl ether) is the sodium salt of a partially substituted poly(sulfobutyl) ether of betadex.

Content

— *sulfobutylbetadex sodium*: 95.0 per cent to 105.0 per cent (anhydrous substance);

— *average number of sulfobutyl groups per cyclodextrin ring, expressed as average degree of substitution (DS)*: 5.9 to 6.6.

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

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Freely soluble in water, practically insoluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sulfobutylbetadex sodium CRS*.

Results The spectrum obtained with the substance to be examined shows the same absorption bands as the spectrum obtained with *sulfobutylbetadex sodium CRS*. Due to differences in the degree of substitution of the substance, the relative intensity of some absorption bands may vary.

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 7.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

pH (2.2.3)

5.0 to 7.5 for solution S.

Use intensive nitrogen purging to avoid carbon dioxide absorption during measurement.

Reducing sugars

Maximum 0.05 per cent.

Reagent solution Dissolve 1.0 g of *triphenyltetrazolium chloride R* in 100 mL of *aldehyde-free methanol R*.

Test solution Dissolve 0.45 g of the substance to be examined in 2.0 mL of *dimethyl sulfoxide R* in a test tube and add 0.5 mL of a 40 g/L solution of *sodium hydroxide R* and 7.5 mL of the reagent solution. Mix and store at room temperature.

Reference solution Prepare at the same time and in the same manner as for the test solution, using 0.10 mL of a 2.25 g/L solution of *glucose R* instead of the substance to be examined.

After 1 h, measure the absorbance (2.2.25) of the solutions at the absorption maximum at 482 nm. The absorbance of the test solution is not greater than that of the reference solution.

Impurities A, C and D

Liquid chromatography (2.2.29).

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Test solution Dissolve 0.300 g of the substance to be examined in *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 15.0 mg of *betadex CRS* (impurity A) in *water R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *water R*.

Reference solution (b) Dissolve 15.0 mg of *sulfobutylbetadex impurity C CRS* in *water R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solution (c) Dissolve 15.0 mg of *sulfobutylbetadex impurity D CRS* in *water R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solution (d) Dissolve 0.300 g of *sulfobutylbetadex sodium CRS* in 1.0 mL of reference solution (b) and 0.5 mL of reference solution (c), and dilute to 5.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *4-dimethylaminobenzylcarbamidesilyl silica gel for chromatography R* (3 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: to 4.0 mL of *triethylamine R* add 900 mL of *water for chromatography R* and adjust to pH 4.5 with *anhydrous formic acid R*; dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 8	90 → 60	10 → 40
8 - 14	60 → 40	40 → 60
14 - 20	40	60

Flow rate 1.1 mL/min.

Detection Evaporative light-scattering detector; the following settings have been found to be suitable; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criteria.

— *carrier gas*: *nitrogen R*;

— *flow rate*: 1.5 L/min;

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— *evaporator temperature*: 50 °C.

Equilibration At initial isocratic conditions for 10 min.

Injection 10 µL of the test solution and reference solutions (a) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities C and D.

Relative retention With reference to impurity A (retention time = about 2.9 min): impurity C = about 0.7; impurity D = about 2.0; sulfobutylbetadex elutes as several peaks after impurity D unless heart-cutting is applied.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurities C and A in the chromatogram obtained with reference solution (d);

— *repeatability*: maximum relative standard deviation of 3.0 per cent for the area of the peak due to impurity A determined on 5 injections of reference solution (a), using the initial isocratic conditions for 4 min.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.05 per cent);

— disregard the peak due to the sodium counter-ion (corresponding to the dead volume of the column) and any peak eluting after impurity D (due to sulfobutylbetadex).

Impurity B

Gas chromatography (2.2.28). *Prepare the solutions immediately before use.*

Internal standard solution Dissolve 25.0 mg of *diethyl sulfone R* in 10.0 mL of *dimethylformamide R* and dilute to 1000.0 mL with *water R*. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Test solutions (a), (b), (c) and (d) In 4 test tubes with screw caps, prepare 4 solutions as indicated in Table 2804.-1. Mix each test tube on a vortex mixer for 30 s and allow to stand for at least 5 min or until complete separation of the phases. Decant the organic phase into a vial and seal.

Reference solution (a) Dissolve 50.0 mg of *sulfobutylbetadex impurity B CRS* in 5.0 mL of *dimethylformamide R* and dilute with *water R* to obtain a concentration of 2.0 µg/mL.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 2.0 mL with *water R*.

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Reference solution (c) Dilute 1.0 mL of reference solution (a) to 4.0 mL with *water R*.

Blank solution Prepare as described for test solution (d), but omitting the substance to be examined.

Table 2804.-1.

	Substance to be examined (g)	Internal standard solution (mL)	Solvent/solution (mL)	*Methylene chloride R* (mL)	Final content of *sulfobutylbetadex impurity B CRS* (µg)
Blank solution	0	4.0	*Water R*, 1.0	1.0	0
Test solution (a)	1.000	4.0	Reference solution (a), 1.0	1.0	2.0
Test solution (b)	1.000	4.0	Reference solution (b), 1.0	1.0	1.0
Test solution (c)	1.000	4.0	Reference solution (c), 1.0	1.0	0.5
Test solution (d)	1.000	4.0	*Water R*, 1.0	1.0	0

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.4 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	100 → 200
	10 - 11.5	200 → 250

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	Time (min)	Temperature (°C)
	11.5 - 16.5	250
Injection port		250
Detector		270

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to the internal standard (retention time = about 6.5 min): impurity B = about 1.4.

System suitability:

— *repeatability*: maximum relative standard deviation of 10.0 per cent for the corrected ratios (as described under Calculation of content) determined on 5 injections of test solution (b).

Calculation of content Calculate the ratio of the area of the peak due to impurity B to the area of the peak due to the internal standard in the chromatograms obtained with test solutions (a), (b), (c) and (d) respectively. Subtract from these values the ratio of the area of the peak due to impurity B to the area of the peak due to the internal standard in the chromatogram obtained with the blank solution (diethyl sulfone may contain trace amounts of impurity B). Plot the added quantity of impurity B (in micrograms) as the abscissa and the corrected ratios as the ordinates. Extrapolate the line joining the points on the graph until it meets the *x*-axis. The distance between this point and the origin corresponds to the content of impurity B in micrograms per gram (ppm) of the substance to be examined.

Limit:

— *impurity B*: maximum 0.5 ppm.

Chlorides (2.4.4)

Maximum 0.12 per cent (corresponding to 0.20 per cent expressed as sodium chloride).

Dissolve a quantity of the substance to be examined corresponding to 42 mg of anhydrous substance in 15.0 mL of *water R*.

Water (2.5.12)

Maximum 10.0 per cent, determined on 0.200 g.

Microbial contamination

If intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

If not intended for use in the manufacture of parenteral preparations:

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— TAMC: acceptance criterion 10^3 CFU/g (2.6.12);

— TYMC: acceptance criterion 10^2 CFU/g (2.6.12);

— absence of *Escherichia coli* (2.6.13);

— absence of *Salmonella* (2.6.13).

ASSAY

Sulfobutylbetadex sodium

Size-exclusion chromatography (2.2.30).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 0.100 g of *sulfobutylbetadex sodium CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *polymethacrylate gel R*.

Mobile phase Dissolve 10.11 g of *potassium nitrate R* in a mixture of 1 volume of *acetonitrile for chromatography R* and 4 volumes of *water for chromatography R* and dilute to 1000 mL with the same mixture of solvents.

Flow rate 1.0 mL/min.

Detection Differential refractometer maintained at 35 ± 2 °C.

Injection 20 µL.

Between-run rinsing Rinse the column with a mixture of 1 volume of *acetonitrile for chromatography R* and 9 volumes of *water for chromatography R*.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the area of the peak due to sulfobutylbetadex, determined on 5 injections;

— *symmetry factor*: maximum 1.8.

Calculate the percentage content of sulfobutylbetadex sodium taking into account the assigned content of *sulfobutylbetadex sodium CRS*.

Average degree of substitution

Nuclear magnetic resonance spectrometry (2.2.33).

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The average degree of substitution (*DS*) is calculated from the ratio between the signals of the inner-chain protons of the sulfobutyl ether groups (-O-CH_2-**CH_2-CH_2**-CH_2-SO_3H) and the signals of the glycosidic protons attached to the C1 carbon of the anhydroglucose units.

Test solution Introduce not less than 10.0 mg of the substance to be examined, previously dried for at least 1 day in a desiccator, into a 5 mm NMR tube. Add about 0.70 mL of *deuterium oxide R1*. Cap the tube and mix thoroughly.

Apparatus FT-NMR spectrometer operating at minimum 250 MHz and suitable for recording at 25 °C.

Acquisition of ^1H NMR spectra The following parameters may be used:

— *sweep width*: 10 ppm (0 to + 10.0 ppm);

— *irradiation frequency offset*: none;

— *time domain*: 32 K;

— *pulse width*: 90°;

— *pulse delay*: 15 s;

— *dummy scans*: 2;

— *number of scans*: 16.

Call the integration sub-routine after phase corrections and baseline correction between - 1 ppm and + 9 ppm.

The signal of exchangeable protons (solvent) at + 4.8 ppm is used as reference.

Make a zero filling at least twice in size relative to the acquisition data file and transform the FID to the spectrum without any correction of the Gaussian broadening factor (GB = 0) and with a line broadening factor not greater than 0.3 Hz (LB ≤ 0.3). Adjust integral level and tilting.

Measure the peak areas of the signals between 1.43 ppm and 2.12 ppm (A_1, -O-CH_2-**CH_2-CH_2**-CH_2-SO_3H), and the signals of the glycosidic protons between 4.95 ppm and 5.41 ppm (A_2, -O-**CH**-O-).

Calculate the average degree of substitution (*DS*) using the following expression:

$$\frac{7 \times A_1}{4 \times A_2}$$

A_1 = area of the peaks due to the inner methylene protons (indicated in bold) of the sulfobutyl ether functional group;

A_2 = area of the peaks due to the glycosidic protons (indicated in bold).

STORAGE

In an airtight container.

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LABELLING

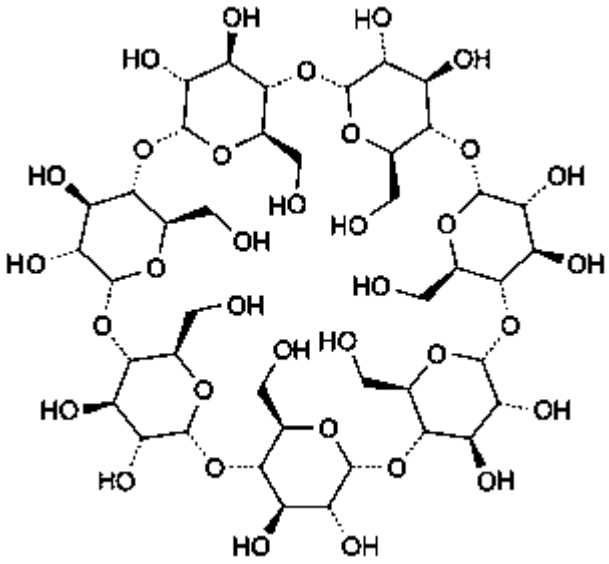
The label states:

— the average degree of substitution (*DS*);

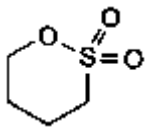
— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, B, C, D.*

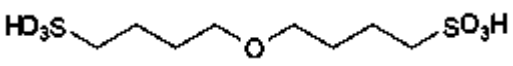


A. cycloheptakis-(1→4)-(α-D-glucopyranosyl) (betadex or cyclomaltoheptaose or β-cyclodextrin),



B. 1,2λ^6-oxathiane-2,2-dione,

C. 4-hydroxybutane-1-sulfonic acid,



D. 4,4′-oxydi(butane-1-sulfonic acid).

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Sulfur

General Notices

Sulfur for External Use

Sulphur for External Use

(Ph. Eur. monograph 0953)

S 32.06 *7704-34-9*

Action and use

Keratolytic.

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

Yellow powder.

Solubility

Practically insoluble in water, soluble in carbon disulfide, slightly soluble in vegetable oils.

mp

About 120 °C.

The size of most of the particles is not greater than 20 µm and that of almost all the particles is not greater than 40 µm.

IDENTIFICATION

A. Heated in the presence of air, it burns with a blue flame, emitting sulfur dioxide which changes the colour of moistened *blue litmus paper R* to red.

B. Heat 0.1 g with 0.5 mL of *bromine water R* until decolourised. Add 5 mL of *water R* and filter. The solution gives reaction (a) of sulfates (*2.3.1*).

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TESTS

Solution S

To 5 g add 50 mL of *carbon dioxide-free water R* prepared from *distilled water R*. Allow to stand for 30 min with frequent shaking and filter.

Appearance of solution

Solution S is colourless (*2.2.2, Method II*).

Odour (*2.3.4*)

It has no perceptible odour of hydrogen sulfide.

Acidity or alkalinity

To 5 mL of solution S add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Add 0.2 mL of *0.01 M sodium hydroxide*. The solution is red. Add 0.3 mL of *0.01 M hydrochloric acid*. The solution is colourless. Add 0.15 mL of *methyl red solution R*. The solution is orange-red.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Sulfides

To 10 mL of solution S add 2 mL of *buffer solution pH 3.5 R* and 1 mL of a freshly prepared 1.6 g/L solution of *lead nitrate R* in *carbon dioxide-free water R*. Shake. After 1 min any colour in the solution is not more intense than that in a reference solution prepared at the same time using 1 mL of *lead standard solution (10 ppm Pb) R*, 9 mL of *carbon dioxide-free water R*, 2 mL of *buffer solution pH 3.5 R* and 1.2 mL of *thioacetamide reagent R*.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Carry out the oxygen-flask method (*2.5.10*), using 60.0 mg in a 1000 mL combustion flask. Absorb the combustion products in a mixture of 5 mL of *dilute hydrogen peroxide solution R* and 10 mL of *water R*. Heat to boiling, boil gently for 2 min and cool. Using 0.2 mL of *phenolphthalein solution R* as indicator, titrate with *0.1 M sodium hydroxide* until the colour changes from colourless to red. Carry out a blank titration under the same conditions.

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1 mL of *0.1 M sodium hydroxide* is equivalent to 1.603 mg of S.

STORAGE

Protected from light.

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Sulfuric Acid

General Notices

Sulphuric Acid

(Ph. Eur. monograph 1572)

H_2SO_4 98.1 *7664-93-9*

Preparation

Dilute Sulfuric Acid

Ph Eur

DEFINITION

Content

95.0 per cent *m/m* to 100.5 per cent *m/m*.

CHARACTERS

Appearance

Colourless, oily liquid, very hygroscopic.

Solubility

Miscible with water and with ethanol (96 per cent) producing intense heat.

Relative density

About 1.84.

IDENTIFICATION

A. Carefully add 1 mL to 100 mL of *water R*. The solution is strongly acid (*2.2.4*).

B. The solution obtained in identification test A gives reaction (a) of sulfates (*2.3.1*).

TESTS

Appearance of solution

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The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Carefully pour, while cooling, 5 mL into 30 mL of *water R* and dilute to 50 mL with the same solvent.

Chlorides (*2.4.4*)

Maximum 50 ppm.

Mix carefully, while cooling, 3.3 g with 30 mL of *water R*. Neutralise with *ammonia R* and dilute to 50 mL with *water R*.

Nitrates

Add 5 mL to 5 mL of *water R*. Cool to room temperature and add 0.5 mL of *indigo carmine solution R*. The blue colour persists for at least 1 min.

Iron (*2.4.9*)

Maximum 25 ppm.

Cautiously evaporate 10.0 g and ignite to dull redness. Dissolve the ignition residue in 1 mL of *dilute hydrochloric acid R* with gentle heating and dilute to 25 mL with *water R*. Dilute 1 mL of this solution to 10 mL with *water R*.

ASSAY

Weigh accurately a ground-glass-stoppered flask containing 30 mL of *water R*. Introduce 0.2 mL, cool and weigh again. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 49.04 mg of H_2SO_4.

STORAGE

In an airtight container.

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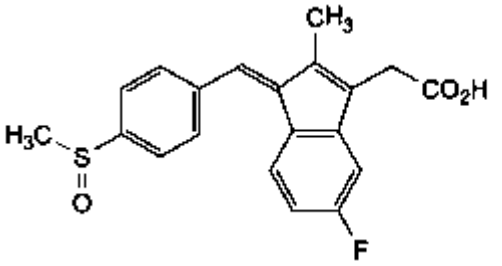
Sulindac

General Notices

(Ph. Eur. monograph 0864)



and enantiomer

$C_{20}H_{17}FO_3S$ 356.4 *38194-50-2*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparation

Sulindac Tablets

Ph Eur

DEFINITION

[(1*Z*)-6-Fluoro-3-[[4-[(*RS*)-methanesulfinyl]phenyl]methylidene]-2-methyl-3*H*-inden-1-yl]acetic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

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It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison sulindac CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of hot methanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of sulindac for system suitability CRS (containing impurities B, C and D) in the mobile phase and dilute to 2 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: silica gel for chromatography R (10 µm).

Mobile phase glacial acetic acid R, ethanol (96 per cent) R, ethyl acetate R, methylene chloride R (1:4:100:400 *V/V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 2.5 times the retention time of sulindac.

Identification of impurities Use the chromatogram supplied with sulindac for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C and D.

Relative retention With reference to sulindac (retention time = about 10 min): impurity C = about 0.20; impurity B = about 0.25; impurity D = about 0.7.

System suitability Reference solution (b):

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— *resolution*: minimum 2.0 between the peaks due to impurities C and B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 2;

— for each impurity, use the concentration of sulindac in reference solution (a).

Limits:

— *impurity C*: maximum 0.5 per cent;

— *impurity B*: maximum 0.4 per cent;

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C at a pressure not exceeding 0.7 kPa.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.64 mg of $C_{20}H_{17}FO_3S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities B, C, D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.

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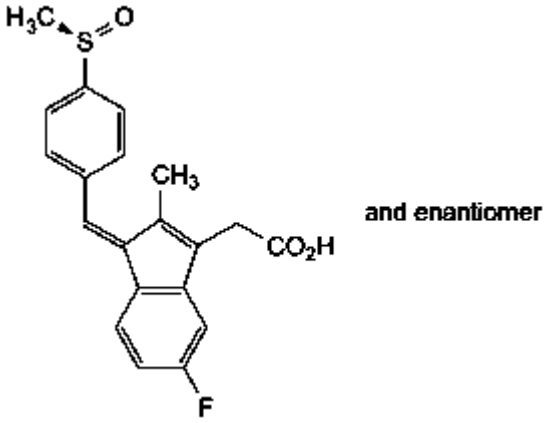
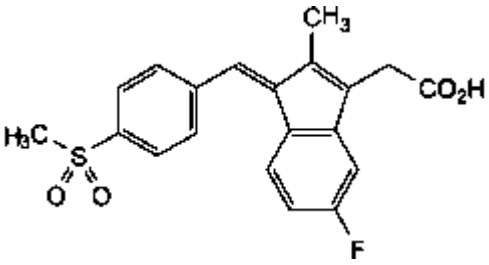
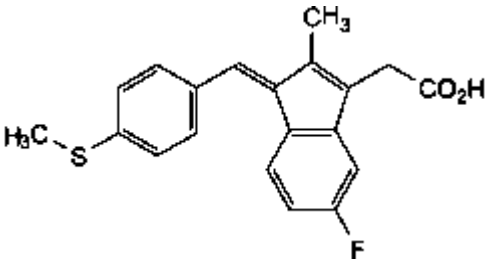


and enantiomer

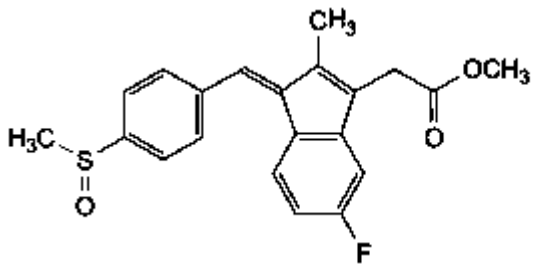
A. [(1*E*)-6-fluoro-3-[[4-[(*RS*)-methanesulfinyl]phenyl]methylidene]-2-methyl-3*H*-inden-1-yl]acetic acid,



B. [(1*Z*)-6-fluoro-3-[[4-(methanesulfonyl)phenyl]methylidene]-2-methyl-3*H*-inden-1-yl]acetic acid,



C. [(1*Z*)-6-fluoro-2-methyl-3-[[4-(methylsulfanyl)phenyl]methylidene]-3*H*-inden-1-yl]acetic acid,



and enantiomer

D. methyl [(1*Z*)-6-fluoro-3-[[4-[(*RS*)-methanesulfinyl]phenyl]methylidene]-2-methyl-3*H*-inden-1-yl]acetate.

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Sulindac Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Sulindac Tablets contain Sulindac.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sulindac, $C_{20}H_{17}FO_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Sulindac with 10 mL of a mixture of equal volumes of *chloroform* and *methanol* for 10 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of sulindac (*RS 323*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution obtained in the Assay exhibits two maxima, at 284 nm and 327 nm, and a less well-defined maximum at 258 nm.

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *phosphate buffer pH 7.2* and rotate the paddle at 50 revolutions per minute. Withdraw a sample of 10 mL of the medium, filter and dilute with *phosphate buffer pH 7.2* to give a solution expected to contain 0.001% w/v of Sulindac. Measure the *absorbance* of this solution, Appendix II B, at 327 nm using *phosphate buffer pH 7.2* in the reference cell. Calculate the total content of $C_{20}H_{17}FO_3S$ in the medium taking 373 as the value of A(1%, 1 cm) at the maximum at 327 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Mix 160 volumes of *tetrahydrofuran* and 840 volumes of *methanol* (solution A). Mix equal volumes of solution A and a solution containing 0.358% w/v of *disodium hydrogen orthophosphate* and 0.34% w/v of *tetrabutylammonium hydrogen sulfate* (the mixture is solution B). For solution (1) shake a quantity of whole tablets containing 1 g of Sulindac with 175 mL of solution A mechanically for 15 minutes and then with the aid of ultrasound until the tablets have fully disintegrated (at least 15 minutes). Allow the resulting suspension to cool, add sufficient of solution B to produce 200 mL and mix. Dilute 10 mL of the resulting solution to 100 mL with solution B and filter through a 0.45-µm filter (Millipore Millex is suitable). For solution (2) dilute 1 volume of solution (1) to 100 volumes with solution B and further dilute 1 volume to 2 volumes with the same mixture of

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solvents. Solution (3) contains 0.050% w/v of *sulindac BPCRS* (which has an assigned content of the *E*-isomer) in solution B. For solution (4) add 0.05 mL of a 3% w/v solution of *potassium permanganate* to 5 mL of solution (1) (generation of sulfoxide impurity). For solution (5) add a few granules of *zinc*, in *fine powder* to 5 mL of solution (1), add 0.2 mL of *hydrochloric acid*, mix and filter through a 0.45-µm filter (generation of desoxy impurity). For solution (6) add 0.3 mL of *methanol* to 5 mL of solution (1), add 0.2 mL of *sulfuric acid* and mix (generation of methyl ester). For solution (7) add 0.3 mL of *absolute ethanol* to 5 mL of solution (1), add 0.2 mL of *sulfuric acid* and mix (generation of ethyl ester).

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Beckman Ultrasphere C8 is suitable), (b) as mobile phases A and B with a flow rate of 2 mL per minute the solutions described below and (c) a detection wavelength of 330 nm. Carry out a linear gradient elution using the following conditions.

Mobile phase A Mix 160 volumes of *tetrahydrofuran* and 840 volumes of *methanol* (solution C). Prepare a solution containing 0.358% w/v of *disodium hydrogen orthophosphate* and 0.34% w/v of *tetrabutylammonium hydrogen sulfate* and mix 380 volumes of solution C with 620 volumes of this solution, adjust the pH of the mixture to 6.0 with *orthophosphoric acid* or a 50% w/v solution of *sodium hydroxide*, mix with the aid of ultrasound for 10 minutes and filter through a 0.45-µm filter.

Mobile phase B *Acetonitrile*.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)
0	100	0
10	100	0
20	40	60
22	40	60
23	100	0
27	100	0

Inject 20 µL of solution (3) and continue the chromatography for twice the retention time of the principal peak. The chromatogram obtained shows a principal peak corresponding to sulindac and a peak corresponding to the *E*-isomer with a retention time relative to sulindac of about 1.25.

From the chromatograms obtained with solution (1) and solution (3) calculate the content of *E*-isomer in the preparation being examined using the declared content of the *E*-isomer in *sulindac BPCRS*; the *E*-isomer content is not more than 0.5%. In the chromatogram obtained with solution (1), the area of any peaks corresponding to the desoxy impurity, the sulfoxide impurity, the ethyl ester impurity or the methyl ester impurity (identified by reference to the chromatograms obtained with solutions (4) to (7)) are not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%) and the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing 0.1 g of Sulindac with 80 mL of 0.1M *methanolic hydrochloric acid* for 10 minutes and dilute to 100 mL with the same solvent. Filter and dilute 3 mL of the filtrate to 200 mL with the same

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solvent. Measure the *absorbance* of the resulting solution at the maximum at 327 nm, Appendix II B, and calculate the content of $C_{20}H_{17}FO_3S$ taking 373 as the value of A(1%, 1 cm) at the maximum at 327 nm.

STORAGE

Sulindac Tablets should be protected from light.

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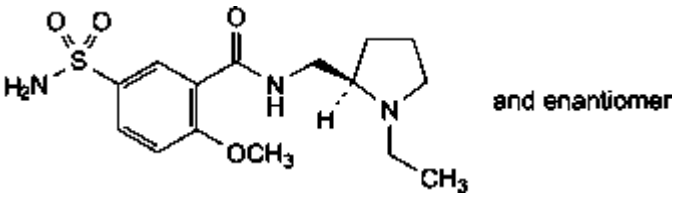
Sulpiride

General Notices

(Ph. Eur. monograph 1045)



and enantiomer

$C_{15}H_{23}N_3O_4S$ 341.4 *15676-16-1*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Sulpiride Tablets

Ph Eur

DEFINITION

N-[[(2*RS*)-1-Ethylpyrrolidin-2-yl)]methyl]-2-methoxy-5-sulfamoylbenzamide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

IDENTIFICATION

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First identification: B.

Second identification: A, C, D.

A. Melting point (2.2.14): 177 °C to 181 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *sulpiride CRS*.

C. Examine the chromatograms obtained in the test for impurity A.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To about 1 mg in a porcelain dish, add 0.5 mL of *sulfuric acid R* and 0.05 mL of *formaldehyde solution R*. Examined in ultraviolet light at 365 nm, the solution shows blue fluorescence.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method I*).

Dissolve 1.0 g in *dilute acetic acid R* and dilute to 10 mL with the same acid.

Impurity A. Thin-layer chromatography (2.2.27)

Test solution (a) Dissolve 0.20 g of the substance to be examined in *methanol R*, sonicate until dissolution is complete and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methanol R*.

Reference solution (a) Dissolve 20 mg of *sulpiride CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dissolve 5.0 mg of *sulpiride impurity A CRS* in *methanol R* and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *dioxan R*, *methanol R*, *methylene chloride R* (2:10:14:90 *V/V/V/V*).

Application 10 µL.

Development Over 1/2 of the plate.

Drying In air.

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Detection Examine in ultraviolet light at 254 nm for identification test C and then spray with *ninhydrin solution R*; heat at 100-105 °C for 15 min and examine in daylight.

Limit Test solution (a):

— *impurity A*: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *sulpiride impurity B CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 10 volumes of *acetonitrile R*, 10 volumes of *methanol R* and 80 volumes of a solution containing 6.8 g/L of *potassium dihydrogen phosphate R* and 1 g/L of *sodium octanesulfonate R*, previously adjusted to pH 3.3 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time Twice the retention time of sulpiride.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to sulpiride (retention time = about 15 min): impurity B = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity B and sulpiride.

Calculation of percentage contents:

— for each impurity, use the concentration of sulpiride in reference solution (a).

Limits:

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— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 100 ppm.

Shake 1.0 g with 20 mL of *water R*. Filter through a sintered-glass filter (40) (2.1.2). To 10 mL of the filtrate add 5 mL of *water R*.

Iron (2.4.9)

Maximum 10 ppm.

Ignite 1.0 g in a silica crucible. To the residue add 1 mL of *1 M hydrochloric acid*, 3 mL of *water R* and 0.1 mL of *nitric acid R*. Heat on a water-bath for about 5 min. Place the solution in a test-tube. Rinse the crucible with 4 mL of *water R*. Collect the rinsings in the test-tube and dilute to 10 mL with *water R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 34.14 mg of $C_{15}H_{23}N_3O_4S$.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, G.*

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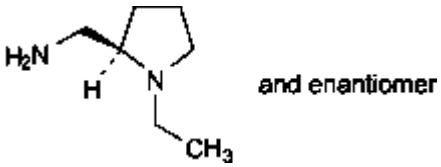
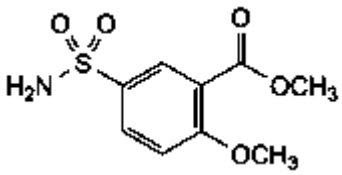
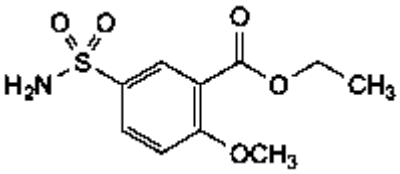


and enantiomer

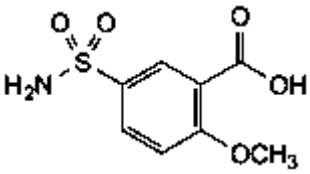
A. [(2*RS*)-1-ethylpyrrolidin-2-yl]methanamine,



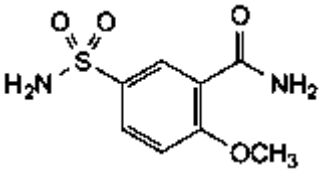
B. methyl 2-methoxy-5-sulfamoylbenzoate,



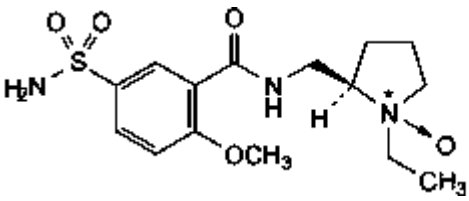
C. ethyl 2-methoxy-5-sulfamoylbenzoate,



D. 2-methoxy-5-sulfamoylbenzoic acid,



E. 2-methoxy-5-sulfamoylbenzamide,



and enantiomer

F. *N*-[[(2*RS*)-1-ethyl-1-oxidopyrrolidin-2-yl]methyl]-2-methoxy-5-sulfamoylbenzamide,

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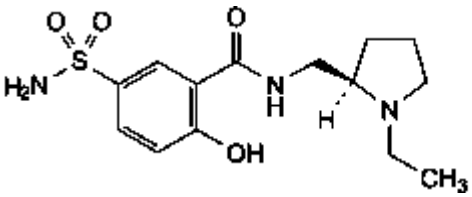

and enantiomer

G. *N*-[[(2*RS*)-1-éthylpyrrolidin-2-yl]méthyl]-2-hydroxy-5-sulfamoylbenzamide.

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Sulpiride Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Sulpiride Tablets contain Sulpiride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sulpiride, $C_{15}H_{23}N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 0.2 g of Sulpiride add 20 mL of *methanol*, shake for 5 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of sulpiride (*RS 391*).

Related substances

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 20 mL of *methanol* to a quantity of the powdered tablets containing 0.2 g of Sulpiride, shake for 5 minutes, filter, evaporate the filtrate to dryness and dissolve the residue in 10 mL of *methanol*.

(2) 0.02% w/v of *sulpiride impurity A EPCRS* in *methanol*.

(3) Dilute 1 volume of solution (2) to 10 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel HF_{254}* precoated plate (Analtech Uniplates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air, spray with *ninhydrin solution* and heat at 100° to 105° for 15 minutes.

MOBILE PHASE

2 volumes of 13.5M *ammonia*, 10 volumes of *1,4-dioxan*, 14 volumes of *methanol* and 90 volumes of *dichloromethane*.

LIMITS

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Any spot in the chromatogram obtained with solution (1) corresponding to the principal spot in the chromatogram obtained with solution (2) is not more intense than the spot in the chromatogram obtained with solution (3) (0.1%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of *methanol* to a quantity of the powdered tablets containing 0.2 g of Sulpiride, shake for 5 minutes, filter, evaporate the filtrate to dryness and dissolve the residue in sufficient of the mobile phase to produce 200 mL.

(2) Dilute 3 volumes of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 10 volumes with the mobile phase.

(3) 0.01% w/v of *sulpiride BPCRS* and 0.01% w/v of *sulpiride impurity B EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax RX C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) and solution (2) allow the chromatography to proceed for 2.5 times the retention time of sulpiride.

MOBILE PHASE

10 volumes of *acetonitrile*, 10 volumes of *methanol* and 80 volumes of a solution containing 6.8% w/v of *potassium dihydrogen orthophosphate* and 0.1% w/v of *sodium octanesulfonate*, adjusted to pH 3.3 using *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

ASSAY

Weigh and powder 20 tablets. Mix a quantity of the powder containing 0.1 g of Sulpiride with about 50 mL of 0.1M *sodium hydroxide* for 5 minutes with the aid of ultrasound, add sufficient 0.1M *sodium hydroxide* to produce 100 mL and filter, discarding the first 10 mL of filtrate. Dilute 5 mL of the filtrate to 100 mL with 0.1M *sodium hydroxide* and measure the *absorbance* of the solution at the maximum at 291 nm, Appendix II B, using 0.1M *sodium hydroxide* in the reference cell. Calculate the content of $C_{15}H_{23}N_3O_4S$ in the tablets from the *absorbance* of a 0.005% w/v solution of *sulpiride BPCRS* in 0.1M *sodium hydroxide* using the declared content of $C_{15}H_{23}N_3O_4S$ in *sulpiride BPCRS*.

IMPURITIES

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The impurities limited by the requirements of this monograph include those listed under Sulpiride.

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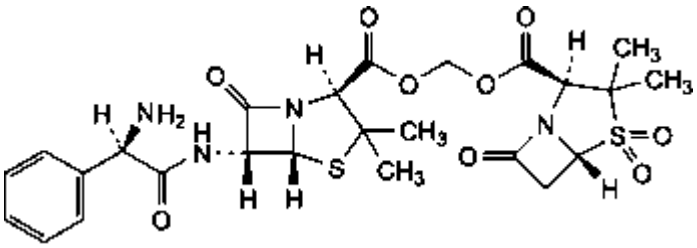
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Sultamicillin

General Notices

(Ph. Eur. monograph 2211)



$C_{25}H_{30}N_4O_9S_2$ 594.7 *76497-13-7*

Action and use

Beta-lactamase inhibitor.

Ph Eur

DEFINITION

Methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Practically insoluble in water, very slightly soluble in methanol, practically insoluble in ethanol (96 per cent).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison sultamicillin CRS.

TESTS

Specific optical rotation (2.2.7)

+ 190 to + 210 (anhydrous substance).

Dissolve 0.500 g in dimethylformamide R and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or keep at 2-8 °C for not more than 6 h.*

Solution A methanol R1, acetonitrile R1 (20:80 *V/V*).

Solution B Dissolve 1.56 g of sodium dihydrogen phosphate R in 900 mL of water R. Add 7.0 mL of phosphoric acid R and dilute to 1000 mL with water R.

Blank solution Solution B, solution A (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 35 mL of solution A and sonicate for about 1 min. Add 13 mL of solution B, mix and sonicate for about 1 min. Dilute to 50.0 mL with solution B and mix.

Reference solution (a) Dissolve 70.0 mg of sultamicillin tosilate CRS in 35 mL of solution A and sonicate for about 1 min. Add 13 mL of solution B, mix and sonicate for about 1 min. Dilute to 50.0 mL with solution B and mix.

Reference solution (b) Suspend 15 mg of sultamicillin tosilate CRS in 20 mL of a 0.4 g/L solution of sodium hydroxide R and sonicate in an ultrasonic bath for about 5 min. Add 20 mL of a 0.36 g/L solution of hydrochloric acid R and dilute to 100 mL with water R.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the blank solution.

Reference solution (d) Dissolve 17.3 mg of ampicillin trihydrate CRS (impurity C) and 15.0 mg of sulbactam CRS (impurity A) in water R and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with water R.

Reference solution (e) Dissolve 5 mg of sultamicillin for peak identification CRS (containing impurity G) in 7.0 mL of solution A and sonicate for about 1 min. Dilute to 10.0 mL with solution B, mix and sonicate for about 1 min.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (3.5 µm);

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— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: 4.68 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	95 → 30	5 → 70
15 - 16	30	70
16 - 16.5	30 → 95	70 → 5
16.5 - 20	95	5

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 5 µL of the blank solution, the test solution and reference solutions (b), (c), (d) and (e).

Identification of impurities Use the chromatogram supplied with *sultamicillin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peak due to impurity G.

Relative retention With reference to sultamicillin (retention time = about 9.3 min): impurity A = about 0.41; ampicillin penicilloic acid = about 0.47; impurity B = about 0.50; impurity C = about 0.55; impurity D = about 0.94; impurity E = about 1.09; impurity F = about 1.26; impurity G = about 1.42.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to ampicillin penicilloic acid and impurity B and minimum 2.5 between the peaks due to impurities B and C.

Limits:

— *impurity G*: not more than the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

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— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *impurities D, E, F*: for each impurity, not more than 0.3 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *any other impurity*: for each impurity, not more than 0.3 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *total*: not more than 3 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (3.0 per cent);

— *disregard limit*: 0.1 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.1 per cent).

Ethyl acetate

Head-space gas chromatography (2.2.28).

Test solution Dissolve 0.200 g in 7.0 mL of a mixture of 1 volume of water R and 99 volumes of dimethylformamide R.

Reference solution Dissolve 0.200 g of ethyl acetate R in 240 mL of a mixture of 1 volume of water R and 99 volumes of dimethylformamide R and dilute to 250.0 mL with the same mixture of solvents. Dilute 5.0 mL of this solution to 7.0 mL with a mixture of 1 volume of water R and 99 volumes of dimethylformamide R.

Close the vials immediately with a tight rubber membrane stopper coated with polytetrafluoroethylene and secure with an aluminium crimp cap. Shake to obtain a homogeneous solution.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.32 mm;

— *stationary phase*: methylpolysiloxane R (film thickness: 1.8 µm or 3 µm).

Carrier gas helium for chromatography R.

Linear velocity 35 cm/s.

Split ratio 1:5.

Static head-space conditions that may be used:

— *equilibration temperature*: 105 °C;

— *equilibration time*: 45 min;

— *transfer-line temperature*: 110 °C;

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— *pressurisation time*: 30 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	70
	6 - 16	70 → 220
	16 - 18	220
Injection port		140
Detector		250

Detection Flame ionisation.

Injection 1 mL.

Relative retention With reference to dimethylformamide (retention time = about 14 min): ethyl acetate = about 0.7.

Limit:

— *ethyl acetate*: maximum 2.5 per cent.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.50 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

Calculate the percentage content of sultamicillin ($C_{25}H_{30}N_4O_9S_2$) from the declared content of $C_{25}H_{30}N_4O_9S_2$ in *sultamicillin tosilate CRS* and by multiplying the sultamicillin tosilate content by 0.7752.

STORAGE

In an airtight container.

IMPURITIES

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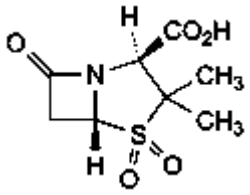
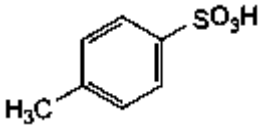
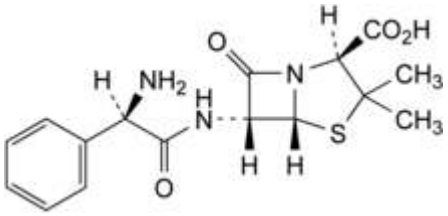
Specified impurities *A, B, C, D, E, F, G.*



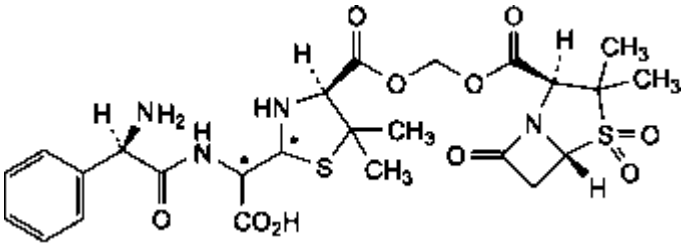
A. (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (sulbactam),



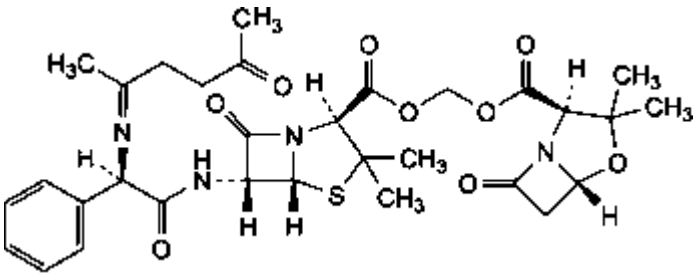
B. 4-methylbenzenesulfonic acid (*p*-toluenesulfonic acid),



C. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (ampicillin),



D. [[(2*R*)-aminophenylacetyl]amino][(4*S*)-4-[[[[[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetic acid (penicilloic acids of sultamicillin),



E. methylene (2*S*,5*R*,6*R*)-3,3-dimethyl-6-[[(2*R*)-[(1-methyl-4-oxopentylidene)amino]phenylacetyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate,

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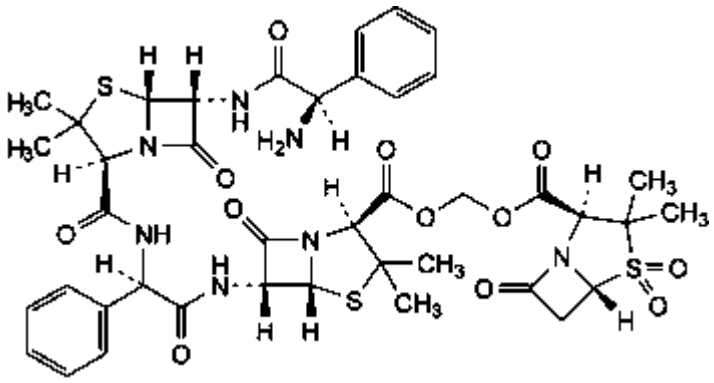
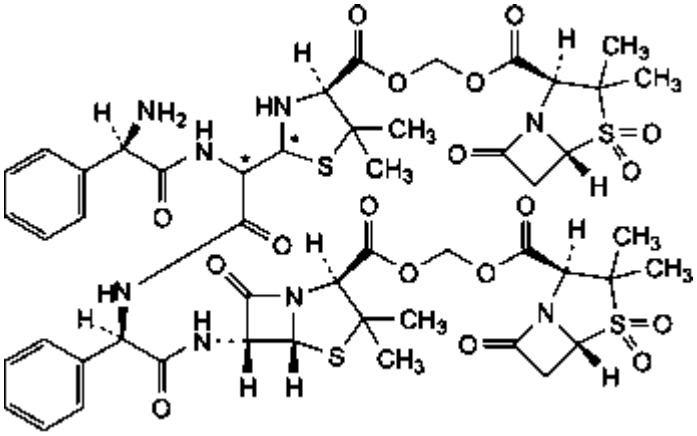


F. methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-[[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (ampicillin sultamicillin amide),



G. methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-[[[[(2*R*)-aminophenylacetyl]amino][(4*S*)-4-[[[[[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (sultamicillin dimer).

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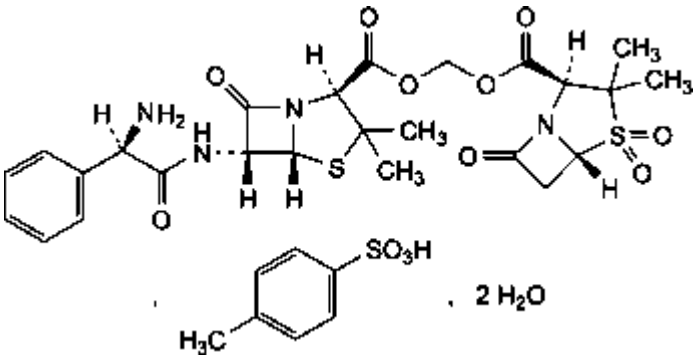
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Sultamicillin Tosilate Dihydrate

General Notices

(Ph. Eur. monograph 2212)



$C_{32}H_{38}N_4O_{12}S_3,2H_2O$ 803

Action and use

Beta-lactamase inhibitor.

Ph Eur

DEFINITION

4-Methylbenzenesulfonate of methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate dihydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl toluenesulfonate esters are genotoxic and are potential impurities in sultamicillin tosilate dihydrate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method 2.5.40. *Methyl, ethyl and isopropyl toluenesulfonate in active substances* is available to assist manufacturers.

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CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison sultamicillin tosilate CRS.

TESTS

Specific optical rotation (2.2.7)

+ 178 to + 195 (anhydrous substance).

Dissolve 1.000 g in dimethylformamide R and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or keep at 2-8 °C for not more than 6 h.*

Solution A methanol R1, acetonitrile R1 (20:80 *V/V*).

Solution B Dissolve 1.56 g of sodium dihydrogen phosphate R in 900 mL of water R. Add 7.0 mL of phosphoric acid R and dilute to 1000 mL with water R.

Blank solution Solution B, solution A (30:70 *V/V*).

Test solution Dissolve 70.0 mg of the substance to be examined in 35 mL of solution A and sonicate for about 1 min. Add 13 mL of solution B, mix and sonicate for about 1 min. Dilute to 50.0 mL with solution B and mix.

Reference solution (a) Dissolve 70.0 mg of sultamicillin tosilate CRS in 35 mL of solution A and sonicate for about 1 min. Add 13 mL of solution B, mix and sonicate for about 1 min. Dilute to 50.0 mL with solution B and mix.

Reference solution (b) Suspend 15 mg of the substance to be examined in 20 mL of a 0.4 g/L solution of sodium hydroxide R and sonicate in an ultrasonic bath for about 5 min. Add 20 mL of a 0.36 g/L solution of hydrochloric acid R and dilute to 100.0 mL with water R.

Reference solution (c) Dissolve 0.200 g of the substance to be examined in 70.0 mL of solution A and sonicate for about 1 min. Add 25.0 mL of solution B, mix and sonicate for about 1 min. Dilute to 100.0 mL with solution B and mix. Dilute 1.0 mL of this solution to 100.0 mL with the blank solution.

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Reference solution (d) Dissolve 32.3 mg of *ampicillin trihydrate CRS* (impurity B) and 7.0 mg of *sulbactam CRS* (impurity A) in *water R* and dilute to 1000 mL with the same solvent.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: 4.68 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	95 → 30	5 → 70
15 - 16	30	70
16 - 16.5	30 → 95	70 → 5
16.5 - 20	95	5

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 5 µL of the blank solution, the test solution and reference solutions (b), (c) and (d).

Relative retention With reference to sultamicillin (retention time = about 9.3 min): impurity A = about 0.41; ampicillin penicilloic acid = about 0.47; tosilate = about 0.50; impurity B = about 0.55; impurity C = about 0.94; impurity D = about 1.09; impurity F = about 1.23; impurity E = about 1.26; impurity G = about 1.42.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to ampicillin penicilloic acid and tosilate and minimum 2.5 between the peaks due to tosilate and impurity B.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (2.0 per cent);

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— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *impurities C, D, E, F, G*: for each impurity, not more than 0.5 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *any other impurity*: for each impurity, not more than 0.5 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *total*: not more than 4 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (4.0 per cent);

— *disregard limit*: 0.1 times the area of the peak due to sultamicillin in the chromatogram obtained with reference solution (c) (0.1 per cent).

Ethyl acetate

Head-space gas chromatography (2.2.28).

Test solution Dissolve 0.200 g in 7.0 mL of a mixture of 1 volume of water R and 99 volumes of dimethylformamide R.

Reference solution Dissolve 0.200 g of ethyl acetate R in 240 mL of a mixture of 1 volume of water R and 99 volumes of dimethylformamide R and dilute to 250.0 mL with the same mixture of solvents. Dilute 5.0 mL of this solution to 7.0 mL with a mixture of 1 volume of water R and 99 volumes of dimethylformamide R.

Immediately close the vials with a tight rubber membrane stopper coated with polytetrafluoroethylene and secure with an aluminium crimp cap. Shake to obtain a homogeneous solution.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.32 mm;

— *stationary phase*: methylpolysiloxane R (film thickness: 1.8 µm or 3 µm).

Carrier gas helium for chromatography R.

Linear velocity 35 cm/s.

Split ratio 1:5.

Static head-space conditions that may be used:

— *equilibration temperature*: 105 °C;

— *equilibration time*: 45 min;

— *transfer-line temperature*: 110 °C;

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— *pressurisation time*: 30 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	70
	6 - 16	70 → 220
	16 - 18	220
Injection port		140
Detector		250

Detection Flame ionisation.

Injection 1 mL.

Relative retention With reference to dimethylformamide (retention time = about 14 min): ethyl acetate = about 0.7.

Limit:

— *ethyl acetate*: maximum 2.0 per cent.

Water (*2.5.12*)

4.0 per cent to 6.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of sultamicillin tosilate ($C_{32}H_{38}N_4O_{12}S_3$) from the declared content of *sultamicillin tosilate CRS*.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

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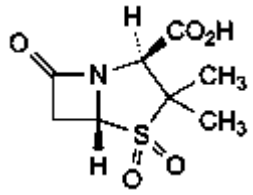
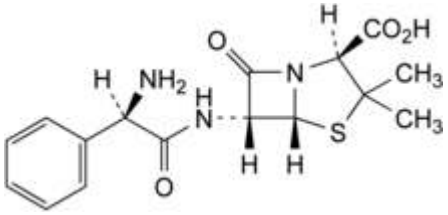
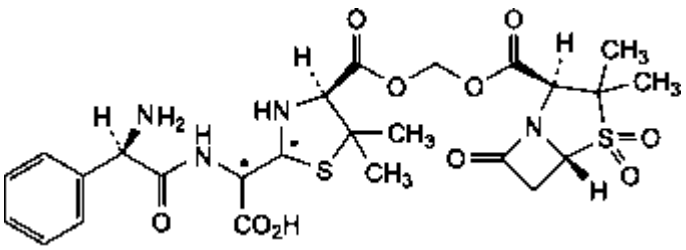


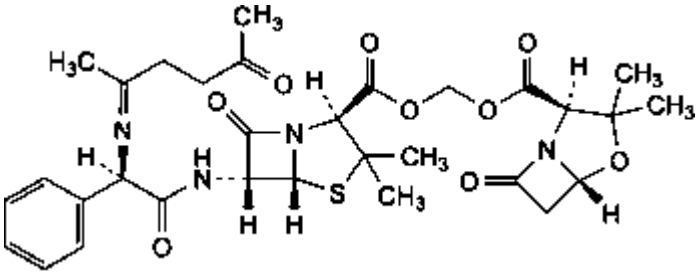
A. (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (sulbactam),



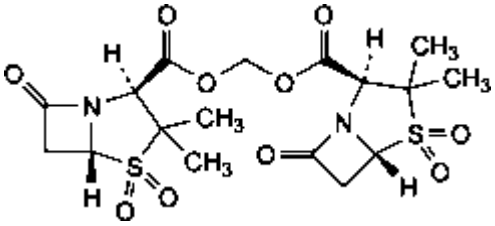
B. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (ampicillin),



C. [[(2*R*)-aminophenylacetyl]amino][(4*S*)-4-[[[[[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetic acid (penicilloic acids of sultamicillin),



D. methylene (2*S*,5*R*,6*R*)-3,3-dimethyl-6-[[(2*R*)-[(1-methyl-4-oxopentylidene)amino]phenylacetyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate,



E. methylene bis[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] (sulbactam methylene ester),

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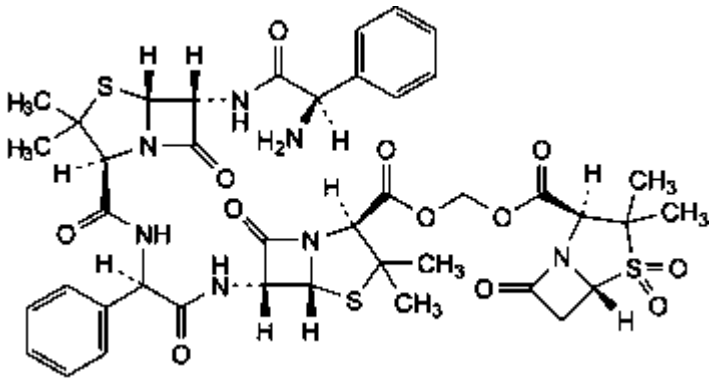
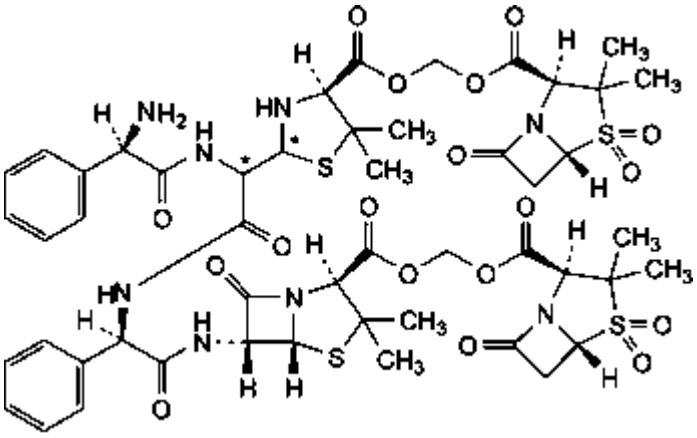


F. methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-[[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (ampicillin sultamicillin amide),



G. methylene (2*S*,5*R*,6*R*)-6-[[(2*R*)-[[[[(2*R*)-amino-phenylacetyl]amino][(4*S*)-4-[[[[[(2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]hept-2-yl]-carbonyl]oxy]methoxy]carbonyl]-5,5-dimethylthiazolidin-2-yl]acetyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2*S*,5*R*)-3,3-dimethyl-4,4,7-trioxo-4λ^6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (sultamicillin dimer).

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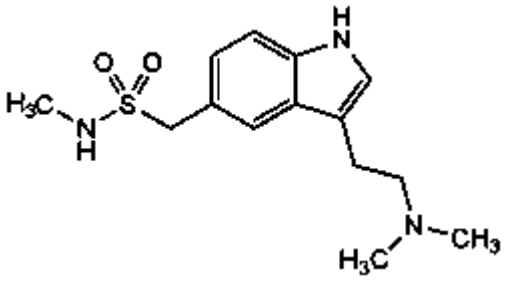
Sumatriptan

General Notices



$C_{14}H_{21}N_3O_2S$ 295.4 *103628-46-2*

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

Preparation

Sumatriptan Nasal Spray

DEFINITION

Sumatriptan is 3-(2-dimethylaminoethyl)indol-5-yl-*N*-methylmethanesulfonamide. It contains not less than 97.5% and not more than 102.0% of $C_{14}H_{21}N_3O_2S$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white to pale yellow powder. Very slightly soluble in *water*.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of sumatriptan *(RS 414)*.

TESTS

The total impurity content in the test for Impurities A and H and the test for Related substances is not greater than 1.5%.

Impurities A and H

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Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume of *acetonitrile* (solution A).

(1) 0.2% w/v of the substance being examined.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute the contents of a vial of *sumatriptan for system suitability EPCRS* to 1 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Spherisorb silica S5W is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 5 times the retention time of the principal peak.

MOBILE PHASE

10 volumes of 10M *ammonium acetate* and 90 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles that supplied with *sumatriptan for system suitability EPCRS* and the *resolution* between impurity A and sumatriptan is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.6%; taking into account the correction factor of 0.6 for impurity A);

the area of any peak due to impurity H is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume of *acetonitrile* (solution A).

(1) 0.2% w/v of the substance being examined.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume of the resulting solution to 10 volumes.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mix 25 volumes of *acetonitrile* with 75 volumes of a solution containing 0.97 g of *dibutylamine*, 0.735 g of *orthophosphoric acid* and 2.93 g of *sodium dihydrogen orthophosphate* in 750 mL *water*, adjust to pH 6.5 with 10M *sodium hydroxide* and dilute to 1000 mL with *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and sumatriptan is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the areas of any peaks corresponding to impurities B, C and D are not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Water

Not more than 1.0% w/w, Appendix IX C. Use 1.0 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D. Prepare solutions (1) and (2) in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume of *acetonitrile* (solution A).

(1) 0.01% w/v of the substance being examined.

(2) 0.014% w/v of *sumatriptan succinate BPCRS*.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL with the mobile phase .

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

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The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and sumatriptan is at least 1.5.

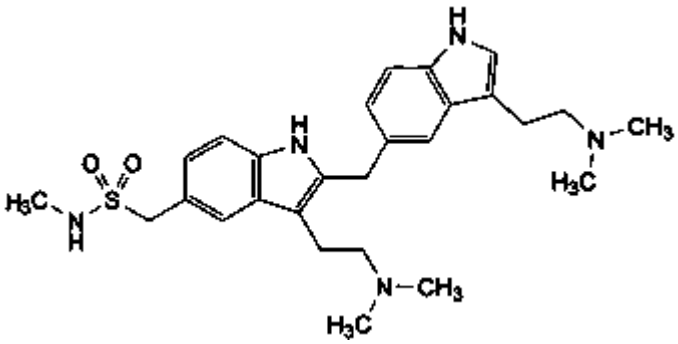
DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{21}N_3O_2S$ using the declared content of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ in *sumatriptan succinate BPCRS*. Each 1 mg of $C_{14}H_{21}N_3O_2S$ is equivalent to 1.4 mg of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$.

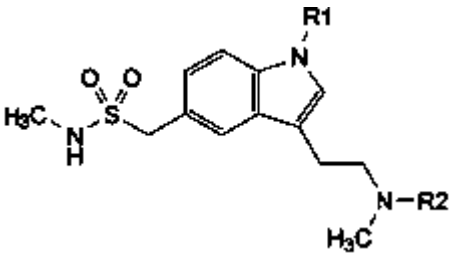
STORAGE

Sumatriptan should be protected from light.

IMPURITIES

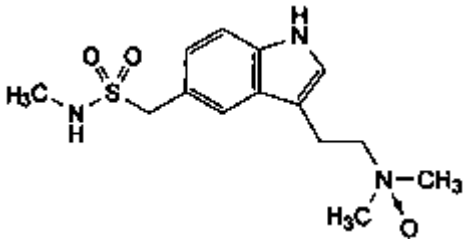


A. [3-[2-(dimethylamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide,



B. R1 = R2 = H: *N*-methyl[3-[2-(methylamino)ethyl]-1*H*-indol-5-yl]methanesulfonamide,

C. R1 = CH_2-OH, R2 = CH_3: [3-[2-(dimethylamino)ethyl]-1-(hydroxymethyl)-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide,



D. *N*,*N*-dimethyl-2-[5-[(methylsulfamoyl)methyl]-1*H*-indol-3-yl]ethanamine *N*-oxide,

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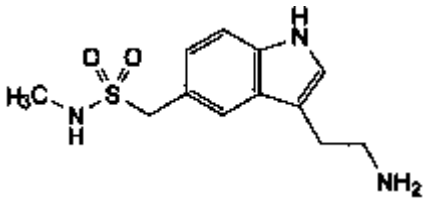
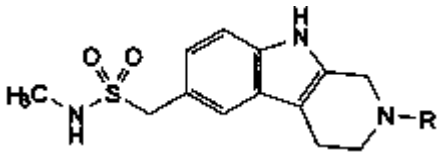
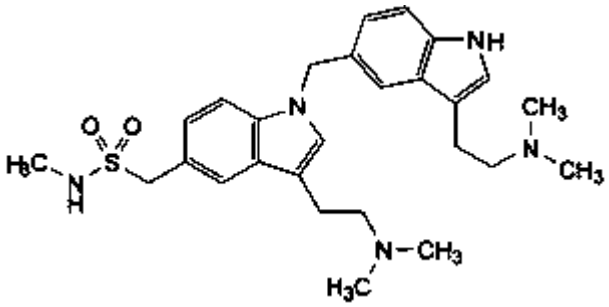


E. [3-(2-aminoethyl)-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide,



F. R = H: *N*-methyl(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-6-yl)methanesulfonamide,

G. R = CH_3: *N*-methyl(2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-6-yl)methanesulfonamide,



H. [3-[2-(dimethylamino)ethyl]-1-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide.

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Sumatriptan Injection

General Notices

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

DEFINITION

Sumatriptan Injection is a sterile isotonic solution of Sumatriptan Succinate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of sumatriptan, $C_{14}H_{21}N_3O_2S$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless to pale yellow solution.

IDENTIFICATION

To a volume of the injection containing the equivalent of 29 mg of sumatriptan add 1 mL of *saturated sodium chloride solution* and 1 mL of *saturated sodium carbonate solution*. Shake vigorously for 30 seconds, add two 2-mL quantities of *propan-2-ol*, shake, allow to separate (this may take up to 24 hours) and discard the aqueous layer. Evaporate under a stream of nitrogen and dry at 100°. The *infrared absorption spectrum* is concordant with the *reference spectrum* of sumatriptan (*RS 414*).

TESTS

Acidity

pH, 4.2 to 5.3, Appendix V L.

Impurities A and H

Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume of *acetonitrile*.

(1) Dilute the injection, if necessary, to contain the equivalent of 0.214% w/v of sumatriptan.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute the contents of a vial of *sumatriptan for system suitability EPCRS* to 1 mL.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (Spherisorb silica S5W is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 5 times the retention time of the principal peak.

MOBILE PHASE

10 volumes of 10M *ammonium acetate* and 90 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3):

the chromatogram resembles that supplied with *sumatriptan for system suitability EPCRS*;

the *resolution* between impurity A and sumatriptan is at least 1.5.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity A using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity A by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity H is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume *acetonitrile*.

(1) Dilute the injection, if necessary, to contain the equivalent of 0.214% w/v of sumatriptan.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution containing 0.97 g of *dibutylamine*, 0.735 g of *orthophosphoric acid* and 2.93 g of *sodium dihydrogen orthophosphate* in 750 mL of *water*, adjusted to pH 7.5 with 10M *sodium hydroxide* and diluted to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions the retention times with reference to sumatriptan (retention time about 17 minutes) are: impurity D, about 0.2; impurity 2, about 0.3; impurity 1, about 0.4; impurity E, about 0.5; impurity B, about 0.6; impurity F, about 0.7 and impurity C, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained solution (3), the *resolution* between impurity C and sumatriptan is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurity 1 and impurity 2 using the reference chromatogram for *sumatriptan impurity standard BPCRS*. Multiply the area of any peak corresponding to impurity 1 by a correction factor of 0.2 and multiply the area of any peak corresponding to impurity 2 by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

The total impurity content in the test for Impurities A and H and the test for Related substances is not greater than 4.0%.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing the equivalent of 3.6 mg of sumatriptan per mL (solution A). The endotoxin limit concentration is less than 350.0 IU of endotoxin per mL.

ASSAY

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Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume of *acetonitrile*.

(1) Dilute the injection to contain the equivalent of 0.021% w/v of sumatriptan.

(2) 0.03% w/v of *sumatriptan succinate BPCRS*.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and sumatriptan is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{21}N_3O_2S$ in the injection using the declared content of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ in *sumatriptan succinate BPCRS*. 1 mg of $C_{14}H_{21}N_3O_2S$ is equivalent to 1.400 mg of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$.

STORAGE

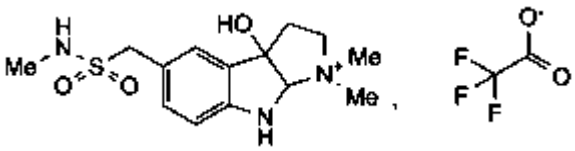
Sumatriptan Injection should be protected from light.

LABELLING

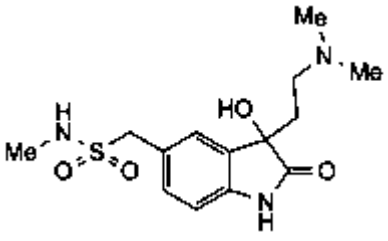
The quantity of the active ingredient is stated in terms of the equivalent amount of sumatriptan.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sumatriptan Succinate and the following:



1. 3a-hydroxy-1,1-dimethyl-5-{[(methylamino)sulfonyl]methyl}-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-1-ium trifluoroacetate,



2. 1-{3-[2-(dimethylamino)ethyl]-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-5-yl}-*N*-methylmethanesulfonamide.

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Sumatriptan Nasal Spray

General Notices

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

DEFINITION

Sumatriptan Nasal Spray is a solution of Sumatriptan containing suitable buffering agents in a suitable container fitted with a suitable nasal delivery system.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of sumatriptan, $C_{14}H_{21}N_3O_2S$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A clear, pale to dark yellow solution.

IDENTIFICATION

To a volume of nasal spray containing 40 mg of Sumatriptan add 1 mL of *saturated sodium chloride solution* and 1 mL of *saturated sodium carbonate solution*. Shake vigorously for 30 seconds, add two 2-mL quantities of *propan-2-ol*, shake, allow to separate and discard the aqueous layer. The separation may take up to 24 hours. Evaporate under a stream of nitrogen and dry at 100°.

The *infrared absorption spectrum* is concordant with the *reference spectrum* of sumatriptan *(RS 414)*.

TESTS

Acidity

pH, 5.0 to 6.0, Appendix V L.

Impurities A and H

Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5 and 1 volume of *acetonitrile*.

(1) Dilute the nasal spray, if necessary, to contain 0.1% w/v of Sumatriptan.

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(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Dilute the contents of a vial of *sumatriptan for system suitability EPCRS* to 1 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Spherisorb silica S5W is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of the principal peak.

MOBILE PHASE

10 volumes of 10M *ammonium acetate* and 90 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles that supplied with *sumatriptan for system suitability EPCRS* and the *resolution* between impurity A and sumatriptan is at least 1.5.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity A using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity A by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 3 times the area of the principal peak obtained in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity H is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume of *acetonitrile*.

(1) Dilute the nasal spray, if necessary, to contain 0.1% w/v of Sumatriptan.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

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(b) Use isocratic elution and the mobile phase below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution containing 0.97 g of *dibutylamine*, 0.735 g of *orthophosphoric acid* and 2.93 g of *sodium dihydrogen orthophosphate* in 750 mL *water*, adjusted to pH to 6.5 with 10M *sodium hydroxide* and diluted to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to sumatriptan (retention time about 17 minutes) are: impurity D, about 0.2; impurity 2, about 0.3; impurity 1, about 0.4; impurity E, about 0.5; impurity B, about 0.6; impurity F, about 0.7 and impurity C, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and sumatriptan is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurity 1 and impurity 2 using the reference chromatogram for *sumatriptan impurity standard BPCRS*. Multiply the area of any peak corresponding to impurity 1 by a correction factor of 0.2 and multiply the area of any peak corresponding to impurity 2 by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

The total impurity content in the test for Impurities A and H and the test for Related substances is not greater than 4.0%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D. Prepare the solutions in a mixture containing 3 volumes of 0.025M *sodium dihydrogen orthophosphate*, the pH of which has been adjusted to 6.5, and 1 volume of *acetonitrile*.

(1) Dilute the nasal spray, if necessary, to contain 0.05% w/v of Sumatriptan.

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(2) 0.07% w/v of *sumatriptan succinate BPCRS*.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

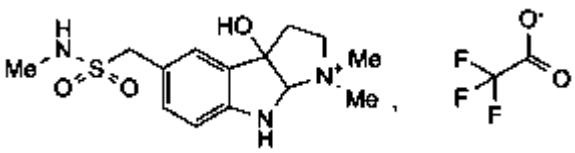
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and sumatriptan is at least 1.5.

DETERMINATION OF CONTENT

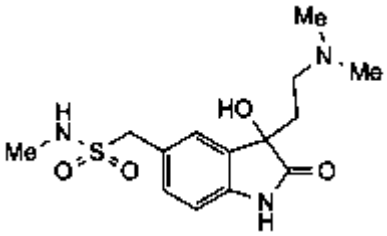
Calculate the content of $C_{14}H_{21}N_3O_2S$ using the declared content of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ in *sumatriptan succinate BPCRS*. 1 mg of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ is equivalent to 0.714 mg of $C_{14}H_{21}N_3O_2S$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sumatriptan Succinate and the following:



1. 3a-hydroxy-1,1-dimethyl-5-{[methylamino)sulfonyl]methyl}-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-1-ium trifluoroacetate];



2. 1-{3-[2-(dimethylnitroyl)ethyl]-1*H*-indol-5-yl}-*N*-methylmethanesulfonamide.

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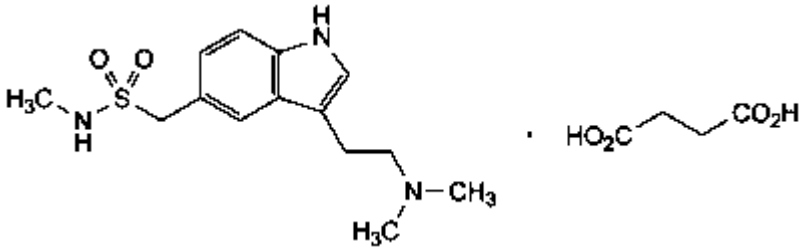
Sumatriptan Succinate

General Notices

(Ph. Eur. monograph 1573)



$C_{18}H_{27}N_3O_6S$ 413.5 *103628-48-4*

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

Preparations

Sumatriptan Injection

Sumatriptan Tablets

Ph Eur

DEFINITION

1-[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide hydrogen butanedioate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *sumatriptan succinate CRS*.

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

pH (2.2.3)

4.5 to 5.3.

Dilute 2.5 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Absorbance (2.2.25)

Maximum 0.10, determined at 440 nm on solution S.

Impurities A and H

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 3 mg of *sumatriptan for system suitability CRS* (containing impurities A and H) in the mobile phase and dilute to 1.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm).

Mobile phase Mix 10 volumes of a 771 g/L solution of *ammonium acetate R* and 90 volumes of *methanol R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 282 nm.

Injection 20 µL.

Run time 5 times the retention time of sumatriptan.

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Identification of impurities Use the chromatogram supplied with *sumatriptan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and H.

Relative retention With reference to sumatriptan (retention time = about 2 min): impurity A = about 1.9; impurity H = about 2.6.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities A and H.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.6;

— *impurity A*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *impurity H*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solution A Dissolve 2.925 g of *sodium dihydrogen phosphate R* in 600 mL of *water R*, adjust to pH 6.5 with *strong sodium hydroxide solution R*, dilute to 750 mL with *water R*, add 250 mL of *acetonitrile R* and mix.

Test solution (a) Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Test solution (b) Dissolve 15.0 mg of the substance to be examined in solution A and dilute to 100.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *sumatriptan impurity mixture CRS* (containing impurities B, C, D and E) in the mobile phase and dilute to 1 mL with the mobile phase.

Reference solution (c) Dissolve 15.0 mg of *sumatriptan succinate CRS* in solution A and dilute to 100.0 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 25 volumes of *acetonitrile R* with 75 volumes of a solution prepared as follows: dissolve 0.970 g of *dibutylamine R*, 0.735 g of *phosphoric acid R* and 2.93 g of *sodium dihydrogen phosphate R* in 750 mL of *water R*, adjust to pH 6.5 with *strong sodium hydroxide solution R* and dilute to 1000 mL with *water R*.

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 282 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Run time 4 times the retention time of sumatriptan.

Identification of impurities Use the chromatogram supplied with *sumatriptan impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D and E.

Relative retention With reference to sumatriptan (retention time = about 7 min): impurity E = about 0.5; impurity B = about 0.6; impurity D = about 0.7; impurity C = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity C and sumatriptan;

— the chromatogram shows 5 clearly separated peaks.

Limits:

— *impurities B, C, D*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity E*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{18}H_{27}N_3O_6S$ taking into account the assigned content of *sumatriptan succinate CRS*.

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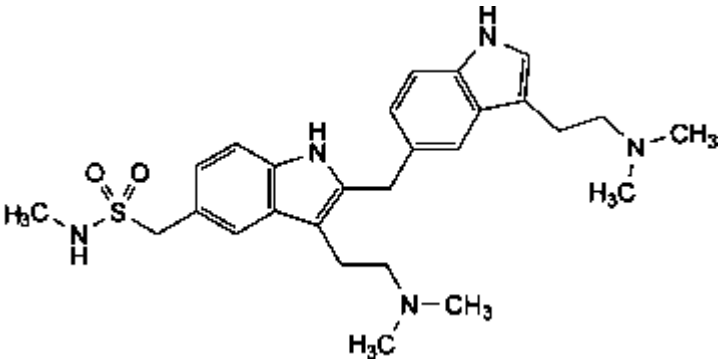
STORAGE

Protected from light.

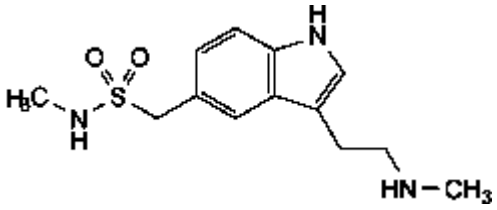
IMPURITIES

Specified impurities *A, B, C, D, E, H*.

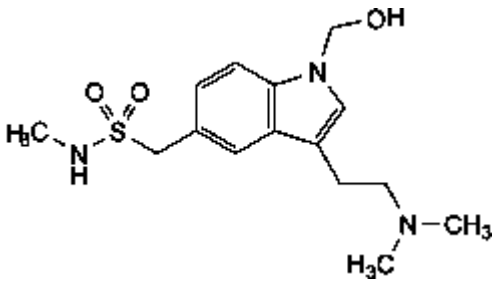
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F, G*.



A. 1-[3-[2-(dimethylamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide,



B. *N*-methyl-1-[3-[2-(methylamino)ethyl]-1*H*-indol-5-yl]methanesulfonamide,



C. 1-[3-[2-(dimethylamino)ethyl]-1-(hydroxymethyl)-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide,

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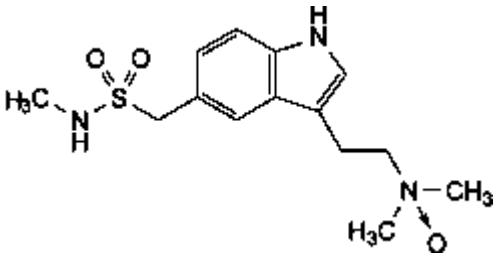
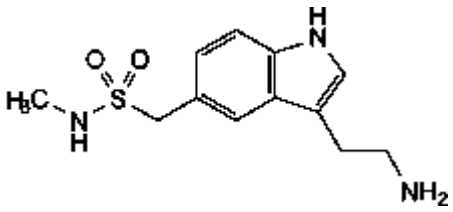
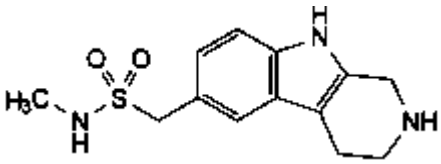


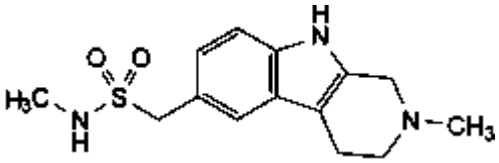
D. *N*,*N*-dimethyl-2-[5-[(methylsulfamoyl)methyl]-1*H*-indol-3-yl]ethan-1-amine *N*-oxide,



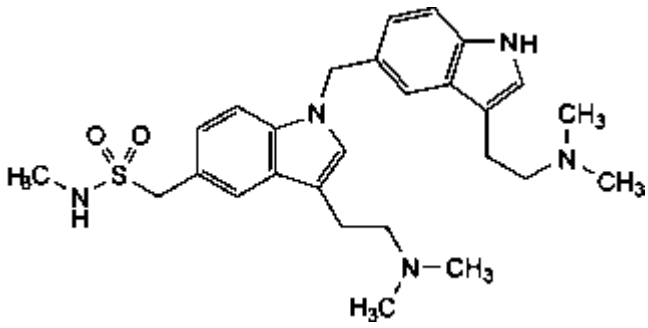
E. 1-[3-(2-aminoethyl)-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide,



F. *N*-methyl-1-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-6-yl)methanesulfonamide,



G. *N*-methyl-1-(2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-6-yl)methanesulfonamide,



H. 1-[3-[2-(dimethylamino)ethyl]-1-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfon amide.

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Sumatriptan Tablets

General Notices

Action and use

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

DEFINITION

Sumatriptan Tablets contain Sumatriptan Succinate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sumatriptan, $C_{14}H_{21}N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Add 10 mL of *methanol* to a quantity of powdered tablets containing the equivalent of 70 mg of sumatriptan, mix with the aid of ultrasound for 5 minutes, filter through a 0.45-µm PTFE filter, evaporate the filtrate and dry under reduced pressure for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of sumatriptan succinate (*RS 413*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 15 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, to give a solution expected to contain the equivalent of 0.0011% w/v of sumatriptan, at the maximum at 282 nm, Appendix II B using *water* in the reference cell.

(2) Measure the *absorbance*, of 0.0013% w/v solution of *sumatriptan succinate BPCRS* in *water* using *water* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of $C_{14}H_{21}N_3O_2S$, in the medium from the absorbances obtained and using the declared content of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ in *sumatriptan succinate BPCRS*. 1 mg of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ is equivalent to 0.714 mg of $C_{14}H_{21}N_3O_2S$.

Impurities A and H

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 100 mL of *0.1M hydrochloric acid* to a quantity of the powdered tablets containing the equivalent of 0.14 g of sumatriptan, mix with the aid of ultrasound and filter through a 0.45-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with *0.1M hydrochloric acid* and dilute 3 volumes of the resulting solution to 4 volumes with the same solvent.

(3) Dilute the contents of a vial of *sumatriptan for system suitability EPCRS* to 1 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (Spherisorb silica S5W is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 5 times the retention time of the principal peak.

MOBILE PHASE

10 volumes of 10M *ammonium acetate* and 90 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, using solution (3):

the chromatogram resembles that supplied with *sumatriptan for system suitability EPCRS*;

the *resolution* between impurity A and sumatriptan is at least 1.5.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity A using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity A by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.75%);

the area of any peak corresponding to impurity H is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 100 mL of *0.1M hydrochloric acid* to a quantity of the powdered tablets containing the equivalent of 0.14 g of sumatriptan, mix with the aid of ultrasound and filter through a 0.45-µm PTFE filter.

(2) Dilute 3 volumes of solution (1) to 100 volumes with *0.1M hydrochloric acid* and dilute 1 volume of the resulting solution to 10 volumes with *0.1M hydrochloric acid*.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 282 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution containing 0.97 g of *dibutylamine*, 0.735 g of *orthophosphoric acid* and 2.93 g of *sodium dihydrogen orthophosphate* in 750 mL of *water*, adjusted to pH 7.5 with 10M *sodium hydroxide* and diluted to 1000 mL with *water*.

SYSTEM SUITABILITY

The test is not valid unless in solution (3):

the chromatogram resembles that supplied with *sumatriptan impurity mixture EPCRS*;

the *resolution* between impurity C and sumatriptan is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peaks corresponding to impurities B, C or D is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%);

the area of any other *secondary peak* is not greater than area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

Disregard any peak with an area less than a third of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

The total impurity content in the test for Impurities A and H and the test for Related substances is not greater than 2.0%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Add 100 mL of *0.1M hydrochloric acid* to a quantity of the powdered tablets containing the equivalent of 0.1429 g of sumatriptan, mix with the aid of ultrasound, filter through a 0.45-µm PTFE filter and dilute 1 volume to 10 volumes with *0.1M hydrochloric acid*.

(2) 0.02% w/v of *sumatriptan succinate BPCRS* in *0.1M hydrochloric acid*.

(3) Dilute the contents of a vial of *sumatriptan impurity mixture EPCRS* to 1 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity C and sumatriptan is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{21}N_3O_2S$ in the tablets using the declared content of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ in *sumatriptan succinate BPCRS.* 1 mg of $C_{14}H_{21}N_3O_2S,C_4H_6O_4$ is equivalent to 0.714 mg of $C_{14}H_{21}N_3O_2S$.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of sumatriptan.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sumatriptan Succinate.

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Surgical Spirit

General Notices

DEFINITION

Methyl Salicylate	5 mL
Diethyl Phthalate	20 mL
Castor Oil	25 mL
Industrial Methylated Spirit	Sufficient to produce 1000 mL

The spirit complies with the requirements stated under Spirits and with the following requirements.

Content of methyl salicylate, $C_8H_8O_3$

0.45 to 0.55% v/v.

Content of diethyl phthalate, $C_{12}H_{14}O_4$

1.80 to 2.20% v/v.

IDENTIFICATION

A. To 1 mL add 0.5 mL of 0.4M *iron(III) chloride hexahydrate*. A violet colour is produced.

B. To 1 mL add 50 mg of *resorcinol* and 1 mL of *sulfuric acid*, heat for 1 minute, cool, pour into *water* and make alkaline with 5M *sodium hydroxide*. A distinct green fluorescence is produced which disappears when the solution is made acidic and reappears when it is made alkaline.

TESTS

Weight per mL

0.817 to 0.827 g, Appendix V G.

ASSAY

For methyl salicylate

Dilute 5 mL to 100 mL with *absolute ethanol*, further dilute 10 mL of this solution to 100 mL with *absolute ethanol* and measure the *absorbance* of the resulting solution at the maximum at 306 nm, Appendix II B. Calculate the content of $C_8H_8O_3$ taking 335 as the value of the *absorbance* of a 1% v/v solution of methyl salicylate at the maximum at 306 nm using a 1 cm cell.

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For diethyl phthalate

Further dilute 10 mL of the final solution prepared in the Assay for methyl salicylate to 50 mL with *absolute ethanol* and measure the *absorbance* of the resulting solution at 227 nm, Appendix II B. Subtract from the observed absorbance the absorbance due to the methyl salicylate present, as determined above, taking 432 as the value of the *absorbance* of a 1% v/v solution of methyl salicylate using a 1 cm cell. For the purposes of calculation take 419 as the value of the *absorbance* of a 1% v/v solution of diethyl phthalate at 227 nm using a 1 cm cell.

LABELLING

The label states that the preparation is flammable and should be kept away from a naked flame.

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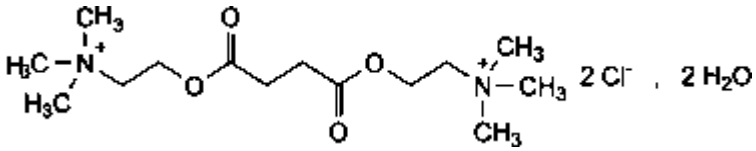
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Suxamethonium Chloride

General Notices

(Ph. Eur. monograph 0248)



$C_{14}H_{30}Cl_2N_2O_4,2H_2O$ 397.3 *6101-15-1*

Action and use

Depolarizing neuromuscular blocker.

Preparation

Suxamethonium Chloride Injection

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DEFINITION

Suxamethonium chloride contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 2,2′-[butanedioylbis(oxy)]bis(*N,N,N*-trimethylethanaminium) dichloride, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, hygroscopic, freely soluble in water, slightly soluble in ethanol (96 per cent).

It melts at about 160 °C, determined without previous drying.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *suxamethonium chloride CRS*. Examine the substances prepared as discs.

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B. To 1 mL of solution S (see Tests) add 9 mL of *water R*, 10 mL of *dilute sulfuric acid R* and 30 mL of *ammonium reineckate solution R*. A pink precipitate is formed. Allow to stand for 30 min, filter, wash with *water R*, with *alcohol R* and then with *ether R* and dry at 80 °C. The melting point (*2.2.14*) of the precipitate is 180 °C to 185 °C.

C. Dissolve about 25 mg in 1 mL of *water R* and add 0.1 mL of a 10 g/L solution of *cobalt chloride R* and 0.1 mL of *potassium ferrocyanide solution R*. A green colour is produced.

D. About 20 mg gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*). Dilute 4 mL of solution S to 10 mL with *water R*. The solution is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*. The pH of the solution is 4.0 to 5.0.

Choline chloride

Examine by thin-layer chromatography (*2.2.27*), using *cellulose for chromatography R1* as the coating substance.

Test solution Dissolve 0.4 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.4 g of *suxamethonium chloride CRS* and 2 mg of *choline chloride R* in *methanol R* and dilute to 10 mL with the same solvent.

Apply to the plate 5 µL of each solution. Prepare the mobile phase as follows: shake together for 10 min, 10 volumes of *anhydrous formic acid R*, 40 volumes of *water R* and 50 volumes of *butanol R*; allow to stand and use the upper layer. Develop over a path of 15 cm. Dry the plate in a current of air and spray with *potassium iodobismuthate solution R*. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot corresponding to choline chloride in the chromatogram obtained with the reference solution (0.5 per cent). The test is not valid unless the chromatogram obtained with the reference solution shows two clearly separated spots.

Water (*2.5.12*)

8.0 per cent to 10.0 per cent, determined on 0.30 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.150 g in 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 18.07 mg of $C_{14}H_{30}Cl_2N_2O_4$.

STORAGE

Store in an airtight container, protected from light.

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Suxamethonium Chloride Injection

General Notices

Action and use

Depolarizing neuromuscular blocker.

DEFINITION

Suxamethonium Chloride Injection is a sterile solution of Suxamethonium Chloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of suxamethonium chloride, $C_{14}H_{30}Cl_2N_2O_4,2H_2O$

90.0 to 107.5% of the stated amount.

IDENTIFICATION

Dilute a volume containing 20 mg of Suxamethonium Chloride to 50 mL with *water*. To 0.5 mL add 2 mL of *chloroform*, 2 mL of a solution containing 0.16% w/v of *citric acid* and 6.6% w/v of *disodium hydrogen orthophosphate* and 0.1 mL of a solution containing 0.15% w/v of *bromothymol blue* and 0.15% w/v of *anhydrous sodium carbonate*. Shake for 2 minutes and allow to separate. The chloroform layer is yellow.

TESTS

Acidity

pH, 3.0 to 5.0, Appendix V L.

Hydrolysis products

The volume of *0.1M sodium hydroxide VS* required for the preliminary neutralisation in the Assay is not more than one tenth of the total volume of *0.1M sodium hydroxide VS* required for the preliminary neutralisation and the hydrolysis.

ASSAY

To a volume containing 0.2 g of Suxamethonium Chloride add 30 mL of *carbon dioxide-free water* and shake with five 20-mL quantities of *ether*. Wash the combined ether solutions with two 10-mL quantities of *water* and discard the ether. Shake the combined washings with two 10-mL quantities of *ether*, add the washings to the original aqueous solution and neutralise with *0.1M sodium hydroxide VS* using *bromothymol blue solution R3* as indicator. Add 25 mL of *0.1M sodium hydroxide VS*, heat under a reflux condenser for 40 minutes, allow to cool and titrate the excess of alkali with *0.1M hydrochloric acid VS* using *bromothymol blue solution R3* as indicator. Repeat the operation

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using 40 mL of *carbon dioxide-free water* and beginning at the words ‘Add 25 mL...’. The difference between the titrations represents the amount of sodium hydroxide required. Each mL of *0.1M sodium hydroxide VS* is equivalent to 19.87 mg of $C_{14}H_{30}Cl_2N_2O_4,2H_2O$.

STORAGE

Suxamethonium Chloride Injection should be stored at a temperature of 2° to 8°. It should not be allowed to freeze. Under these conditions it may be expected to continue to meet the requirements of the monograph for not less than 18 months after the date of preparation.

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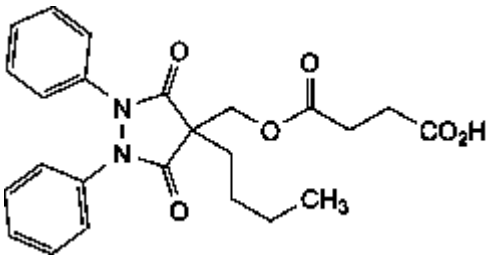
Suxibuzone

General Notices

(Ph. Eur. monograph 1574)



$C_{24}H_{26}N_2O_6$ 438.5 *27470-51-5*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

4-[(4-Butyl-3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)methoxy]-4-oxobutanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *suxibuzone CRS*.

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TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 1 g in anhydrous ethanol R and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.10 g of the substance to be examined in acetonitrile R and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 2.8 mg of phenylbutazone CRS (impurity A), 2.8 mg of suxibuzone impurity B CRS and 2.8 mg of suxibuzone impurity C CRS in acetonitrile R and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with acetonitrile R.

Reference solution (b) Dissolve 4 mg of phenylbutazone CRS (impurity A) in acetonitrile R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with acetonitrile R.

Reference solution (c) Dissolve 10 mg of phenylbutazone CRS (impurity A) in acetonitrile R and dilute to 25.0 mL with the same solvent. Mix 10.0 mL of this solution with 1.0 mL of the test solution and dilute the mixture to 25.0 mL with acetonitrile R.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 44 volumes of acetonitrile R and 56 volumes of a solution prepared as follows: dissolve 6.7 g of citric acid monohydrate R and 2.4 g of tris(hydroxymethyl)aminomethane R in 950 mL of water R, adjust to pH 3.0 with citric acid monohydrate R and dilute to 1000 mL with water R.

Flow rate 1 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Relative retention With reference to suxibuzone (retention time = about 7 min): impurity C = 0.7; impurity A = 1.4; impurity B = 3.3.

System suitability Reference solution (c):

— resolution: minimum of 2.0 between the peaks due to suxibuzone and impurity A.

Limits:

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— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (a) (0.07 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven *in vacuo* at 60 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in previously neutralised *anhydrous ethanol R* and dilute to 10 mL with the same solvent. Carry out a potentiometric titration (2.2.20) using *0.1 M sodium hydroxide*.

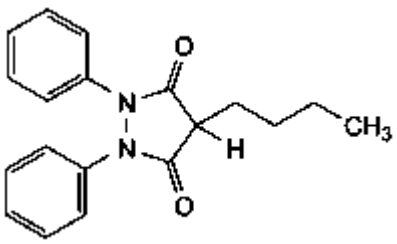
1 mL of *0.1 M sodium hydroxide* is equivalent to 43.85 mg of $C_{24}H_{26}N_2O_6$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



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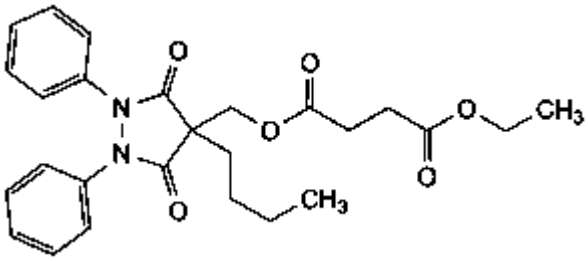
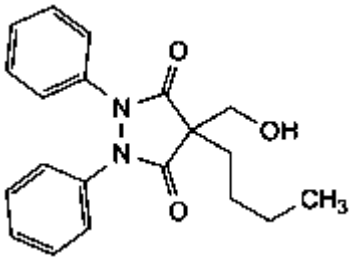
A. 4-butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone),



B. (4-butyl-3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)methyl ethyl butanedioate,



C. 4-butyl-4-(hydroxymethyl)-1,2-diphenyl-1,2-dihydro-4*H*-pyrazole-3,5-dione.

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Synthetic Air

General Notices

(Synthetic Medicinal Air, Ph. Eur. monograph 1684)

When Synthetic Air is intended for use in a room in which magnetic resonance imaging (MRI) is being performed, the cylinder and fittings should be made from suitable non-ferromagnetic materials and labelled accordingly.

Ph Eur

DEFINITION

Mixture of *Nitrogen (1247)* and *Oxygen (0417)*.

Content

95.0 per cent to 105.0 per cent of the nominal value which is between 21.0 per cent *V/V* to 22.5 per cent *V/V* of oxygen (O_2).

CHARACTERS

Colourless and odourless gas.

Solubility

At a temperature of 20 °C and a pressure of 101 kPa, 1 volume dissolves in about 50 volumes of water.

PRODUCTION

Water (*2.5.28*)

Maximum 67 ppm *V/V*.

Assay (*2.5.27*)

Carry out the determination of oxygen in gases.

IDENTIFICATION

First identification: C.

Second identification: A, B.

A. In a conical flask containing the substance to be examined, place a glowing splinter of wood. The splinter remains glowing.

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B. Use a gas burette (Figure 1684.-1) of 25 mL capacity in the form of a chamber, in the middle of which is a tube graduated in 0.2 per cent between 19.0 per cent and 23.0 per cent, and isolated at each end by a tap with a conical barrel. The lower tap is joined to a tube with an olive-shaped nozzle and is used to introduce the gas into the apparatus. A cylindrical funnel above the upper tap is used to introduce the absorbent solution. Wash the burette with *water R* and dry. Open both taps. Connect the nozzle to the source of the substance to be examined and set the flow rate to 1 L/min. Flush the burette by passing the substance to be examined through it for 1 min. Close the lower tap of the burette and immediately afterwards the upper tap. Rapidly disconnect the burette from the source of the substance to be examined. Rapidly give a half turn of the upper tap to eliminate any excess pressure in the burette. Keeping the burette vertical, fill the funnel with a freshly prepared mixture of 21 mL of a 560 g/L solution of *potassium hydroxide R* and 130 mL of a 200 g/L solution of *sodium dithionite R*. Open the upper tap slowly. The solution absorbs the oxygen and enters the burette. Allow to stand for 10 min without shaking. Read the level of the liquid meniscus on the graduated part of the burette. This figure represents the percentage *V/V* of oxygen. The value read is 95.0 per cent to 105.0 per cent of the nominal value.

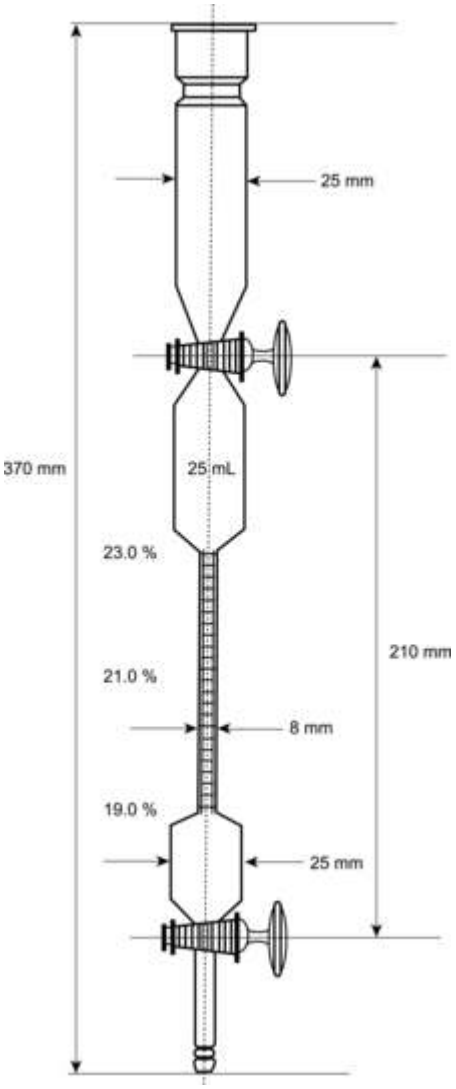

Figure 1684.-1.– *Gas burette*

C. It complies with the limits of the assay.

TESTS

Water vapour

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Maximum 67 ppm *V/V*, determined using a water vapour detector tube (*2.1.6*).

STORAGE

As a compressed gas in suitable containers complying with the legal regulations or as a compressed gas supplied by a pipe network, after mixing of the components.

LABELLING

The label states the nominal content of O_2 in per cent *V/V*.

IMPURITIES

A. H_2O: water.

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Synthetic Retinol Concentrate (Oily Form)

General Notices

(Vitamin A Concentrate (Oily Form) Synthetic, Ph. Eur. monograph 0219)

Action and use

Vitamin A.

Ph Eur

DEFINITION

Oily concentrate prepared from synthetic retinol ester (*0217*) as is or by dilution with a suitable vegetable fatty oil.

Content

95.0 per cent to 110.0 per cent of the vitamin A content stated on the label, which is not less than 500 000 IU/g.

It may contain suitable stabilisers such as antioxidants.

CHARACTERS

Appearance

Yellow or brownish-yellow, oily liquid.

Solubility

Practically insoluble in water, soluble or partly soluble in anhydrous ethanol, miscible with organic solvents.

Partial crystallisation may occur in highly concentrated solutions.

IDENTIFICATION

Thin-layer chromatography (*2.2.27*).

Test solution Prepare a solution containing about 3.3 IU of vitamin A per microlitre in *cyclohexane R* containing 1 g/L of *butylhydroxytoluene R*.

Reference solution Prepare a 10 mg/mL solution of *retinol esters CRS* (i.e. 3.3 IU of each ester per microlitre) in *cyclohexane R* containing 1 g/L of *butylhydroxytoluene R*.

Plate *TLC silica gel F_{254} plate R*.

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Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 3 µL.

Development Immediately, over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution:

— the chromatogram shows the individual spots of the corresponding esters. The elution order from bottom to top is: retinol acetate, retinol propionate and retinol palmitate.

Results The composition of the test solution is confirmed by the correspondence of the principal spot or spots with those obtained with the reference solution.

TESTS

Acid value (*2.5.1*)

Maximum 2.0, determined on 2.0 g.

Peroxide value (*2.5.5, Method A*)

Maximum 10.0.

Use *carbon dioxide-free water R* instead of *water R* and titrate with *0.01 M sodium thiosulfate* at a rate of 5 mL/min, stirring with a magnetic stirrer. Determine the end-point potentiometrically (*2.2.20*).

Related substances

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Carry out the assay as rapidly as possible, avoiding exposure to actinic light, air, oxidising agents, oxidation catalysts (e.g. copper, iron), acids and prolonged heat; use freshly prepared solutions. If partial crystallisation has occurred, homogenise the material at about 65 °C, but avoid prolonged heating.

Carry out the assay according to Method A. If the assay is not shown to be valid, use Method B.

Method A

Ultraviolet absorption spectrophotometry (*2.2.25*).

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Dissolve an appropriate quantity of the preparation to be examined (25.0-100.0 mg) in 5 mL of *pentane R* and dilute with *2-propanol R1* to a presumed concentration of 10-15 IU/mL.

Verify that the absorption maximum of the solution lies between 325 nm and 327 nm and measure the absorbances at 300 nm, 326 nm, 350 nm and 370 nm. Repeat the readings at each wavelength and take the mean values. Calculate the ratio A_λ/A_{326} for each wavelength.

If the ratios do not exceed: 0.60 at 300 nm, 0.54 at 350 nm, 0.14 at 370 nm, calculate the content of vitamin A in International Units per gram using the following expression:

$$\frac{A_{326} \times V \times 1900}{100 \times m}$$

A_{326}	=	absorbance at 326 nm,
m	=	mass of the preparation to be examined used, in grams,
V	=	total volume to which the preparation to be examined is diluted to give 10-15 IU/mL,
1900	=	factor to convert the specific absorbance of esters of retinol into International Units per gram.

If one or more of the ratios A_λ/A_{326} exceeds the values given, or if the wavelength of the absorption maximum does not lie between 325 nm and 327 nm, use Method B.

Method B

Liquid chromatography (*2.2.29*).

Test solution Introduce 0.100 g of the preparation to be examined into a 100 mL volumetric flask and dissolve immediately in 5 mL of *pentane R*. Add 40 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* and swirl gently. Let the mixture react for 10 min at 60-65 °C for hydrolysis, swirling occasionally. Allow to cool to room temperature, dilute to 100.0 mL with *2-propanol R* containing 1 g/L of *butylhydroxytoluene R*, and homogenise carefully to avoid air bubbles (solution A). Dilute this solution with *2-propanol R* to a final concentration of 100 IU/mL. Homogenise carefully to avoid air bubbles.

Reference solution Introduce about 0.100 g of *retinol acetate CRS* into a 100 mL volumetric flask and proceed as described for solution A. Dilute the solution with *2-propanol R* to a final concentration of 100 IU/mL. Homogenise carefully to avoid air bubbles.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *methanol R* (5:95 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 325 nm.

Injection 10 µL.

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Run time 1.5 times the retention time of retinol.

Retention time Retinol = about 3 min.

Calculate the content of vitamin A in International Units per gram using the following expression:

$$\frac{A_1 \times C \times m_2}{A_2 \times m_1}$$

A_1	=	area of the peak due to retinol in the chromatogram obtained with the test solution,
A_2	=	area of the peak due to retinol in the chromatogram obtained with the reference solution,
C	=	concentration of *retinol acetate CRS*, in International Units per gram, determined by method A; the absorption ratios A_λ/A_{326} must conform,
m_1	=	mass of the preparation to be examined used to prepare the test solution, in milligrams,
m_2	=	mass of *retinol acetate CRS* used to prepare the reference solution , in milligrams.

STORAGE

In an airtight container, protected from light.

Once the container has been opened, its contents are to be used as soon as possible; any part of the contents not used at once must be protected under an inert gas.

LABELLING

The label states:

— the number of International Units per gram;

— the name of the ester or esters;

— the name of any added stabilisers;

— the method of restoring the solution if partial crystallisation has occurred.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Synthetic Retinol Concentrate (Powder Form)

General Notices

(Vitamin A Concentrate (Powder Form), Synthetic, Ph. Eur. monograph 0218)

Action and use

Vitamin A.

Ph Eur

DEFINITION

Powder concentrate obtained by dispersing a synthetic retinol ester (*0217*) in a matrix of *Gelatin (0330)* or *Acacia (0307)* or other suitable material.

Content

95.0 per cent to 115.0 per cent of the vitamin A content stated on the label, which is not less than 250 000 IU/g.

It may contain suitable stabilisers such as antioxidants.

CHARACTERS

Appearance

Yellowish powder usually in the form of particles of almost uniform size.

Solubility

Practically insoluble in water, swells or forms an emulsion, depending on the formulation.

IDENTIFICATION

Thin-layer chromatography (*2.2.27*).

Test solution Introduce a quantity of the preparation to be examined containing about the equivalent of 17 000 IU of vitamin A into a 20 mL glass-stoppered test tube. Add about 20 mg of *bromelains R*, 2 mL of *water R* and about 150 µL of *2-propanol R*, swirling gently for 2-5 min in a water-bath at 60-65 °C. Cool to below 30 °C and add 5 mL of *2-propanol R* containing 1 g/L of *butylhydroxytoluene R*. Shake vigorously for 1 min, allow to stand for a few minutes and use the supernatant .

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Reference solution Prepare a 10 mg/mL solution of *retinol esters CRS* (i.e. 3.3 IU of each ester per microlitre) in *2-propanol R* containing 1 g/L of *butylhydroxytoluene R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 3 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution:

— the chromatogram shows the individual spots of the corresponding esters. The elution order from bottom to top is: retinol acetate, retinol propionate and retinol palmitate.

Results The composition of the test solution is confirmed by the correspondence of the principal spot or spots with those obtained with the reference solution.

TESTS

Related substances

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Carry out the assay as rapidly as possible, avoiding exposure to actinic light, air, oxidising agents, oxidation catalysts (e.g. copper, iron), acids and prolonged heat.

Liquid chromatography (*2.2.29*).

Test solution (a) Introduce 0.200 g of the preparation to be examined into a 100 mL volumetric flask. Add 20-30 mg of *bromelains R*, 5.0 mL of *water R* and 0.15 mL of *2-propanol R*. Heat gently in a water-bath at 60 °C for about 5 min, swirling occasionally. Add 40 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol*. Swirl gently and let the mixture react for 10 min at 60-65 °C for hydrolysis, swirling occasionally. Ensure that all sample material is wetted. Allow to cool to room temperature, dilute to 100.0 mL with *2-propanol R* containing 1 g/L of *butylhydroxytoluene R*, and homogenise carefully to avoid air bubbles. The solution may be turbid.

Test solution (b) Dilute test solution (a) with *2-propanol R* to a final concentration of 100 IU/mL. Filter before injection.

Reference solution (a) Introduce about 0.100 g of *retinol acetate CRS* into a 100 mL volumetric flask and dissolve immediately in 5 mL of *pentane R*. Add 40 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol*. Swirl gently and let the mixture react for 10 min at 60-65 °C

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for hydrolysis, swirling occasionally. Allow to cool to room temperature, dilute to 100.0 mL with *2-propanol R* containing 1 g/L of *butylhydroxytoluene R*, and homogenise carefully to avoid air bubbles.

Reference solution (b) Dilute reference solution (a) with *2-propanol R* to a final concentration of 100 IU/mL. Homogenise carefully to avoid air bubbles.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water R*, *methanol R* (5:95 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 325 nm.

Injection 10 µL of test solution (b) and reference solution (b).

Run time 1.5 times the retention time of retinol.

Retention time Retinol = about 3 min.

Calculate the content of vitamin A using the following expression:

$$\frac{A_1 \times C \times m_2}{A_2 \times m_1}$$

A_1	=	area of the peak due to retinol in the chromatogram obtained with test solution (b),
A_2	=	area of the peak due to retinol in the chromatogram obtained with reference solution (b),
C	=	concentration of *retinol acetate CRS* in International Units per gram, determined by the method below,
m_1	=	mass of the substance to be examined in test solution (a), in milligrams,
m_2	=	mass of *retinol acetate CRS* in reference solution (a), in milligrams.

The exact concentration of *retinol acetate CRS* is assessed by ultraviolet absorption spectrophotometry (*2.2.25*). Dissolve 25-100 mg of *retinol acetate CRS*, weighed with an accuracy of 0.1 per cent, in 5 mL of *pentane R* and dilute with *2-propanol R1* to a presumed concentration of 10-15 IU/mL.

Verify that the absorption maximum of the solution lies between 325 nm and 327 nm and measure the absorbances at 300 nm, 326 nm, 350 nm and 370 nm. Repeat the readings at each wavelength and take the mean values. Calculate the ratio A_λ/A_{326} for each wavelength.

If the ratios do not exceed: 0.60 at 300 nm, 0.54 at 350 nm, 0.14 at 370 nm, calculate the content of vitamin A in International Units per gram using the following expression:

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$$\frac{A_{326} \times V \times 1900}{100 \times m}$$

A_{326}	=	absorbance at 326 nm,
m	=	mass of *retinol acetate CRS*, in grams,
V	=	total volume to which the *retinol acetate CRS* is diluted to give 10-15 IU/mL,
1900	=	factor to convert the specific absorbance of esters of retinol into International Units per gram.

The absorbance ratios A_λ/A_{326} must conform.

STORAGE

In an airtight container, protected from light.

Once the container has been opened, its contents are to be used as soon as possible; any part of the contents not used at once should be protected by an atmosphere of inert gas.

LABELLING

The label states:

— the number of International Units per gram,

— the name of the ester or esters,

— the name of the principal excipient or excipients used and the name of any added stabilisers.

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Synthetic Retinol Concentrate, Solubilisate/Emulsion

General Notices

Synthetic Retinol Concentrate (Water-dispersible Form)

(Vitamin A Concentrate, (Solubilisate/Emulsion), Synthetic, Ph. Eur. monograph 0220)

Ph Eur

DEFINITION

Liquid concentrate (water is generally used as solvent) of a synthetic retinol ester (*0217*) and a suitable solubiliser.

Content

95.0 per cent to 115.0 per cent of the vitamin A content stated on the label, which is not less than 100 000 IU/g.

It may contain suitable stabilisers such as antimicrobial preservatives and antioxidants.

CHARACTERS

Appearance

Yellow or yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperature or take the form of a gel.

A mixture of 1 g with 10 mL of *water R* previously warmed to 50 °C gives, after cooling to 20 °C, a uniform, slightly opalescent and slightly yellow dispersion.

IDENTIFICATION

Thin-layer chromatography (*2.2.27*).

Test solution Introduce a quantity of the preparation to be examined containing about the equivalent of 17 000 IU of vitamin A into a 20 mL glass-stoppered test tube. Add 5 mL of *2-propanol R* containing 1 g/L of *butylhydroxytoluene R* and mix thoroughly.

Reference solution Prepare a 10 mg/mL solution of *retinol esters CRS* (i.e. 3.3 IU of each ester per microlitre) in *2-propanol R* containing 1 g/L of *butylhydroxytoluene R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 3 µL.

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Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution:

— the chromatogram shows the individual spots of the corresponding esters. The elution order from bottom to top is: retinol acetate, retinol propionate and retinol palmitate.

Results The composition of the test solution is confirmed by the correspondence of the principal spot or spots with those obtained with the reference solution.

TESTS

Related substances

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Carry out the assay as rapidly as possible, avoiding exposure to actinic light, air, oxidising agents, oxidation catalysts (e.g. copper, iron), acids and prolonged heat.

Liquid chromatography (*2.2.29*).

Test solution (a) Introduce 0.200 g of the preparation to be examined into a 100 mL volumetric flask. Add 40 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol*. Swirl into dispersion and let the mixture react for 10 min at 60-65 °C for hydrolysis, swirling occasionally. Ensure that all sample material is wetted. Allow to cool to room temperature, dilute to 100.0 mL with *2-propanol R* containing 1 g/L of *butylhydroxytoluene R* and homogenise carefully to avoid air bubbles. Residue of the matrix may make the solution more or less cloudy.

Test solution (b) Dilute test solution (a) with *2-propanol R* to a final concentration of 100 IU/mL. Filter before injection.

Reference solution (a) Introduce about 0.100 g of *retinol acetate CRS* into a 100 mL volumetric flask and dissolve immediately in 5 mL of *pentane R*. Add 40 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol*. Swirl gently and let the mixture react for 10 min at 60-65 °C for hydrolysis, swirling occasionally. Allow to cool to room temperature, dilute to 100.0 mL with *2-propanol R* containing 1 g/L of *butylhydroxytoluene R*, and homogenise carefully to avoid air bubbles.

Reference solution (b) Dilute reference solution (a) with *2-propanol R* to a final concentration of 100 IU/mL. Homogenise carefully to avoid air bubbles.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm,

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water R*, *methanol R* (5:95 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 325 nm.

Injection 10 µL of test solution (b) and reference solution (b).

Run time 1.5 times the retention time of retinol.

Retention time Retinol = about 3 min.

Calculate the content of vitamin A using the following expression:

$$\frac{A_1 \times C \times m_2}{A_2 \times m_1}$$

A_1	=	area of the peak due to retinol in the chromatogram obtained with test solution (b),
A_2	=	area of the peak due to retinol in the chromatogram obtained with reference solution (b),
C	=	concentration of *retinol acetate CRS* in International Units per gram, determined by the method below,
m_1	=	mass of the substance to be examined in test solution (a), in milligrams,
m_2	=	mass of *retinol acetate CRS* in reference solution (a), in milligrams.

The exact concentration of *retinol acetate CRS* is assessed by ultraviolet absorption spectrophotometry (*2.2.25*). Dissolve 25-100 mg of *retinol acetate CRS*, weighed with an accuracy of 0.1 per cent, in 5 mL of *pentane R* and dilute with *2-propanol R1* to a presumed concentration of 10-15 IU/mL.

Verify that the absorption maximum of the solution lies between 325 nm and 327 nm and measure the absorbances at 300 nm, 326 nm, 350 nm and 370 nm. Repeat the readings at each wavelength and take the mean values. Calculate the ratio A_λ/A_{326} for each wavelength.

If the ratios do not exceed: 0.60 at 300 nm, 0.54 at 350 nm, 0.14 at 370 nm, calculate the content of vitamin A in International Units per gram using the following expression:

$$\frac{A_{326} \times V \times 1900}{100 \times m}$$

A_{326}	=	absorbance at 326 nm,
m	=	mass of *retinol acetate CRS*, in grams,
V	=	total volume to which the *retinol acetate CRS* is diluted to give 10-15 IU/mL,
1900	=	factor to convert the specific absorbance of esters of retinol into International Units per gram.

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The absorbance ratios A_λ/A_{326} must conform.

STORAGE

In an airtight container, protected from light, at the temperature stated on the label.

Once the container has been opened, its contents are to be used as soon as possible; any part of the contents not used at once should be protected by an atmosphere of inert gas.

LABELLING

The label states:

— the number of International Units per gram,

— the name of the ester or esters,

— the name of the principal solubiliser or solubilisers used and the name of any added stabilisers,

— the storage temperature.

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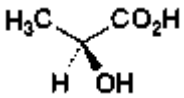
(*S*)-Lactic Acid

General Notices

(Ph. Eur. monograph 1771)



$C_3H_6O_3$ 90.1

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DEFINITION

Mixture of (*S*)-2-hydroxypropanoic acid, its condensation products, such as lactoyl-lactic acid and polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature.

Content

88.0 per cent *m/m* to 92.0 per cent *m/m* of $C_3H_6O_3$, not less than 95.0 per cent of which is the (*S*)-enantiomer.

CHARACTERS

Appearance

Colourless or slightly yellow, syrupy liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in 10 mL of *water R*. The solution is strongly acidic (2.2.4).

B. Relative density (2.2.5): 1.20 to 1.21.

C. It gives the reaction of lactates (2.3.1).

D. It complies with the limits of the assay.

TESTS

Solution S

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Dissolve 5.0 g in 42 mL of *1 M sodium hydroxide* and dilute to 50 mL with *distilled water R*.

Appearance

The substance to be examined is not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Ether-insoluble substances

Dissolve 1.0 g in 25 mL of *ether R*. The solution is not more opalescent than the solvent used for the test.

Sugars and other reducing substances

To 1 mL of solution S add 1 mL of *1 M hydrochloric acid*, heat to boiling, allow to cool and add 1.5 mL of *1 M sodium hydroxide* and 2 mL of *cupri-tartaric solution R*. Heat to boiling. No red or greenish precipitate is formed.

Methanol (*2.4.24*)

Maximum 50 ppm, if intended for use in the manufacture of parenteral preparations.

Citric, oxalic and phosphoric acids

To 5 mL of solution S add *dilute ammonia R1* until slightly alkaline (*2.2.4*). Add 1 mL of *calcium chloride solution R*. Heat on a water-bath for 5 min. Both before and after heating, any opalescence in the solution is not more intense than that in a mixture of 1 mL of *water R* and 5 mL of solution S.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 5 IU/g if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. Before use, neutralise the test solution to pH 7.0-7.5 with *strong sodium hydroxide solution R* and shake vigorously.

ASSAY

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Place 1.000 g in a ground-glass-stoppered flask and add 10 mL of *water R* and 20.0 mL of *1 M sodium hydroxide*. Close the flask and allow to stand for 30 min. Using 0.5 mL of *phenolphthalein solution R* as indicator, titrate with *1 M hydrochloric acid* until the pink colour is discharged.

1 mL of *1 M sodium hydroxide* is equivalent to 90.1 mg of $C_3H_6O_3$.

(*S*)-enantiomer

Transfer an amount of the substance to be examined equivalent to 2.00 g of lactic acid into a round-bottomed flask, add 25 mL of *1 M sodium hydroxide* and boil gently for 15 min. Cool down and adjust to pH 7.0 using *1 M hydrochloric acid*. Add 5.0 g of *ammonium molybdate R*, dissolve and dilute to 50.0 mL with *water R*. Filter and measure the angle of optical rotation (*2.2.7*). Calculate the percentage content of (*S*)-enantiomer using the expression:

$$50 + \left(24.18 \times \alpha \times \frac{2.222}{m} \times \frac{90}{c}\right)$$

α	=	angle of optical rotation (absolute value),
m	=	mass of the substance to be examined, in grams,
c	=	percentage content of $C_3H_6O_3$ in the substance to be examined.

The complex of (*S*)-lactic acid formed under these test conditions is laevorotatory.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

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Acacia, Dried Dispersion

General Notices

Spray-dried Acacia

(Ph. Eur. monograph 0308)

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DEFINITION

Powder obtained from a dispersion of *Acacia (0307)* after a drying process.

CHARACTERS

It dissolves completely, after about 20 min, in twice its mass of water. The liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent and weakly acid to blue litmus paper. It is practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Examine under a microscope using *ethanol (96 per cent) R* as the mounting medium. The preparation to be examined consists of predominantly spheroidal or irregular and angular particles varying in size (4-500 µm), with 1 or more rounded cavities containing 1 or several air bubbles; a few flat fragments are also present. Only traces of starch granules are visible and no plant tissue is observed.

B. Examine the chromatograms obtained in the test for glucose and fructose.

Results See below the sequence of zones present in the chromatograms obtained with reference solution (a) and the test solution.

Top of the plate	
	3 blue zones, very faint
Rhamnose: a greenish-brown zone	A greenish-brown zone, very faint to equivalent (rhamnose)
Xylose: a brownish-grey zone	

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Top of the plate	
Arabinose: a brownish-grey zone	A brownish-grey zone, intense (arabinose)
Glucose: a greyish-blue zone	
Galactose: a greyish-blue zone	A greyish-blue zone, intense (galactose)
	1 or 2 brownish-grey zones, very faint to equivalent
	1 or 2 blue zones, faint to equivalent
Reference solution (a)	**Test solution**

C. Dissolve 1 g of the preparation to be examined in 2 mL of *water R* by stirring frequently for 20 min. Add 2 mL of *ethanol (96 per cent) R*. After shaking, a white gelatinous mucilage is formed that becomes fluid upon addition of 10 mL of *water R*.

TESTS

Solution S

Dissolve 3.0 g of the preparation to be examined in 25 mL of *water R* by stirring for 10 min. Allow to stand for 20 min and dilute to 30 mL with *water R*.

Glucose and fructose

High-performance thin-layer chromatography (*2.8.25*)

Test solution To 0.1 g in a thick-walled centrifuge tube add 2 mL of a 100 g/L solution of *trifluoroacetic acid R* and shake vigorously. Stopper the tube and heat the mixture at 120 °C for 1 h. Centrifuge, transfer 1 mL of the clear supernatant into a 10 mL flask and add 5 mL of *methanol R*.

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Reference solution (a) Dissolve 5 mg of *arabinose R*, 5 mg of *galactose R*, 5 mg of *glucose R*, 5 mg of *rhamnose R* and 5 mg of *xylose R* in 1 mL of *water R* and dilute to 10.0 mL with *methanol R*.

Reference solution (b) Dilute 2.5 mL of reference solution (a) to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 5 mg of *galactose R* and 5 mg of *glucose R* in 1 mL of *water R* and dilute to 10 mL with *methanol R*.

Intensity marker Galactose.

Plate *TLC silica gel F_{254} plate R* (2-10 µm).

Mobile phase *water R*, *acetonitrile R* (15:85 *V/V*).

Application 4 µL of the test solution and reference solutions (a) and (b), and 2 µL of reference solution (c), as bands of 8 mm.

Development A 70 mm from the lower edge of the plate, in an unsaturated tank.

Drying A In air.

Development B 70 mm from the lower edge of the plate, in an unsaturated tank, using freshly prepared mobile phase.

Drying B In air.

Detection Treat with a solution prepared as follows: dissolve 4 g of *diphenylamine R* and 4 mL of *aniline R* in 160 mL of *acetone R* and add *phosphoric acid R* until the precipitate formed dissolves again (about 30 mL). Heat at 120 °C for 5-10 min and examine in daylight.

System suitability Reference solution (c):

— the chromatogram shows in the middle third 2 distinct zones, which may be touching; the lower zone (galactose) and the upper zone (glucose) are greyish-blue.

Results The chromatogram obtained with the test solution shows no greyish-blue zone and no reddish zone between the zones due to galactose and arabinose in the chromatogram obtained with reference solution (a).

Starch, dextrin and agar

To 10 mL of solution S, previously boiled and cooled, add 0.1 mL of *0.05 M iodine*. No blue or reddish-brown colour develops.

Sterculia gum

A. Place 0.2 g in a 10 mL ground-glass-stoppered cylinder graduated in 0.1 mL. Add 10 mL of *ethanol (60 per cent V/V) R* and shake. Any gel formed occupies not more than 1.5 mL.

B. To 1.0 g add 100 mL of *water R* and shake. Add 0.1 mL of *methyl red solution R*. Not more than 5.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Tannins

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To 10 mL of solution S add 0.1 mL of *ferric chloride solution R1*. A gelatinous precipitate is formed, but neither the precipitate nor the liquid is dark blue.

Tragacanth

Examine the chromatograms obtained in the test for glucose and fructose.

Results The chromatogram obtained with the test solution shows no faint to intense brownish-grey zone corresponding to the zone due to xylose in the chromatogram obtained with reference solution (a).

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Total ash (*2.4.16*)

Maximum 4.0 per cent.

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for acacia dried dispersion used as a viscosity-increasing agent and/or suspending agent in aqueous preparations.

Apparent viscosity

Determine the dynamic viscosity using a capillary viscometer (*2.2.9*) or a rotating viscometer (*2.2.10*) on a 100 g/L solution of acacia, dried dispersion (dried substance).

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Arginine Hydrochloride Sterile Concentrate

General Notices

Sterile Arginine Hydrochloride Concentrate

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Amino acid; nutrient.

DEFINITION

Arginine Hydrochloride Sterile Concentrate is a sterile solution containing Arginine Hydrochloride in a suitable solvent.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements. Where appropriate, the concentrate also complies with the requirements stated under Unlicensed Medicines.

Content of arginine hydrochloride, $C_6H_{14}N_4O_2$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Evaporate to dryness 5 mL of the concentrate over *silica gel* at 40° under reduced pressure. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of arginine hydrochloride *(RS 470)*.

B. Dilute a suitable volume of the concentrate with sufficient *water* to produce a solution containing 0.5% w/v of Arginine Hydrochloride. The resulting solution yields reaction A characteristic of *chlorides*.

TESTS

Acidity

pH, 5.0 to 6.5, Appendix V L.

Ninhydrin-positive substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute the concentrate to contain 1.0% w/v of Arginine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume to 4 volumes.

(3) 0.04% w/v of each of *arginine hydrochloride BPCRS* and *lysine hydrochloride EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat it at 100° to 105° until the ammonia is removed. Spray with *ninhydrin solution* and heat at 100° to 105° for 15 minutes.

MOBILE PHASE

30 volumes of *concentrated ammonia* and 70 volumes of *propan-2-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the concentrate with sufficient *water* to produce a solution containing 0.02% w/v of Arginine Hydrochloride.

(2) 0.02% w/v of *arginine hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *methanol R1* and 60 volumes of 0.05M *sodium dihydrogen orthophosphate* containing 0.075% w/v of *sodium dodecyl sulfate*; adjust the pH to 3.3 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The Assay is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is between 0.8 and 1.5; if necessary, adjust the content of *methanol* in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_{14}N_4O_2$,HCl in the concentrate using the declared content of $C_6H_{14}N_4O_2$,HCl in *arginine hydrochloride BPCRS*.

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Ciclosporin Sterile Concentrate

General Notices

Sterile Ciclosporin Concentrate

Action and use

Calcineurin inhibitor; immunosuppressant.

DEFINITION

Ciclosporin Sterile Concentrate is a sterile solution of Ciclosporin in a suitable solvent.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of ciclosporin, $C_{62}H_{111}N_{11}O_{12}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the concentrate, if necessary, with sufficient *methanol* to produce a solution containing 0.05% w/v of Ciclosporin.

(2) 0.05% w/v of *ciclosporin EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm with mobile phase A, dry in air and then develop the plate to 15 cm in the same direction with mobile phase B.

(e) After removal of the plate, dry in air, spray the plate with a freshly prepared mixture containing 5 volumes of 1.7% w/v solution of *bismuth subnitrate*, 5 volumes of a 40% w/v solution of *potassium iodide*, 20 volumes of *glacial acetic acid* and 70 volumes of *water*. Immediately spray again with *dilute hydrogen peroxide solution* and examine in daylight.

MOBILE PHASE

Mobile phase A *ether*.

Mobile phase B 1 volume of *formic acid*, 2 volumes of *water*, 40 volumes of *butan-2-one* and 60 volumes of *ethyl acetate*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2)

TESTS

Acidity or alkalinity

pH, 6.0 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the concentrate containing 30 mg of Ciclosporin to 25 mL with a mixture of equal volumes of *acetonitrile R1* and *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of equal volumes of *acetonitrile R1* and *water*.

(3) Dissolve the contents of a vial of *ciclosporin for system suitability EPCRS* in 5 mL of the mobile phase.

(4) Dilute 1 volume of solution (2) to 20 volumes with a mixture of equal volumes of *acetonitrile R1* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (3-5 µm) (Supelco Superspher is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 80°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for at least 2.6 times the retention time of the principal peak.

MOBILE PHASE

0.1 volume of *orthophosphoric acid*, 5 volumes of *1,1-dimethylethyl methyl ether*, 46 volumes of *acetonitrile R1* and 49 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions the peak due to ciclosporin has a retention time of 25 to 30 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.4, where H_p = height above the baseline of the peak due to ciclosporin U and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ciclosporin. If necessary, adjust the ratio of *1,1-dimethyethyl methyl ether* to *acetonitrile R1* in the mobile phase.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.3%);

the area of not more than one such peak is greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of equal volumes of *acetonitrile* and *water*.

(1) Dilute a quantity of the concentrate containing 30 mg of Ciclosporin to 25 mL with a mixture of equal volumes of *acetonitrile R1* and *water*.

(2) 0.12% w/v of *ciclosporin EPCRS* in a mixture of equal volumes of *acetonitrile R1* and *water*.

(3) Dissolve the contents of a vial of *ciclosporin for system suitability EPCRS* in 5 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.4, where H_p = height above the baseline of the peak due to ciclosporin U and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ciclosporin. If necessary, adjust the ratio of *1,1-dimethyethyl methyl ether* to *acetonitrile R1* in the mobile phase.

Inject solution (2) six times. The Assay is not valid unless the relative standard deviation of the area of the principal peak is not more than 1.0%.

DETERMINATION OF CONTENT

Calculate the content of $C_{62}H_{111}N_{11}O_{12}$ in the concentrate using the declared content of $C_{62}H_{111}N_{11}O_{12}$ in *ciclosporin EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ciclosporin.

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Doxorubicin Sterile Concentrate

General Notices

Sterile Doxorubicin Concentrate; Doxorubicin Injection; Doxorubicin Infusion

This monograph does not apply to formulations where Doxorubicin Hydrochloride is present in a pegylated liposomal formulation.

Action and use

Anthracycline antibacterial; cytotoxic.

DEFINITION

Doxorubicin Sterile Concentrate is a sterile solution of Doxorubicin Hydrochloride in a suitable solvent.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of doxorubicin hydrochloride, $C_{27}H_{29}NO_{11}$,HCl

92.5 to 110.0% of the stated amount.

CHARACTERISTICS

A red solution.

IDENTIFICATION

A. Dilute the concentrate with sufficient *ethanol (96%)* to produce a solution containing 0.001% w/v of Doxorubicin Hydrochloride. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 550 nm exhibits two maxima, at 234 and 252nm, and two less clearly defined maxima at 288 and 495 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.5 to 3.5, Appendix V L.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. The solutions should be prepared immediately before use.

(1) Dilute a quantity of the concentrate to produce a solution containing 0.1% w/v of Doxorubicin Hydrochloride.

(2) Dilute 1 volumes of solution (1) to 100 volumes.

(3) 0.002% w/v each of *doxorubicin hydrochloride BPCRS* and *epirubicin hydrochloride BPCRS*.

(4) Dissolve 10 mg of *doxorubicin hydrochloride BPCRS* in a mixture of 5 mL of *water* and 5 mL of *orthophosphoric acid* and allow to stand for 30 minutes. Adjust the pH to 2.6 with an 8% w/v solution of *sodium hydroxide*, add 15 mL of *acetonitrile* and 10 mL of *methanol* and mix (generation of impurity D).

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3.5 times the retention time of the principal peak.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of a solution containing 0.288% w/v of *sodium dodecyl sulfate* and 0.225% w/v of *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the relative retention of impurity D with reference to doxorubicin (retention time about 8 minutes) is about 0.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to doxorubicin and epirubicin is at least 2.0.

LIMITS

Use the retention time and the chromatogram obtained with solution (4) to identify the peak due to impurity D.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than three times the area of the peak due to doxorubicin in the chromatogram obtained with solution (2) (3%);

the area of any other *secondary peak* is not greater than 1.5 times the area of the peak due to doxorubicin in the chromatogram obtained with solution (2) (1.5%).

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the sum of the areas of any secondary peaks is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. The solutions should be prepared immediately before use.

(1) Dilute a quantity of the concentrate to produce a solution containing 0.01% w/v of Doxorubicin Hydrochloride.

(2) 0.01% w/v of *doxorubicin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{29}NO_{11}$,HCl in the concentrate using the declared content of $C_{27}H_{29}NO_{11}$,HCl in *doxorubicin hydrochloride BPCRS*.

STORAGE

Doxorubicin Sterile Concentrate should be stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Doxorubicin Hydrochloride.

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Lidocaine Sterile Solution

General Notices

Lidocaine Sterile Cutaneous Solution

Sterile Lidocaine Solution

Action and use

Local anaesthetic; Class I antiarrhythmic.

DEFINITION

Lidocaine Sterile Solution is a sterile *cutaneous solution*. It contains Lidocaine Hydrochloride Monohydrate in Purified Water.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of lidocaine hydrochloride monohydrate, $C_{14}H_{22}N_2O,HCl,H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Make a volume containing 0.1 g of Lidocaine Hydrochloride Monohydrate alkaline with 5M *sodium hydroxide*, filter, wash the residue with *water*, dissolve it in 1 mL of *ethanol (96%)*, add 0.5 mL of a 10% w/v solution of *cobalt(II) chloride* and shake for 2 minutes. A bluish-green precipitate is produced.

B. To a volume containing 0.1 g of Lidocaine Hydrochloride Monohydrate add 10 mL of *picric acid solution R1*. The *melting point* of the precipitate, after washing with *water* and drying at 105°, is about 229°, Appendix V A.

C. Yields the reactions characteristic of *chlorides*, Appendix VI.

2,6-Dimethylaniline

Dilute the solution to contain 0.25% w/v of Lidocaine Hydrochloride Monohydrate. To 10 mL of this solution add 2M *sodium hydroxide* until the solution is just alkaline and extract with three 5 mL quantities of *chloroform*, dry the combined chloroform extracts over *anhydrous sodium sulfate*, filter, wash with a further 5 mL of *chloroform* and evaporate the filtrate to dryness at a pressure of 2 kPa. Dissolve the residue in 2 mL of *methanol*, add 1 mL of a 1% w/v solution of *4-dimethylaminobenzaldehyde* in *methanol* and 2 mL of *glacial acetic acid* and allow to stand at room temperature for 10 minutes. Any yellow colour produced is not more intense than the colour obtained by repeating the operation using 10 mL of a solution of *2,6-dimethylaniline* in *water* containing 1 µg per mL in place of the solution being examined (400 ppm).

TESTS

Sterility

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Sterility.

Complies with the *test for sterility*, Appendix XVI A.

ASSAY

Make a quantity containing 0.1 g of Lidocaine Hydrochloride Monohydrate alkaline with 2M *sodium hydroxide* and extract with three 20 mL quantities of *chloroform*, washing each extract with the same 10 mL of *water*. Filter the washed extracts through a filter paper moistened with *chloroform* and wash the filter with 10 mL of *chloroform*. Add the washings to the filtrate and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *0.02M perchloric acid VS* as titrant and *crystal violet solution* as indicator. Each mL of *0.02M perchloric acid VS* is equivalent to 5.776 mg of $C_{14}H_{22}N_2O,HCl,H_2O$.

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Paracetamol and Caffeine Soluble Tablets

General Notices

Soluble Paracetamol and Caffeine Tablets

Action and use

Analgesic; antipyretic; central nervous system stimulant.

DEFINITION

Paracetamol and Caffeine Soluble Tablets contain Paracetamol and Caffeine in either a suitable soluble basis or a suitable soluble, effervescent basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

Content of caffeine, $C_8H_{10}N_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of paracetamol (*RS 258*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 65 mg of Caffeine in 10 mL of *methanol*, and filter (a 1.2-µm Whatman GF/C is suitable).

(2) 0.65% w/v of *caffeine BPCRS* in *methanol*.

(3) 0.65% w/v of *caffeine BPCRS* and 5% w/v of *paracetamol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

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MOBILE PHASE

5 volumes of *acetic acid*, 5 volumes of *ethanol*, 5 volumes of *water* and 50 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The spot corresponding to caffeine in the chromatogram obtained with solution (1) corresponds in position to the principal spot in the chromatogram obtained with solution (2).

C. In the Assay for caffeine, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A: 0.23% w/v of *sodium chloride* in a mixture of 30 volumes of mobile phase B and 70 volumes of mobile phase A.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Paracetamol with 50 mL and filter (Chromafil RC 45/25 is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.0001% w/v of *4-aminophenol* (paracetamol impurity K).
(4) 0.00001% w/v of *4'-chloroacetanilide* (paracetamol impurity J).
(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex C18 100A is suitable).
(b) Use gradient elution and the mobile phase as described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use a column temperature of 35°.
(e) Use detection wavelengths of 212 nm and 246 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 mM *sodium octanesulfonate*, adjusted to pH 2.2 with *orthophosphoric acid*.

Mobile phase B *methanol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	80→70	20→30	linear gradient

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
2.5-20	70	30	isocratic
20-30	70→20	30→80	linear gradient
30-32	20→80	80→20	linear gradient
32-37	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to paracetamol (retention time about 3 minutes) are: caffeine impurity B, about 0.6; caffeine impurity F, about 1.2; caffeine impurity A, about 1.3; caffeine, about 1.6; paracetamol impurity K, about 2.3; caffeine impurity E, about 2.5; paracetamol impurity J, about 6.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3) at 212 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity K is at least 10.

in the chromatogram obtained with solution (4) at 246 nm, the *signal-to-noise ratio* of the peak due to paracetamol impurity J is at least 10.

LIMITS

For paracetamol impurity J at 246 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to paracetamol impurity J is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (10 ppm).

For all other impurities at 212 nm

Identify any peaks due to caffeine impurity B and E, and multiply the peak areas by a correction factor of 2.9 and 3.3, respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to paracetamol impurity K is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (100 ppm);

the area of any other *secondary peak* is not greater than the area of the peak due to paracetamol in the chromatogram obtained with solution (5) (0.1%);

The total impurity content is not greater than 0.5%.

Disregard any peak, excluding paracetamol impurities J and K, with an area less than half the area of the peak due to paracetamol in the chromatogram obtained with solution (5) (0.05%).

ASSAY

For paracetamol

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Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Paracetamol with 100 mL of the mobile phase, dilute to 200 mL with the same solvent, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 250 mL with the mobile phase.
(2) 0.005% w/v of *paracetamol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 243 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium pentanesulfonate* in a mixture of 22 volumes of *methanol* and 78 volumes of *water*, the pH of the solution being adjusted to 2.8 using 2M *hydrochloric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_9NO_2$ in the tablets from the chromatograms obtained and using the declared content of $C_8H_9NO_2$ in *paracetamol BPCRS*.

For caffeine

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing 30 mg of Caffeine with 100 mL of the mobile phase, filter through a glass-fibre filter (Whatman GF/C is suitable) and dilute 5 mL of the filtrate to 50 mL with the mobile phase.
(2) 0.003% w/v of *caffeine BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Assay for paracetamol may be used with a detection wavelength of 220 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{10}N_4O_2$ in the tablets from the chromatograms obtained and using the declared content of $C_8H_{10}N_4O_2$ in *caffeine BPCRS*.

LABELLING

The label states (1) that the tablets should be dissolved in water immediately before use; (2) where applicable, that the tablets are effervescent; (3) the quantities of Paracetamol and Caffeine.

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IMPURITIES

The impurities limited by the requirements of this monograph include impurities J and K listed under Paracetamol, and impurities A, B, E and F listed under Caffeine.

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Paracetamol Soluble Tablets

General Notices

Soluble Paracetamol Tablets

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Soluble Tablets contain Paracetamol in a suitable soluble basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve on the addition of warm *water* to produce a slightly opalescent solution.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits a maximum only at 257 nm.

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *toluene*, 25 volumes of *acetone* and 65 volumes of *chloroform* as the mobile phase but allowing the solvent front to ascend 14 cm above the line of application. Apply separately to the plate 40 µL of each of solutions (1), (2) and (3). Pour the mobile phase into the unlined tank, immediately place the prepared plate in the tank and close the tank. For solution (1) add 50 mL of *ethanol* (*96%*) to a quantity of the powdered tablets containing 0.10 g of Paracetamol, shake for 10 minutes, add sufficient *ethanol* (*96%*) to produce 100 mL and filter. Solution (2) contains 0.10% w/v of *paracetamol BPCRS* in *ethanol* (*96%*). For solution (3) dissolve 0.25 g of *4′-chloroacetanilide* and 0.10 g of *paracetamol* in sufficient *ethanol* (*96%*) to produce 100 mL. After removal of the plate, dry it in a current of warm air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots, the spot corresponding to 4′-chloroacetanilide having the higher Rf value.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light. For solution (1) disperse a quantity of powdered tablets containing 0.2 g of Paracetamol in 8 mL of the mobile phase

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with the aid of ultrasound, add sufficient mobile phase to produce 10 mL, mix well and filter. For solution (2) dilute 1 volume of solution (1) to 20 volumes with mobile phase and dilute 1 volume of this solution to 20 volumes with mobile phase . Solution (3) contains 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.Solution (4) contains 0.00002% w/v of *4′-chloroacetanilide* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute, with a temperature of 35°C, a mixture of 250 volumes of *methanol* containing 1.15 g of a 40% v/v solution of *tetrabutylammonium hydroxide* with 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate* and (c) a detection wavelength of 245 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

Inject solution (1) and allow the chromatography to proceed for 12 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in solution (3) (0.1%), the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in solution (4) (10 ppm) and no other impurity is greater than the area of the principal peak obtained with solution (2) (0.25%).

ASSAY

Weigh and powder 20 tablets. Add 50 mL of 0.1M *sodium hydroxide* slowly to a quantity of the powdered tablets containing 0.2 g of Paracetamol. Dilute with 100 mL of *water*, shake for 15 minutes and add sufficient *water* to produce 250 mL. Mix, filter and dilute 10 mL of the filtrate to 100 mL with *water*. Add 10 mL of the resulting solution to 10 mL of 0.1M *sodium hydroxide*, dilute to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 257 nm, Appendix II B. Calculate the content of $C_8H_9NO_2$ taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

STORAGE

Paracetamol Soluble Tablets should be protected from light.

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Potassium Chloride Sterile Concentrate

General Notices

Sterile Potassium Chloride Concentrate

DEFINITION

Potassium Chloride Sterile Concentrate is a sterile solution of Potassium Chloride in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of potassium chloride, KCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The residue on evaporation yields the reactions characteristic of *potassium salts* and the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Acidity or alkalinity

Dilute, if necessary, the concentrate being examined with *carbon dioxide-free water* to contain 10.0% w/v of Potassium Chloride. To 50 mL add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of 0.01M *hydrochloric acid* or 0.01M *sodium hydroxide* is required to change the colour of the indicator.

Bacterial endotoxins

Carry out the test for *bacterial endotoxins*, Appendix XIV C. Dilute the concentrate being examined with *water BET* to contain 0.5% w/v of Potassium Chloride and adjust the pH, if necessary, to 7 (solution A). The endotoxin limit concentration of solution A is 3.0 IU of endotoxin per mL. Carry out the test using a lysate with a declared sensitivity not less sensitive than 0.0625 IU of endotoxin per mL.

ASSAY

Dilute 5 mL to 100 mL with *water*. To a volume of the solution containing 0.15 g of Potassium Chloride add 30 mL of *water* and titrate with *0.1M silver nitrate VS* using *potassium chromate solution* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 7.456 mg of KCl.

LABELLING

The label states the approximate concentration of the potassium ions and the chloride ions in mmol in a suitable volume.

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Potassium Dihydrogen Phosphate Sterile Concentrate

General Notices

Potassium Acid Phosphate Injection

Sterile Potassium Dihydrogen Phosphate Concentrate

DEFINITION

Potassium Dihydrogen Phosphate Sterile Concentrate is a 13.6% w/v sterile solution of Potassium Dihydrogen Phosphate in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of potassium dihydrogen phosphate, KH_2PO_4

12.9 to 14.3% w/v.

IDENTIFICATION

The residue on evaporation yields the reactions characteristic of *potassium salts* and the reactions characteristic of *phosphates*, Appendix VI.

TESTS

Acidity

pH, 3.5 to 5.0, Appendix V L.

Sterility

Complies with the *test for sterility*, Appendix XVI A.

ASSAY

Titrate 10 mL, saturated with *sodium chloride*, with *0.5M sodium hydroxide VS* using *phenolphthalein solution* as indicator. Each mL of *0.5M sodium hydroxide VS* is equivalent to 68.05 mg of KH_2PO_4.

LABELLING

The label states the approximate concentration of the potassium ions and the phosphate ions in millimoles in a suitable volume.

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Prednisolone Soluble Tablets

General Notices

Soluble Prednisolone Tablets

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Soluble Tablets contain Prednisolone Sodium Phosphate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of prednisolone, $C_{21}H_{28}O_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add a quantity of powdered tablets containing the equivalent of 7.5 mg of prednisolone to 10 mL of *water*, leave to stand for 30 minutes, swirl and filter.

(2) 0.1% w/v of *prednisolone sodium phosphate BPCRS*.

(3) Equal volumes of solutions (1) and (2).

(4) Equal volumes of solution (2) and a 0.1% w/v solution of *betamethasone sodium phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 105° for 10 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

33 volumes of *water*, 47 volumes of *glacial acetic acid* and 120 volumes of *butan-1-ol*, prepared immediately before use.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two principal spots with almost identical Rf values.

CONFIRMATION

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The chromatograms obtained with solutions (1), (2) and (3) show single principal spots with similar Rf values.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to prednisolone sodium phosphate in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 15 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, to produce a solution expected to contain the equivalent of 0.00055% w/v of prednisolone.

(2) 0.00074% w/v of *prednisolone sodium phosphate BPCRS* in *water*.

(3) 0.0006% w/v each of *prednisolone sodium phosphate BPCRS* and *prednisolone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Luna C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 247 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

26 volumes of *acetonitrile* and 74 volumes of *water* containing 0.544% w/v of *potassium dihydrogen orthophosphate* and 0.240% w/v of *hexylamine*. When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to prednisolone sodium phosphate (retention time about 6.5 minutes) of prednisolone is about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone sodium phosphate and prednisolone is at least 4.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_5$ (prednisolone) in the medium using the calculated content of $C_{21}H_{27}Na_2O_8P$ in *prednisolone sodium phosphate BPCRS*. Each mg of $C_{21}H_{27}Na_2O_8P$ is equivalent to 0.7440 mg of $C_{21}H_{28}O_5$.

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LIMITS

The amount of prednisolone released is not less than 75% (Q) of the stated amount.

Free prednisolone

In the test for Related substances, the area of any peak due to prednisolone in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (4%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add a quantity of powdered tablets containing the equivalent of 20 mg of prednisolone to 8 mL of the mobile phase, leave to stand for 30 minutes and swirl. Add sufficient mobile phase to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase.
(3) 0.004% w/v each of *prednisolone sodium phosphate BPCRS* and *prednisolone BPCRS* in the mobile phase.
(4) Dilute 1 volume of solution (2) to 20 volumes with the mobile phase.
(5) Dilute 1 volume of solution (1) to 25 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 20 µL. Allow the chromatography to proceed for 3 times the retention time of prednisolone sodium phosphate.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone sodium phosphate and prednisolone is at least 4.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of not more than one *secondary peak* is greater than half the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak due to prednisolone and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Add a quantity of powdered tablets containing the equivalent of 5 mg of prednisolone to 5 mL of *water*, leave to stand for 30 minutes and swirl. Add sufficient *water* to produce 20 mL and filter.

(2) 0.034% w/v of *prednisolone sodium phosphate BPCRS*.

(3) 0.025% w/v each of *prednisolone sodium phosphate BPCRS* and *prednisolone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 20 µL.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to prednisolone sodium phosphate and prednisolone is at least 4.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_5$ (prednisolone) in the tablets using the calculated content of $C_{21}H_{27}Na_2O_8P$ in *prednisolone sodium phosphate BPCRS*. Each mg of $C_{21}H_{27}Na_2O_8P$ is equivalent to 0.7440 mg of $C_{21}H_{28}O_5$.

STORAGE

Prednisolone Soluble Tablets should be protected from light.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of prednisolone.

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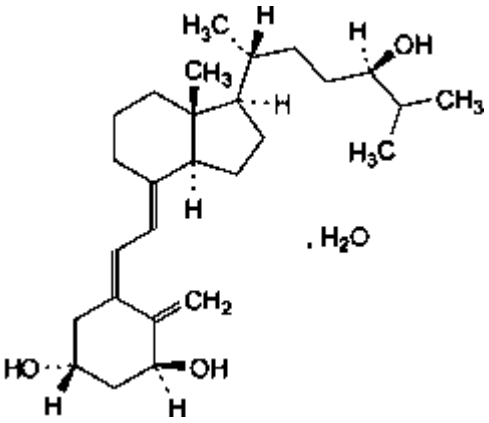
Tacalcitol Monohydrate

General Notices

(Ph. Eur. monograph 2272)



$C_{27}H_{44}O_3,H_2O$ 434.7 *93129-94-3*

Action and use

Vitamin D_3 analogue.

Ph Eur

DEFINITION

(5*Z*,7*E*)-(24*R*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,24-triol.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

A reversible isomerisation to pre-tacalcitol takes place in solution, depending on temperature and time. The activity is due to both compounds.

It is sensitive to air, heat and light.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Practically insoluble in water, freely soluble in anhydrous ethanol and in ethyl acetate.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of tacalcitol monohydrate*.

B. It complies with test B for related substances (see Tests).

C. Water (see Tests).

TESTS

Related substances

A. Liquid chromatography (2.2.29). *Prepare the solutions immediately before use avoiding exposure to light and air*.

Test solution Dissolve 5.0 mg of the substance to be examined in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *tacalcitol monohydrate CRS* in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Heat 3 mL of the test solution at 80 °C for 30 min. Cool the solution to room temperature.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (d) Dissolve the contents of a vial of *tacalcitol impurity A CRS* in 1 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *acetonitrile R* (40:60 *V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 50 µL of the test solution and reference solutions (b), (c) and (d).

Run time 2.5 times the retention time of tacalcitol.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (b) to identify the peak due to pre-tacalcitol.

Relative retention With reference to tacalcitol (retention time = about 11 min): pre-tacalcitol = about 0.8; impurity A = about 0.9.

System suitability Reference solution (d):

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— *resolution*: minimum 1.5 between the peaks due to impurity A and tacalcitol.

Calculation of percentage contents:

— for each impurity, use the concentration of tacalcitol monohydrate in reference solution (c).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to pre-tacalcitol.

B. Liquid chromatography (*2.2.29*).

Test solution Dissolve 2.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *tacalcitol for system suitability CRS* (containing impurity B) in 0.5 mL of the mobile phase.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (10 µm).

Mobile phase *anhydrous ethanol R*, *heptane R* (14:86 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 50 µL.

Run time 2.5 times the retention time of tacalcitol.

Identification of impurities Use the chromatogram supplied with *tacalcitol for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to tacalcitol (retention time = about 12 min): impurity A = about 0.7; impurity B = about 0.85.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity B and tacalcitol.

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Calculation of percentage contents:

— for each impurity, use the concentration of tacalcitol monohydrate in reference solution (b).

Limits:

— *impurity B*: maximum 1.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— disregard any peak with a relative retention with reference to tacalcitol of about 0.7 (impurity A).

Water (*2.5.32*)

3.8 per cent to 4.8 per cent, determined on 10.0 mg by direct sample introduction.

ASSAY

Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modification.

Injection Test solution and reference solutions (a) and (b).

Calculate the percentage content of $C_{27}H_{44}O_3$ taking into account the assigned content of *tacalcitol monohydrate CRS* and, if present, the peak due to pre-tacalcitol.

STORAGE

In an airtight container, under an inert gas, protected from light at a temperature not exceeding -15 °C.

IMPURITIES

Test A for related substances: A.

Test B for related substances: B, C.

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*

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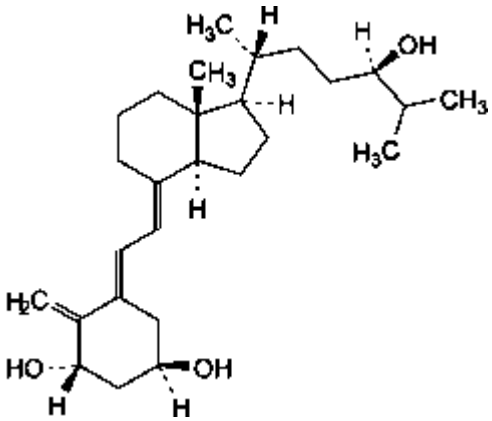
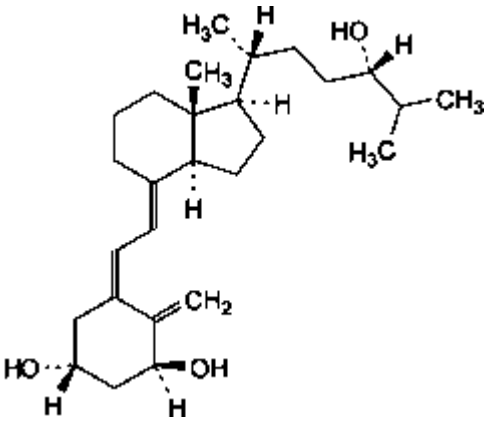
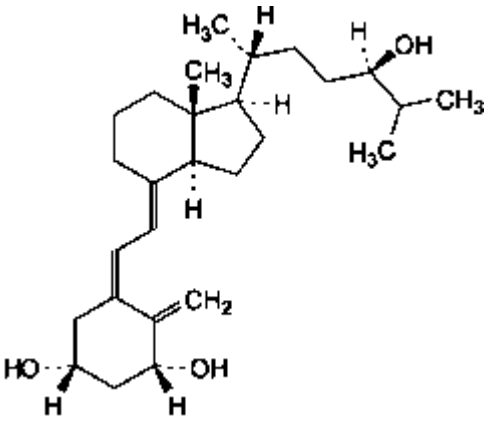


A. (5*E*,7*E*)-(24*R*)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,24-triol (*trans*-tacalcitol),



B. (5*Z*,7*E*)-(24*S*)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,24-triol ((24*S*)-tacalcitol),



C. (5*Z*,7*E*)-(24*R*)-9,10-secocholesta-5,7,10(19)-triene-1β,3β,24-triol (1β-tacalcitol).

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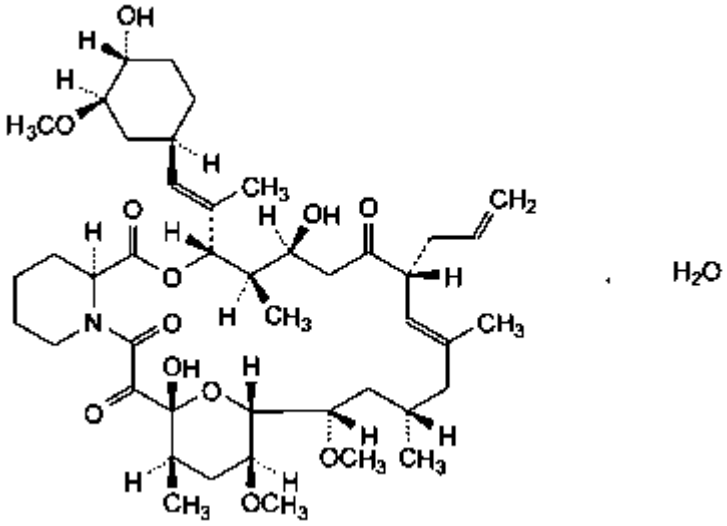
Tacrolimus Monohydrate

General Notices

(Ph. Eur. monograph 2244)



$C_{44}H_{69}NO_{12},H_2O$ 822 *109581-93-3*

Action and use

Calcineurin inhibitor; immunosuppressant.

Ph Eur

DEFINITION

(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-5,19-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(prop-2-en-1-yl)-3,4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-octadecahydro-7H-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone monohydrate.

Substance produced by the growth of certain strains of *Streptomyces tsukubaensis*.

Content

97.0 per cent to 102.0 per cent for the sum of tacrolimus, tacrolimus compound I and tacrolimus compound II (anhydrous substance).

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *tacrolimus monohydrate CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_7 (2.2.2, *Method II*).

Dissolve 0.20 g in *ethanol (96 per cent) R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light. Allow the test and reference solutions to stand for 3 h at room temperature before use.*

Solvent mixture *water R*, *acetonitrile R* (30:70 *V/V*).

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 30.0 mg of *tacrolimus monohydrate CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 3.0 mg of *tacrolimus for system suitability CRS* (containing impurity A) in the solvent mixture and dilute to 1.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 60 °C.

Mobile phase:

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— *mobile phase A*: mix 20 volumes of a mixture of 19 volumes of *1,1-dimethylethyl methyl ether R* and 81 volumes of *acetonitrile for chromatography R* with 80 volumes of a 0.04 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: mix 20 volumes of a 0.04 per cent *V/V* solution of *phosphoric acid R* with 80 volumes of a mixture of 19 volumes of *1,1-dimethylethyl methyl ether R* and 81 volumes of *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	72	28
30 - 53	72 → 15	28 → 85

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Autosampler Set at 4 °C.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *tacrolimus for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to tacrolimus (retention time = about 24 min): tacrolimus compound I = broad peak at about 0.5; impurity B = sharp peak at about 0.5; tacrolimus compound II = about 0.6; impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity A and tacrolimus.

Integration The peak due to impurity B, which co-elutes with tacrolimus compound I, is a rider peak that is to be integrated using tangential skimming. It is necessary that the integration area of the peak due to tacrolimus compound I preserves the Gaussian peak shape.

Calculation of percentage contents:

— for each impurity, use the concentration of tacrolimus monohydrate in reference solution (c).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peaks due to tacrolimus compound I and tacrolimus compound II.

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Water (*2.5.12*)

1.5 per cent to 4.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of the sum of tacrolimus, tacrolimus compound I and tacrolimus compound II taking into account the assigned content of *tacrolimus monohydrate CRS*.

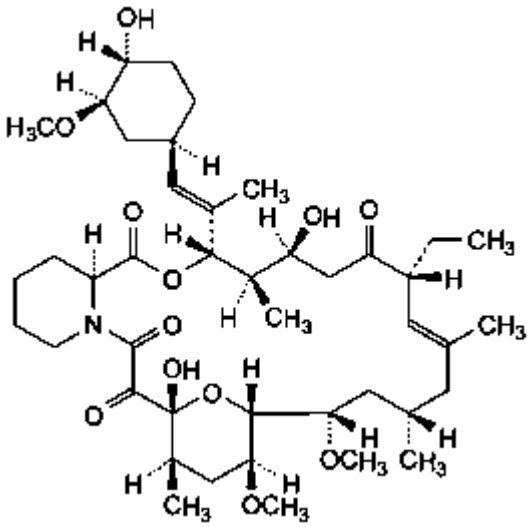
STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, H, I.*



A. (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-8-ethyl-5,19-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-3,4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-

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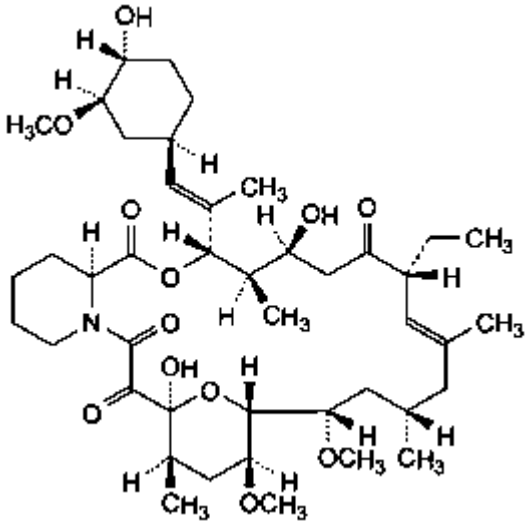
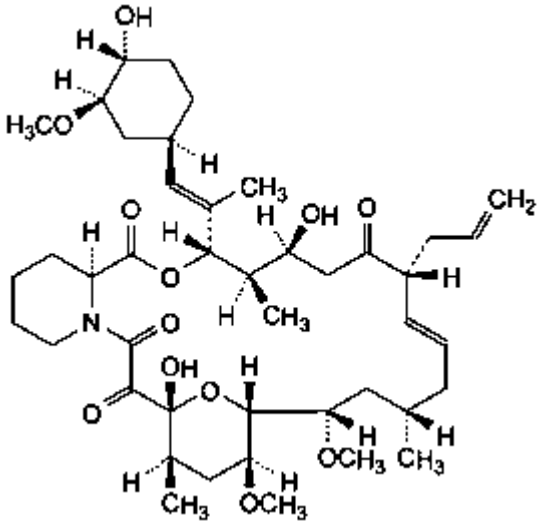
octadecahydro-7*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone,



B. (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*S*,26a*S*)-8-ethyl-5,19-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-3,4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-octadecahydro-7*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone,



C. (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-5,19-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,12,18-trimethyl-8-(prop-2-en-1-yl)-3,4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-octadecahydro-7*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone,

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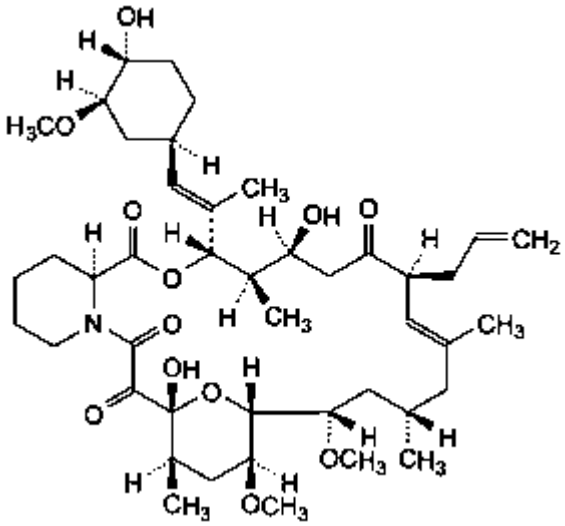
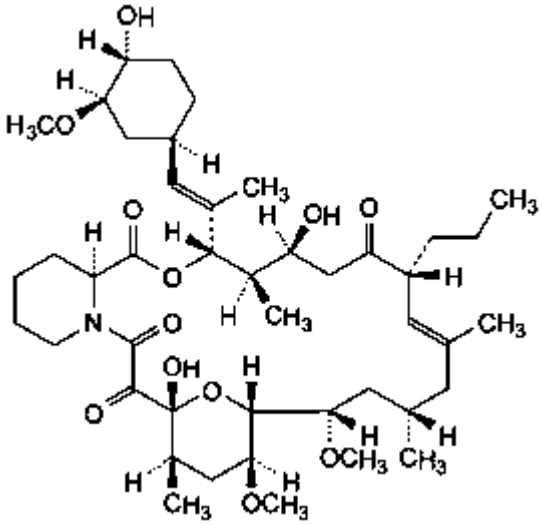


D. (3*S*,4*R*,5*S*,8*S*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-5,19-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(prop-2-en-1-yl)-3,4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-octadecahydro-7*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone,



E. (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-5,19-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-propyl-3,4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-octadecahydro-7*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone,

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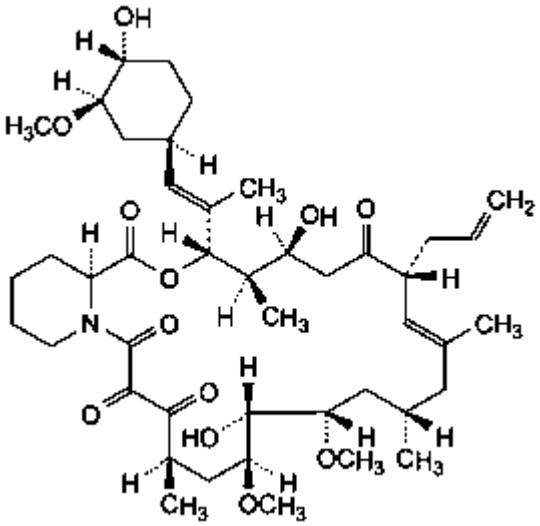
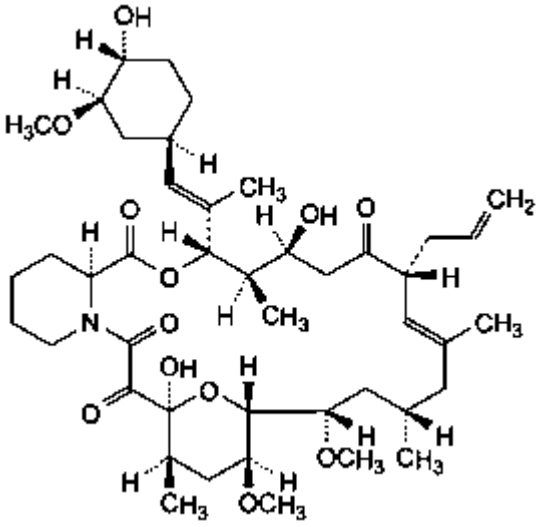


F. (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-5,15-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(prop-2-en-1-yl)-3,4,5,6,11,12,13,14,15,16,17,18,24,25,26,26a-hexadecahydro-7*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,19,20,21(8*H*,23*H*)-pentone (tacrolimus compound I),



G. (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19S,26a*S*)-5,19-dihydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(prop-2-en-1-yl)-3,4,5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-octadecahydro-7*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone (tacrolimus compound II),

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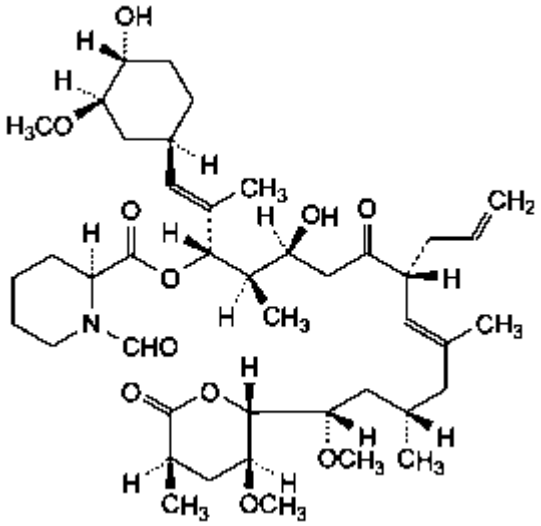
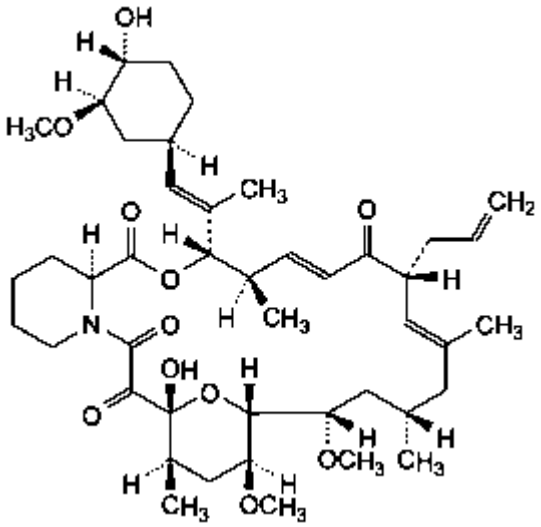


H. (1*E*,3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*)-5-hydroxy-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-14-methoxy-14-[(2*R*,3*S*,5*R*)-3-methoxy-5-methyl-6-oxooxan-2-yl]-2,4,10,12-tetramethyl-7-oxo-8-(prop-2-en-1-yl)tetradeca-1,9-dien-3-yl (2*S*)-1-formylpiperidine-2-carboxylate,



I. (3*S*,4*R*,5*E*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-19-hydroxy-3-[(1*E*)-1-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(prop-2-en-1-yl)-3,4,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-7*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(23*H*)-tetrone.

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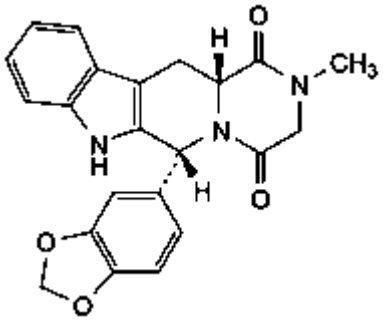
Tadalafil

General Notices

(Ph. Eur. monograph 2606)



$C_{22}H_{19}N_3O_4$ 389.4 *171596-29-5*

Action and use

Selective inhibitor of cyclic GMP-specific phosphodiesterase (Type V) with vasodilator action; treatment of erectile dysfunction.

Ph Eur

DEFINITION

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]-pyrido[3,4-*b*]indole-1,4-dione.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in dimethyl sulfoxide, slightly soluble in methylene chloride.

IDENTIFICATION

Carry out either tests A, B or tests A, C.

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison tadalafil CRS.

B. Liquid chromatography (2.2.29) as described in the test for impurities A, B and C with the following modification.

Injection Test solution and reference solution (a).

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Specific optical rotation (2.2.7): + 78.0 to + 84.0 (dried substance).
Dissolve 0.250 g in dimethyl sulfoxide R and dilute to 25.0 mL with the same solvent.

TESTS

Impurities A, B and C

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, hexane R, 2-propanol R (20:40:40 *V/V/V*).

Solution A Dissolve 27 g of tetrabutylammonium hydroxide R in methanol R and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of tadalafil CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) In order to prepare impurity A *in situ*, dissolve 25 mg of the substance to be examined in 40 mL of the solvent mixture. Add 1 mL of solution A, mix well and allow to stand for 20 min. Add 1 mL of trifluoroacetic acid R and dilute to 100 mL with the solvent mixture.

Reference solution (d) To 1 mL of the test solution add 1 mL of reference solution (c) and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (10 µm);

— *temperature*: 30 °C.

Mobile phase hexane R, 2-propanol R1 (50:50 *V/V*).

Flow rate 0.75 mL/min.

Detection Spectrophotometer at 222 nm.

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Injection 20 µL of the test solution and reference solutions (b) and (d).

Run time 2.2 times the retention time of tadalafil.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention With reference to tadalafil (retention time = about 11 min): impurity A = about 0.8.

System suitability Reference solution (d)

— *resolution*: minimum 2.0 between the peaks due to impurity A and tadalafil.

Limits:

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent).

Related substances

Liquid chromatography (2.2.29). *Do not use sonication during the preparation of the solutions.*

Solvent mixture *acetonitrile R*, *2-propanol R* (50:50 *V/V*).

Solution A Dissolve 27 g of *tetrabutylammonium hydroxide R* in *methanol R* and dilute to 100.0 mL with the same solvent.

Test solution (a) Dissolve 40 mg of the substance to be examined in 50 mL of *acetonitrile R* and dilute to 100.0 mL with mobile phase A.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in 50 mL of *acetonitrile R* and dilute to 100.0 mL with mobile phase A. To 10.0 mL of this solution add 25.0 mL of *acetonitrile R* and dilute to 50.0 mL with mobile phase A.

Reference solution (a) To 1.0 mL of test solution (a) add 50 mL of *acetonitrile R* and dilute to 100.0 mL with mobile phase A. To 1.0 mL of this solution add 5 mL of *acetonitrile R* and dilute to 10.0 mL with mobile phase A.

Reference solution (b) In order to prepare impurity A *in situ*, dissolve 4 mg of the substance to be examined in 50 mL of the solvent mixture. Add 1 mL of solution A, mix, and allow to stand for 40 min. Add 1 mL of *trifluoroacetic acid R* and dilute to 100 mL with the solvent mixture.

Reference solution (c) Dilute 1 mL of reference solution (b) to 50 mL with test solution (a).

Reference solution (d) Dissolve 50.0 mg of *tadalafil CRS* in 50 mL of *acetonitrile R* and dilute to 100.0 mL with mobile phase A. To 10.0 mL of this solution add 25.0 mL of *acetonitrile R* and dilute to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 1.0 mL of *trifluoroacetic acid R* with *water for chromatography R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	85	15
3 - 30	85 → 5	15 → 95
30 - 33	5	95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 285 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurities A + C.

Relative retention With reference to tadalafil (retention time = about 16 min): impurities A and C = about 1.03.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3.3, where H_p = height above the baseline of the peak due to impurities A + C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to tadalafil.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to impurity A and/or C.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase acetonitrile R, mobile phase A (45:55 *V/V*).

Flow rate 1.5 mL/min.

Injection Test solution (b) and reference solution (d).

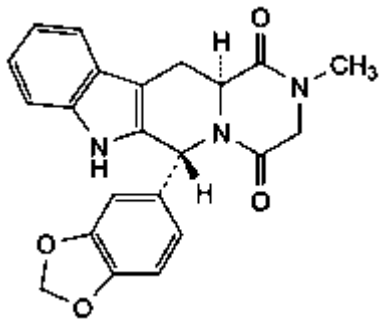
Run time Twice the retention time of tadalafil (retention time = about 4.5 min).

Calculate the percentage content of $C_{22}H_{19}N_3O_4$ from the declared content of tadalafil CRS.

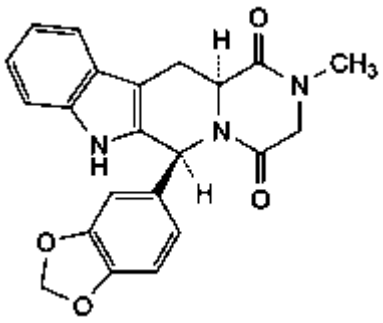
IMPURITIES

Specified impurities *A*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, G, H, I*.



A. (6*R*,12a*S*)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione,



B. (6*S*,12a*S*)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione,

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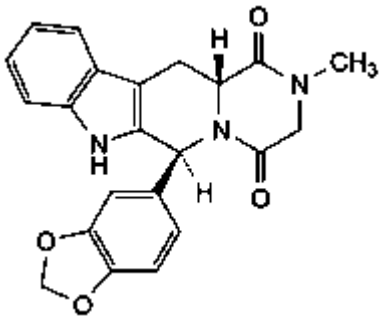
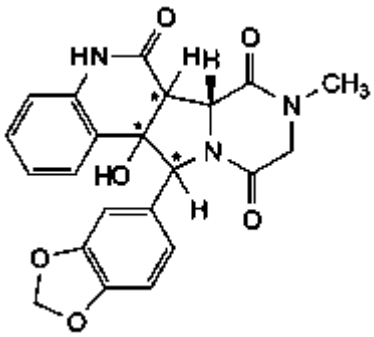
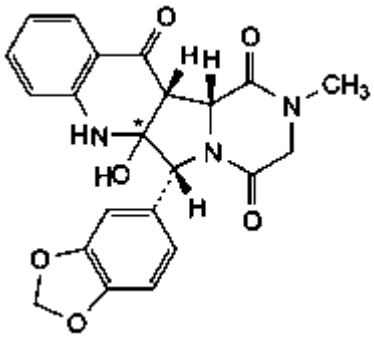


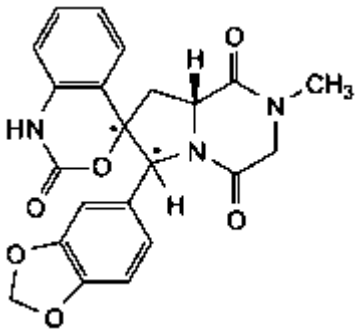
C. (6*S*,12a*R*)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione,



D. (6b*R*)-12-(1,3-benzodioxol-5-yl)-12a-hydroxy-8-methyl-6a,6b,8,9,12,12a-hexahydropyrazino[1′,2′:1,2]pyrrolo[3,4-*c*]quinoline-6,7,10(5*H*)-trione,



E. (6*R*,12a*R*,12b*R*)-6-(1,3-benzodioxol-5-yl)-6a-hydroxy-2-methyl-2,3,6a,7,12a,12b-hexahydropyrazino[1′,2′:1,5]pyrrolo[3,4-*b*]quinoline-1,4,12(6*H*)-trione,



F. (8a′*R*)-6′-(1,3-benzodioxol-5-yl)-2′-methyl-2′,3′,8′,8a′-tetrahydro-6′*H*-spiro[3,1-benzoxazine-4,7′-pyrrolo[1,2-*a*]pyrazine]-1′,2,4′(1*H*)-trione,

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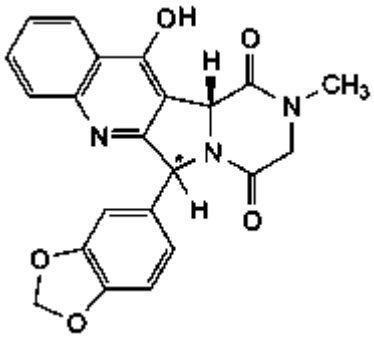
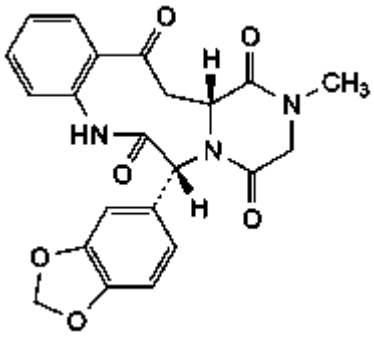
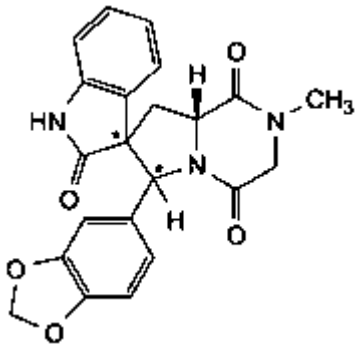


G. (12b*R*)-6-(1,3-benzodioxol-5-yl)-12-hydroxy-2-methyl-2,3,6,12b-tetrahydropyrazino[1′,2′:1,5]pyrrolo[3,4-*b*]quinoline-1,4-dione,



H. (6*R*,14a*R*)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,14,14a-tetrahydropyrazino[1,2-*d*][1,4]benzodiazonine-1,4,7,13(6*H*,8*H*)-tetrone,



I. (8a′*R*)-6′-(1,3-benzodioxol-5-yl)-2′-methyl-2′,3′,8′,8a′-tetrahydro-6′*H*-spiro[indole-3,7′-pyrrolo[1,2-*a*]pyrazine]-1′,2,4′(1*H*)-trione.

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Talc Dusting Powder

General Notices

Talc Cutaneous Powder

DEFINITION

Talc Dusting Powder is a sterile *cutaneous powder* of suitable fineness consisting of 10% of starch[1] and 90% of Purified Talc.

PRODUCTION

The starch is triturated with the Purified Talc and passed through a sieve of suitable mesh size (250 µm may be suitable). Either the Purified Talc is sterilised before use or the final product is subjected to a suitable sterilisation procedure.

The dusting powder complies with the requirements stated under Topical Powders and with the following requirement.

Acid-insoluble matter

86.0 to 91.0% when determined by the following method. Boil 0.5 g with 10 mL of 2M *hydrochloric acid* for 5 minutes, cool, filter through a tared sintered-glass crucible (ISO 4793, porosity grade 4, is suitable), wash the residue with *water* until the washings are free from acid and dry to constant weight at 105°.

1 Maize Starch, Potato Starch, Rice Starch, Wheat Starch or, in tropical and subtropical countries where these are not available, Tapioca Starch may be used.

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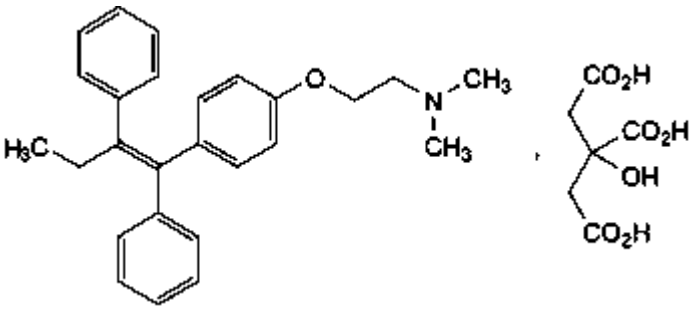
Tamoxifen Citrate

General Notices

(Ph. Eur. monograph 1046)



$C_{32}H_{37}NO_8$ 563.6 *54965-24-1*

Action and use

Selective estrogen receptor modulator.

Preparations

Tamoxifen Oral Solution

Tamoxifen Tablets

Ph Eur

DEFINITION

2-[4-[(*Z*)-1,2-Diphenylbut-1-en-1-yl]phenoxy]-*N*,*N*-dimethylethan-1-amine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Slightly soluble in water, soluble in methanol, slightly soluble in acetone.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20 mg in methanol R and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with methanol R.

Spectral range 220-350 nm.

Absorption maxima At 237 nm and 275 nm.

Absorbance ratio A_{237}/A_{275} = 1.45 to 1.65.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison tamoxifen citrate CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of tamoxifen citrate CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of clomifene citrate CRS and 10 mg of tamoxifen citrate CRS in methanol R and dilute to 10 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase triethylamine R, toluene R (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

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— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light*.

Test solution Dissolve 15 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 3 mg of *tamoxifen citrate for performance test CRS* (containing impurities A and F) in the mobile phase and dilute to 2.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 40 volumes of *acetonitrile R* and 60 volumes of *water R* containing 0.9 g/L of *sodium dihydrogen phosphate R* and 4.8 g/L of *N,N-dimethyloctylamine R*; adjust to pH 3.0 with *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time Twice the retention time of tamoxifen.

Identification of impurities Use the chromatogram supplied with *tamoxifen citrate for performance test CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and F.

Relative retention With reference to tamoxifen (retention time = about 20 min): impurity A = about 0.8; impurity F = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurities A and F; baseline separation between the peaks due to impurity F and tamoxifen.

Limits:

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— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity F*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to the citrate.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 65 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

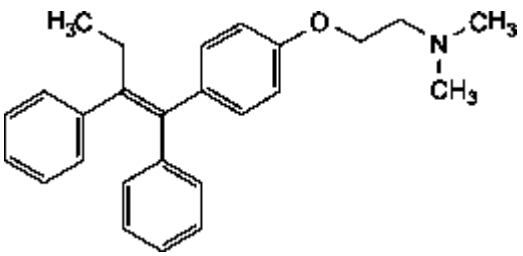
Dissolve 0.400 g in 75 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 56.36 mg of $C_{32}H_{37}NO_8$.

IMPURITIES

Specified impurities *A, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, G, H.*



A. 2-[4-[(*E*)-1,2-diphenylbut-1-en-1-yl]phenoxy]-*N*,*N*-dimethylethan-1-amine ((*E*)-isomer),

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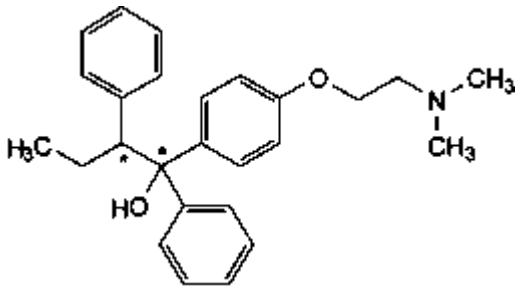
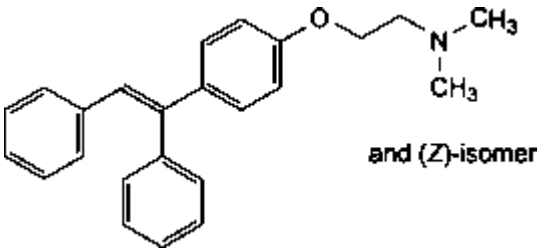
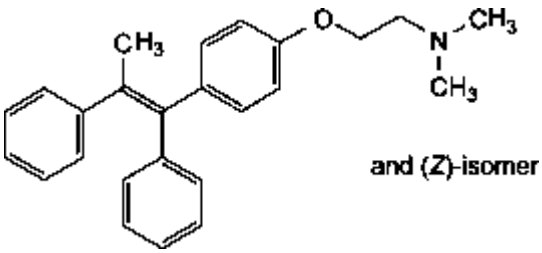


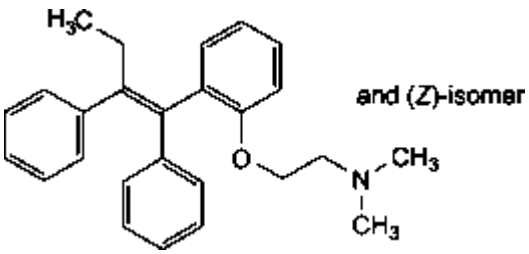
B. 1-[4-[2-(dimethylamino)ethoxy]phenyl]-1,2-diphenylbutan-1-ol,



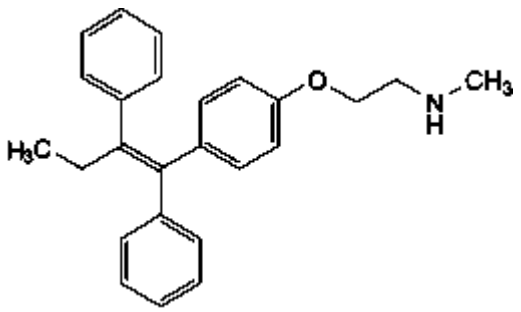
C. 2-[4-[(*EZ*)-1,2-diphenyleth-1-en-1-yl]phenoxy]-*N*,*N*-dimethylethan-1-amine,



D. 2-[4-[(*EZ*)-1,2-diphenylprop-1-en-1-yl]phenoxy]-*N*,*N*-dimethylethan-1-amine,



E. 2-[2-[(*EZ*)-1,2-diphenylbut-1-en-1-yl]phenoxy]-*N*,*N*-dimethylethan-1-amine,



F. 2-[4-[(*Z*)-1,2-diphenylbut-1-en-1-yl]phenoxy]-*N*-methylethan-1-amine,

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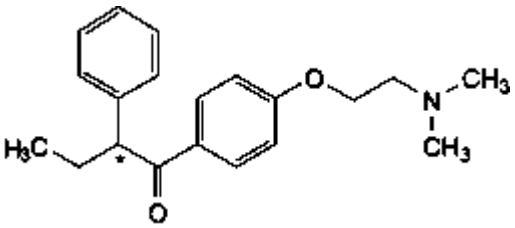
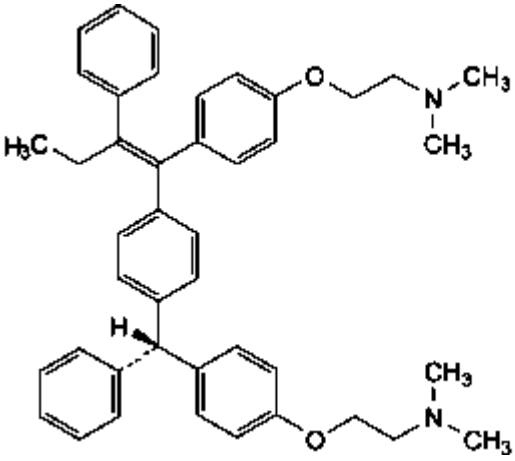


G. 1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbutan-1-one,



and enantiomer

H. 2-[4-[(*RS*)-[4-[(*Z*)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbut-1-en-1-yl]phenyl](phenyl)methyl]phenoxy]-*N*,*N*-dimethylethan-1-amine.

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Tamoxifen Oral Solution

General Notices

Action and use

Selective estrogen receptor modulator.

DEFINITION

Tamoxifen Oral Solution contains Tamoxifen Citrate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of tamoxifen, $C_{26}H_{29}NO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the oral solution containing the equivalent of 0.1 g of tamoxifen add 20 mL of *water*, warm, add 2 mL of 5M *sodium hydroxide* and cool. Extract with two 10-mL quantities of *ether*, filtering each extract in turn. Combine the ether extracts and evaporate to dryness in a current of nitrogen at room temperature. Dry the residue at a pressure not exceeding 0.7 kPa for 30 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* obtained with *tamoxifen citrate BPCRS* treated in the same manner.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light and using the following solutions.

(1) Dilute a quantity of the oral solution containing the equivalent of 50 mg of tamoxifen to 50 mL with the mobile phase.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) 0.15% w/v of *tamoxifen citrate for performance test EPCRS* in the mobile phase.
(4) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Columbus C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.

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(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for twice the retention time of the tamoxifen peak.

MOBILE PHASE

40 volumes of *acetonitrile* and 60 volumes of a mixture containing 0.09% w/v of *sodium dihydrogen orthophosphate* and 0.48% w/v of N,N-*dimethyloctylamine*, adjust the final solution to pH 3.0 with *orthophosphoric acid*.

Under the prescribed conditions the retention times relative to tamoxifen (retention time, about 20 minutes) are: *E*-isomer, about 0.8; impurity F, about 0.9).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to *E*-isomer and to tamoxifen impurity F is at least 3.0;

the resolution between the peaks due to tamoxifen impurity F and tamoxifen is at least 1.5;

the chromatographic profile closely resembles the chromatogram provided with the *tamoxifen citrate for performance test EPCRS.*

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to the *E*-isomer is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak with a retention time of less than 2.5 minutes and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for liquid chromatography, *Appendix III D*, using the following solutions.

(1) Dilute a weighed quantity of the oral solution containing the equivalent of 5 mg of tamoxifen to 50 mL with the mobile phase.
(2) 0.015% w/v of *tamoxifen citrate BPCRS* in the mobile phase.
(3) 0.15% w/v of *tamoxifen citrate for performance test EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to *E*-isomer and to tamoxifen impurity F is at least 3.0;

the resolution between the peaks due to tamoxifen impurity F and tamoxifen is at least 1.5;

the chromatographic profile closely resembles the chromatogram provided with the *tamoxifen citrate for performance test EPCRS.*

DETERMINATION OF CONTENT

Calculate the weight per mL of the oral solution. Calculate the content of tamoxifen, $C_{26}H_{29}NO$, in the oral solution using the declared content of $C_{26}H_{29}NO$, in *tamoxifen citrate BPCRS*.

STORAGE

Tamoxifen Oral Solution should be stored at room temperature and in accordance with the manufacturer's instruction.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of tamoxifen.

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Tamoxifen Tablets

General Notices

Action and use

Selective estrogen receptor modulator.

DEFINITION

Tamoxifen Tablets contain Tamoxifen Citrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tamoxifen, $C_{26}H_{29}NO$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing the equivalent of 0.1 g of tamoxifen add 20 mL of *water*, warm, add 2 mL of 5M *sodium hydroxide* and cool. Extract with two 10-mL quantities of *ether*, filtering each extract in turn. Combine the ether extracts and evaporate to dryness in a current of nitrogen at room temperature. Dry the residue at a pressure not exceeding 0.7 kPa for 30 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of tamoxifen (*RS 328*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 150 revolutions per minute.

(b) Use 1000 mL of *0.02M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, at the maximum at 275 nm, Appendix II B, using 0.02M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of $C_{26}H_{29}NO$ in the medium taking 305 as the value of A(1%, 1 cm) at 275 nm.

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light and using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 50 mg of tamoxifen, add 35 mL of the mobile phase, mix with the aid of ultrasound for 5 minutes, dilute to 50 mL with the mobile phase, mix, centrifuge and filter the supernatant liquid through a membrane filter with a nominal pore size of 0.45 µm.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.15% w/v of *tamoxifen citrate for performance test EPCRS* in the mobile phase.

(4) Dilute 1 volume of solution (2) to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Columbus C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for twice the retention time of the tamoxifen peak.

MOBILE PHASE

40 volumes of *acetonitrile* and 60 volumes of a mixture containing 0.09% w/v of *sodium dihydrogen orthophosphate* and 0.48% w/v of N,N-*dimethyloctylamine*, adjust the final solution to pH 3.0 with *orthophosphoric acid*.

Under the prescribed conditions the retention times relative to tamoxifen (retention time, about 20 minutes) are: *E*-isomer, about 0.8; impurity F, about 0.9).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to *E*-isomer and to tamoxifen impurity F is at least 3.0;

the resolution between the peaks due to tamoxifen impurity F and tamoxifen is at least 1.5;

the chromatographic profile closely resembles the chromatogram provided with the *tamoxifen citrate for performance test EPCRS.*

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to the *E*-isomer is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of all the *secondary peaks*, apart from any peak due to the *E*-isomer, is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

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Disregard any peak with a retention time of less than 2.5 minutes and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 5 mg of tamoxifen, add 35 mL of the mobile phase, mix with the aid of ultrasound for 5 minutes, dilute to 50 mL with the mobile phase and filter.
(2) 0.015% w/v of *tamoxifen citrate BPCRS* in the mobile phase.
(3) 0.15% w/v of *tamoxifen citrate for performance test EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to *E*-isomer and to tamoxifen impurity F is at least 3.0;

the resolution between the peaks due to tamoxifen impurity F and tamoxifen is at least 1.5;

the chromatogram closely resembles the chromatogram provided with the *tamoxifen citrate for performance test EPCRS.*

DETERMINATION OF CONTENT

Calculate the content of tamoxifen, $C_{26}H_{29}NO$, using the declared content of $C_{26}H_{29}NO$, in *tamoxifen citrate BPCRS.*

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of tamoxifen.

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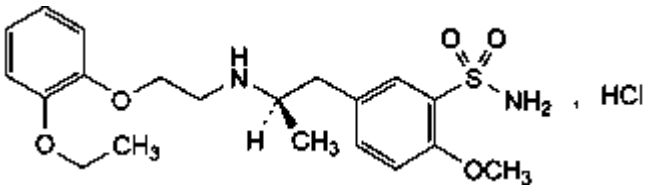
Tamsulosin Hydrochloride

General Notices

(Ph. Eur. monograph 2131)



$C_{20}H_{29}ClN_2O_5S$ 445.0 *106463-17-6*

Action and use

Alpha-1-adrenoceptor antagonist.

Preparations

Tamsulosin Prolonged-release Capsules

Tamsulosin Prolonged-release Tablets

Ph Eur

DEFINITION

5-[(2*R*)-2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in formic acid, slightly soluble in anhydrous ethanol.

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About 230 °C.

IDENTIFICATION

Carry out either tests A, C, D or tests A, B, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tamsulosin hydrochloride CRS*.

B. Specific optical rotation (2.2.7): -20.5 to -17.5 (dried substance).
Dissolve with heating 0.15 g in *water R* and dilute to 20.0 mL with the same solvent.

C. Enantiomeric purity (see Tests).

D. Dissolve with heating 0.75 g in *water R* and dilute to 100.0 mL with the same solvent. Take 5 mL of the solution and cool in an ice-bath. Add 3 mL of *dilute nitric acid R* and shake. Allow to stand at room temperature for 30 min and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

A. Impurities eluting before tamsulosin. Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of *tamsulosin impurity D CRS* and 4 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase. Dilute 2 mL of the solution to 20 mL with the mobile phase.

Reference solution (c) Dissolve 4 mg of *tamsulosin impurity H CRS* and 4 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase. Dilute 2 mL of the solution to 20 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Dissolve 3.0 g of *sodium hydroxide R* in a mixture of 8.7 mL of *perchloric acid R* and 1900 mL of *water for chromatography R*; adjust to pH 2.0 with *0.5 M sodium hydroxide* and dilute to 2000 mL with *water for chromatography R*; to 1400 mL of this solution add 600 mL of *acetonitrile for chromatography R*.

Flow rate 1.3 mL/min.

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Detection Spectrophotometer at 225 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

Run time 1.5 times the retention time of tamsulosin (retention time = about 6 min).

System suitability Reference solution (b):

— *resolution*: minimum 6.0 between the peaks due to impurity D and tamsulosin.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

B. Impurities eluting after tamsulosin. Liquid chromatography (2.2.29) as described in test A with the following modifications.

Mobile phase Dissolve 3.0 g of *sodium hydroxide R* in a mixture of 8.7 mL of *perchloric acid R* and 1900 mL of *water for chromatography R*; adjust to pH 2.0 with *0.5 M sodium hydroxide* and dilute to 2000 mL with *water for chromatography R*; add 2000 mL of *acetonitrile for chromatography R*.

Flow rate 1.0 mL/min.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 5 times the retention time of tamsulosin (retention time = about 2.5 min).

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to tamsulosin and impurity H.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities eluting before tamsulosin in test A and after tamsulosin in test B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 25.0 mL with the same solvent.

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Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *tamsulosin racemate CRS* in *methanol R* and dilute to 25 mL with the same solvent. Dilute 2 mL of the solution to 10 mL with *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R*;

— *temperature*: 40 °C.

Mobile phase *diethylamine R*, *methanol R1*, *anhydrous ethanol R*, *hexane R* (1:150:200:650 *V/V/V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Relative retention With reference to tamsulosin (retention time = about 14 min): impurity G = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity G and tamsulosin.

Limit:

— *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 5.0 mL of *anhydrous formic acid R*, add 75 mL of a mixture of 2 volumes of *acetic anhydride R* and 3 volumes of *glacial acetic acid R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 44.50 mg of $C_{20}H_{29}ClN_2O_5S$.

IMPURITIES

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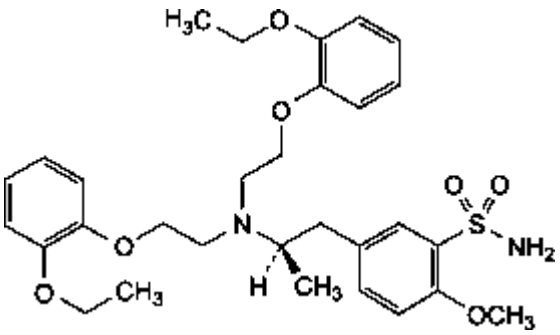
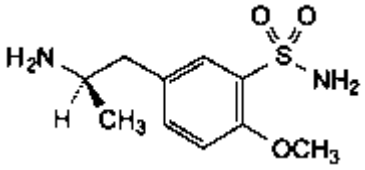
Specified impurities G.

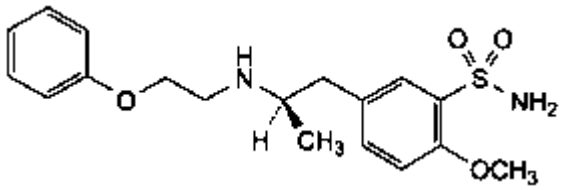
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, H, I.



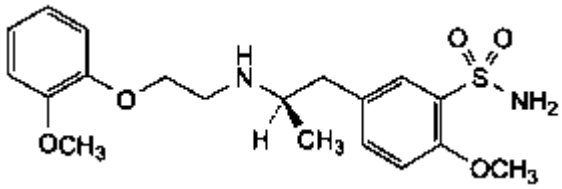
A. 5-[(2*R*)-2-[bis[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide,



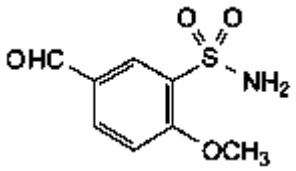
B. 5-[(2*R*)-2-aminopropyl]-2-methoxybenzenesulfonamide,



C. 2-methoxy-5-[(2*R*)-2-[(2-phenoxyethyl)amino]propyl]benzenesulfonamide,



D. 2-methoxy-5-[(2*R*)-2-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]benzenesulfonamide,



E. 5-formyl-2-methoxybenzenesulfonamide,

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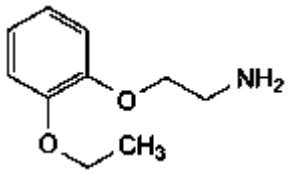
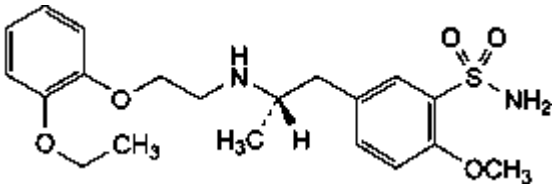
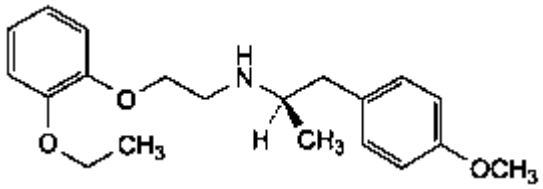


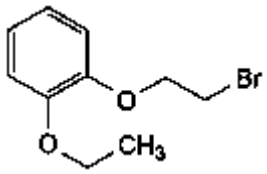
F. 2-(2-ethoxyphenoxy)ethanamine,



G. 5-[(2*S*)-2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide,



H. (2*R*)-*N*-[2-(2-ethoxyphenoxy)ethyl]-1-(4-methoxyphenyl)propan-2-amine,



I. 1-(2-bromoethoxy)-2-ethoxybenzene.

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Tamsulosin Prolonged-release Capsules

General Notices

Prolonged-release Tamsulosin Capsules

Tamsulosin Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Alpha$_1$-adrenoceptor antagonist.

DEFINITION

Tamsulosin Prolonged-release Capsules contain Tamsulosin Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Tamsulosin Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of tamsulosin hydrochloride, $C_{20}H_{28}N_2O_5S,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 400 nm of the solution prepared in the Assay exhibits a single maximum at 225 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Mix for at least 15 minutes with the aid of ultrasound and with intermittent shaking a quantity of the capsules containing 0.8 mg of Tamsulosin Hydrochloride with 10 mL of 1M *methanolic hydrochloric acid* and filter through a 0.7-µm glass fibre filter. To 1 volume of the filtrate add 4 volumes of 1M *methanolic hydrochloric acid*.

(2) Dilute 1 volume of solution (1) to 500 volumes with mobile phase.

(3) 0.0032% w/v of *tamsulosin hydrochloride impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 100Å is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 7 times the retention time of tamsulosin (retention time about 6 minutes).

MOBILE PHASE

300 volumes of *acetonitrile* and 700 volumes of *water* containing 0.44% v/v *perchloric acid* and 0.15% w/v *sodium hydroxide* previously adjusted to pH 2.0 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *tamsulosin hydrochloride impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Tamsulosin Hydrochloride comply with the requirements stated under Capsules using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Mix the contents of 1 capsule with 10 mL of 1M *methanolic hydrochloric acid* for at least 15 minutes with the aid of ultrasound and with intermittent shaking, filter through a 0.7-µm glass fibre filter, dilute 1 volume of the filtrate to 10 volumes with 1M *methanolic hydrochloric acid* and filter through a 0.7-µm glass fibre filter.

(2) Prepare a 0.040% w/v solution of *tamsulosin hydrochloride BPCRS* in *methanol* with the aid of ultrasound, cool and dilute 1 volume to 100 volumes with 1M *methanolic hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{28}N_2O_5S$,HCl in each capsule using the declared content of $C_{20}H_{28}N_2O_5S$,HCl in *tamsulosin hydrochloride BPCRS*.

ASSAY

For capsules containing less than 2 mg and/or less than 2% w/w of tamsulosin hydrochloride

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing 2 mg or more and 2% w/w or more of tamsulosin hydrochloride

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions.

(1) To a quantity of the powdered mixed contents of 20 capsules containing 1.6 mg of Tamsulosin Hydrochloride add 50 mL of 1M *methanolic hydrochloric acid*, mix for at least 15 minutes with the aid of ultrasound, cool and add sufficient 1M *methanolic hydrochloric acid* to produce 100 mL. Filter using a 0.7-µm glass fibre filter and dilute 1 volume of the filtrate to 4 volumes with 1M *methanolic hydrochloric acid*.

(2) Prepare a 0.040% w/v solution of *tamsulosin hydrochloride BPCRS* in *methanol* with the aid of ultrasound, cool and dilute 1 volume to 100 volumes with 1M *methanolic hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{28}N_2O_5S$,HCl in the capsules using the declared content of $C_{20}H_{28}N_2O_5S$,HCl in *tamsulosin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, E, F and H listed under Tamsulosin Hydrochloride.

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Tamsulosin Prolonged-release Tablets

General Notices

Prolonged-release Tamsulosin Tablets

Tamsulosin Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Alpha$_1$-adrenoceptor antagonist.

DEFINITION

Tamsulosin Prolonged-release Tablets contain Tamsulosin Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Tamsulosin Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tamsulosin hydrochloride, $C_{20}H_{28}N_2O_5S,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 400 nm of the solution prepared in the Assay exhibits a single maximum at 225 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Mix a quantity of the powdered tablets containing 0.8 mg of Tamsulosin Hydrochloride for at least 15 minutes with the aid of ultrasound, and with intermittent shaking, with 10 mL of 1M *methanolic hydrochloric acid* and filter through a 0.7-µm glass fibre filter. To 1 volume of the filtrate add 4 volumes of 1M *methanolic hydrochloric acid*.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase. Dilute 1 volume to 5 volumes with mobile phase.

(3) 0.0032% w/v of *tamsulosin hydrochloride impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 100Å is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 7 times the retention time of tamsulosin.

MOBILE PHASE

300 volumes of *acetonitrile* and 700 volumes of a solution containing 0.44% v/v of *perchloric acid* and 0.15% w/v of *sodium hydroxide* previously adjusted to pH 2.0 with 1M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of tamsulosin is about 6 minutes.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *tamsulosin hydrochloride impurity standard BPCRS*.

LIMITS

Identify any peak corresponding to impurity H in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (3) and the chromatogram supplied with *tamsulosin hydrochloride impurity standard BPCRS*.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity H is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the sum of the areas of all the *secondary peaks* is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

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Tablets containing less than 2 mg and/or less than 2% w/w of Tamsulosin Hydrochloride comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Intermittently shake 1 tablet with 10 mL of 1M *methanolic hydrochloric acid* for at least 15 minutes with the aid of ultrasound, filter through a 0.7-µm glass fibre filter, dilute 1 volume of the filtrate to 10 volumes with 1M *methanolic hydrochloric acid* and filter through a 0.7-µm glass fibre filter.
(2) Prepare a 0.04% w/v solution of *tamsulosin hydrochloride BPCRS* in *methanol* with the aid of ultrasound, cool and dilute 1 volume to 100 volumes with 1M *methanolic hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{28}N_2O_5S$,HCl in each tablet using the declared content of $C_{20}H_{28}N_2O_5S$,HCl in *tamsulosin hydrochloride BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of tamsulosin hydrochloride

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of tamsulosin hydrochloride

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 1.6 mg of Tamsulosin Hydrochloride add 50 mL of 1M *methanolic hydrochloric acid*, mix for at least 15 minutes with the aid of ultrasound, cool and add sufficient 1M *methanolic hydrochloric acid* to produce 100 mL. Filter using a 0.7-µm glass fibre filter and dilute 1 volume of the filtrate to 4 volumes with 1M *methanolic hydrochloric acid*.
(2) Prepare a 0.040% w/v solution of *tamsulosin hydrochloride BPCRS* in *methanol* with the aid of ultrasound, cool and dilute 1 volume to 100 volumes with 1M *methanolic hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{28}N_2O_5S$,HCl in the tablets using the declared content of $C_{20}H_{28}N_2O_5S$,HCl in *tamsulosin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, E, F and H listed under Tamsulosin Hydrochloride.

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Tannic Acid

General Notices

(Ph. Eur. monograph 1477)

Action and use

Astringent.

Ph Eur

DEFINITION

Mixture of esters of glucose with gallic acid and 3-galloylgallic acid.

CHARACTERS

Appearance

Yellowish-white or slightly brown amorphous light powder or shiny plates.

Solubility

Very soluble in water, freely soluble in acetone, in ethanol (96 per cent) and in glycerol (85 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Dilute 0.1 mL of solution S (see Tests) to 5 mL with *water R*. Add 0.1 mL of *ferric chloride solution R1*. A blackish-blue colour is produced which becomes green on the addition of 1 mL of *dilute sulfuric acid R*.

B. To 1 mL of solution S, add 3 mL of a 1 g/L solution of *gelatin R*. The mixture becomes turbid and a flocculent precipitate is formed.

C. Dilute 0.1 mL of solution S to 5 mL with *water R*. Add 0.3 mL of *barium hydroxide solution R*. A greenish-blue precipitate is formed.

TESTS

Solution S

Dissolve 4.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*).

Dextrins, gum, salts, sugars

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To 2 mL of solution S, add 2 mL of *ethanol (96 per cent) R*. The solution is clear. Add 1 mL of *ether R*. The solution remains clear for at least 10 min.

Resins

To 5 mL of solution S, add 5 mL of *water R*. The mixture remains clear (*2.2.1*) for at least 15 min.

Loss on drying (*2.2.32*)

Maximum 12.0 per cent, determined on 0.200 g by drying at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

STORAGE

Protected from light.

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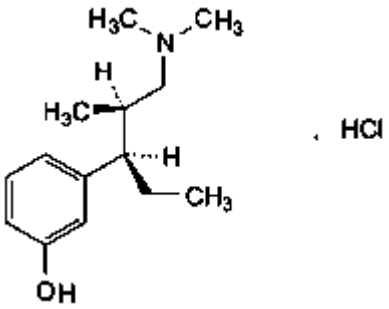
Tapentadol Hydrochloride

General Notices

(Ph. Eur. monograph 3035)



$C_{14}H_{24}ClNO$ 257.8 *175591-09-0*

Action and use

μ-Opioid receptor (OP3, MOR) agonist and noradrenaline reuptake inhibitor; analgesic.

Ph Eur

DEFINITION

3-[(2*R*,3*R*)-1-(Dimethylamino)-2-methylpentan-3-yl]phenol hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in tapentadol hydrochloride. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods 2.5.37. *Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, 2.5.38. *Methyl, ethyl and isopropyl methanesulfonate in active substances* and 2.5.39. *Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

White or almost white powder.

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Solubility

Freely soluble in water and in methanol, soluble in anhydrous ethanol, very slightly soluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tapentadol hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

C. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Solvent mixture *diethylamine R*, *2-propanol R*, *heptane R* (0.2:10:89.8 *V/V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 40 µL of *diethylamine R* and 2 mL of *2-propanol R* using sonication and dilute to 20.0 mL with *heptane R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *tapentadol impurity A CRS* and 5 mg of the substance to be examined in a mixture of 0.2 mL of *diethylamine R* and 10 mL of *2-propanol R* using sonication and dilute to 100 mL with *heptane R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm).

Mobile phase *diethylamine R*, *2-propanol R*, *heptane R* (0.1:2:98 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL.

Run time 1.5 times the retention time of tapentadol.

Relative retention With reference to tapentadol (retention time = about 13 min): impurity A = about 1.2.

System suitability Reference solution (b):

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— *resolution*: minimum 2.0 between the peaks due to tapentadol and impurity A.

Limit:

— *impurity A*: maximum 1.0 per cent, calculated as the ratio of the area of the peak due to impurity A to the sum of the areas of the peaks due to tapentadol and impurity A;

— *reporting threshold*: 0.10 per cent (reference solution (a)).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *phosphoric acid R*, *methanol R*, *water R* (0.1:20:80 *V/V/V*).

Test solution (a) Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 30.0 mg of *tapentadol hydrochloride CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 3 mg of *tapentadol impurity C CRS* in the solvent mixture and dilute to 5 mL with the solvent mixture. Add 0.5 mL of the solution to 30 mg of the substance to be examined and dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *methanol R2*, *water for chromatography R* (0.1:10:90 *V/V/V*);

— *mobile phase B*: *phosphoric acid R*, *water for chromatography R*, *methanol R2* (0.1:10:90 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 44	100 → 61	0 → 39

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
44 - 44.5	61 → 0	39 → 100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL of test solution (a) and reference solutions (b) and (c).

Relative retention With reference to tapentadol (retention time = about 15 min): impurity C = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity C and tapentadol.

Calculation of percentage contents:

— for each impurity, use the concentration of tapentadol hydrochloride in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 0.250 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{14}H_{24}ClNO$ taking into account the assigned content of *tapentadol hydrochloride CRS*.

STORAGE

Protected from light.

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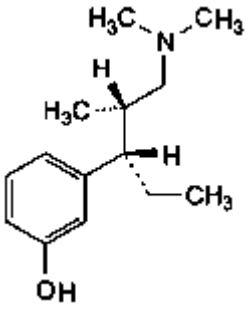
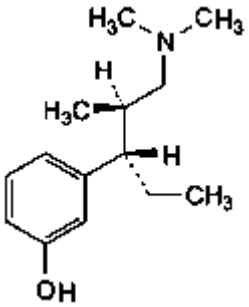
IMPURITIES

Specified impurities A.

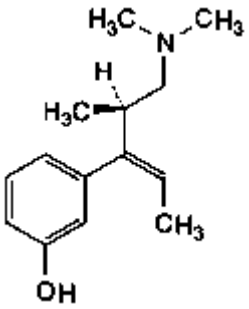
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E.



A. 3-[(2*S*,3*S*)-1-(dimethylamino)-2-methylpentan-3-yl]phenol,



B. 3-[(2*R*,3*S*)-1-(dimethylamino)-2-methylpentan-3-yl]phenol,



C. 3-[(2*Z*,4*R*)-5-(dimethylamino)-4-methylpent-2-en-3-yl]phenol,

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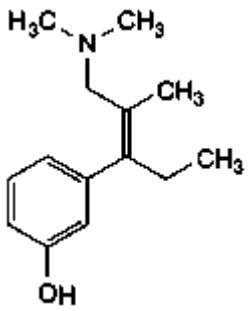
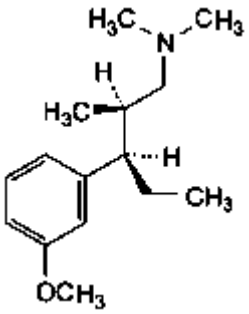


D. 3-[(2*Z*)-1-(dimethylamino)-2-methylpent-2-en-3-yl]phenol,



E. (2*R*,3*R*)-3-(3-methoxyphenyl)-*N*,*N*,2-trimethylpentan-1-amine.

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Tapioca Starch

General Notices

Cassava Starch

Action and use

Excipient.

When Starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch or, in tropical and sub-tropical countries where these are not available, Tapioca Starch may be supplied or used.

DEFINITION

Tapioca Starch is obtained from the rhizomes of *Manihot utilissima* Pohl.

CHARACTERISTICS

Very fine powder which creaks when pressed between the fingers.

Practically insoluble in cold *water* and in *ethanol (96%)*.

IDENTIFICATION

A. Principally simple granules, subspherical, muller-shaped or rounded polyhedral; smaller granules 5 to 10 µm, larger granules 20 to 35 µm in diameter; hilum, central, punctate, linear or triradiate; striations, faint, concentric; compound granules, few, of two to three unequal components.

B. Heat to boiling a suspension of 1 g in 50 mL of *water* for 1 minute and cool. A thin, cloudy mucilage is formed.

C. Mix 0.05 mL of *iodine solution R1* with 1 mL of the mucilage obtained in test B. A dark blue colour is produced which disappears on heating and reappears on cooling.

TESTS

Acidity

Add 10 g of the starch to 100 mL of *ethanol (70%)* previously neutralised to 0.5 mL of *phenolphthalein solution*, shake for 1 hour, filter and titrate 50 mL of the filtrate with *0.1M sodium hydroxide VS*. Not more than 2.0 mL is required to change the colour of the solution.

Foreign matter

Not more than traces of cell membranes and protoplasm are present.

Loss on drying

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When dried to constant weight at 100° to 105°, loses not more than 15.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.6%, Appendix IX A, Method II. Use 1 g.

Microbial contamination

1.0 g is free from *Escherichia coli,* Appendix XVI B1.

STORAGE

Tapioca Starch should be kept in an airtight container.

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Tar

General Notices

Action and use

Used in treatment of psoriasis.

DEFINITION

Tar is bituminous liquid obtained from the wood of various trees of the family Pinaceae by destructive distillation and is known in commerce as Stockholm Tar.

CHARACTERISTICS

Dark brown or nearly black, semi-liquid; denser than water.

Soluble in *ethanol (90%)*, in *ether* and in fixed and volatile oils.

IDENTIFICATION

A. The aqueous liquid obtained by shaking 1 g with 20 mL of *water* for 5 minutes is acidic to *litmus paper*.

B. Carefully add 0.5 g to 10 mL of *petroleum spirit (boiling range, 40° to 60°)* and allow to stand for 30 minutes. When examined in daylight no fluorescence is produced.

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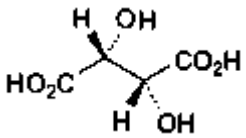
Tartaric Acid

General Notices

(Ph. Eur. monograph 0460)



$C_4H_6O_6$ 150.1 *87-69-4*

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DEFINITION

(2*R*,3*R*)-2,3-Dihydroxybutanedioic acid.

The substance is of natural origin, obtained by extraction of lees during winemaking.

Content

99.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is strongly acid (2.2.4).

B. It gives the reactions of tartrates (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *distilled water R* and dilute to 50 mL with the same solvent.

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Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

+ 12.0 to + 12.8 (dried substance).

Dissolve 5.00 g in *water R* and dilute to 25.0 mL with the same solvent.

Oxalic acid

Maximum 360 ppm, calculated as anhydrous oxalic acid.

Dissolve 0.80 g in 4 mL of *water R*. Add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules and boil for 1 min. Allow to stand for 2 min. Collect the liquid in a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of a 50 g/L solution of *potassium ferricyanide R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 4 mL of a 0.1 g/L solution of *oxalic acid R*.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 150 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 200 ppm.

To 5 mL of solution S add 10 mL of a 50 g/L solution of *sodium acetate R* in *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 0.2 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.650 g in 25 mL of *water R*. Titrate with *1 M sodium hydroxide* using 0.5 mL of *phenolphthalein solution R* as indicator, until a pink colour is obtained.

1 mL of *1 M sodium hydroxide* is equivalent to 75.05 mg of $C_4H_6O_6$.

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Teicoplanin

General Notices

(Ph. Eur. monograph 2358)

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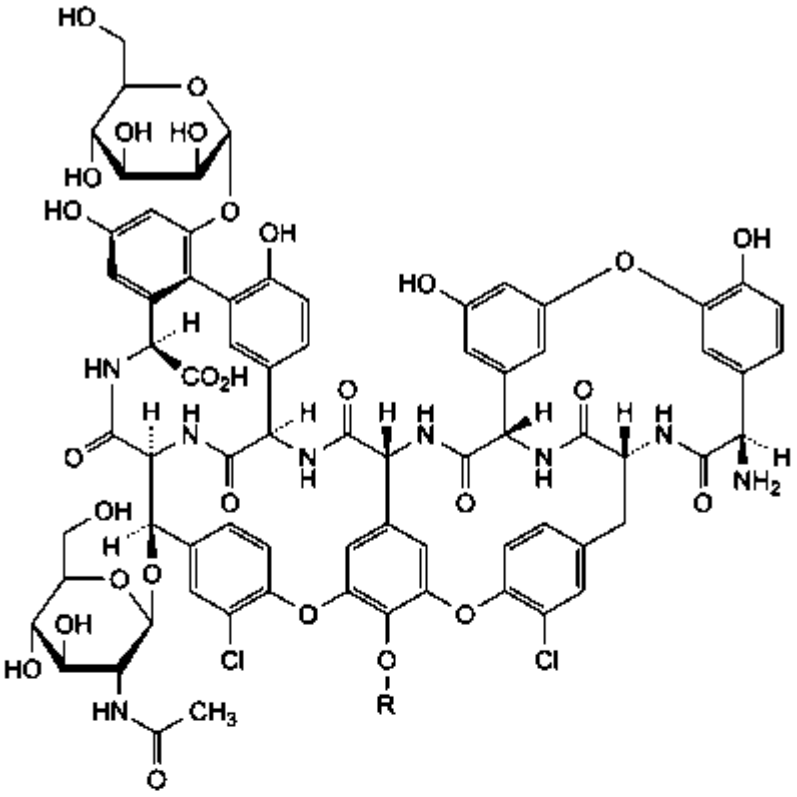
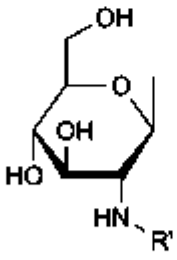
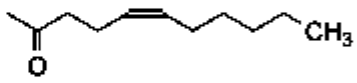
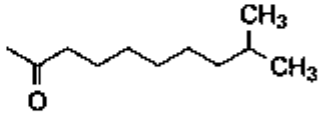
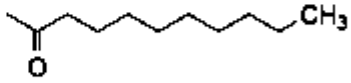
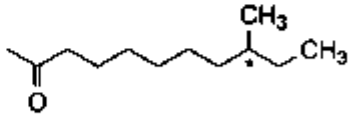
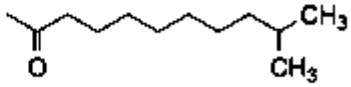


teicoplanin	R	R'
$A_{2\text{-}1}$ $C_{88}H_{95}Cl_2N_9O_{33}$ M_r 1878		
$A_{2\text{-}2}$ $C_{88}H_{97}Cl_2N_9O_{33}$ M_r 1880		
$A_{2\text{-}3}$ $C_{88}H_{97}Cl_2N_9O_{33}$ M_r 1880		
$A_{2\text{-}4}$ $C_{89}H_{99}Cl_2N_9O_{33}$ M_r 1894		
$A_{2\text{-}5}$ $C_{89}H_{99}Cl_2N_9O_{33}$ M_r 1894		
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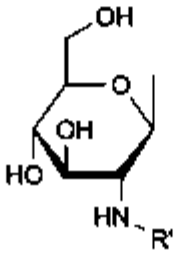
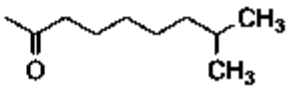
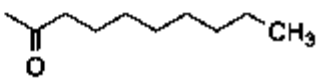
$A_{2\text{-}1a}$ $C_{87}H_{95}Cl_2N_9O_{33}$ M_r 1866		
$A_{2\text{-}1b}$ $C_{87}H_{95}Cl_2N_9O_{33}$ M_r 1866		

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Action and use

Glycopeptide antibacterial.

Preparation

Teicoplanin for Injection

Ph Eur

DEFINITION

Mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus sp.*; the 6 principal components of the mixture are teicoplanins A_{2-1} to A_{2-5} and teicoplanin A_{3-1}, and 2 minor components are teicoplanins A_{2-1a} and A_{2-1b}.

Fermentation product.

Potency

Minimum 900 IU/mg (anhydrous and sodium chloride-free substance).

CHARACTERS

Appearance

White or yellowish, amorphous powder.

Solubility

Freely soluble in water, sparingly soluble in dimethylformamide, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *teicoplanin for identification CRS*.

B. Examine the chromatograms obtained in the test for composition.

Results The principal peaks (teicoplanins A_{3-1}, A_{2-1}, A_{2-2}, A_{2-3}, A_{2-4} and A_{2-5}) and the 2 minor peaks (teicoplanins A_{2-1a} and A_{2-1b}) in the chromatogram obtained with the test solution are similar in retention time and size to the principal peaks in the chromatogram obtained with reference solution (a).

TESTS

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Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_3 or B_4 (2.2.2, Method I).

Dissolve 0.8 g in 10 mL of *water R*.

pH (2.2.3)

6.5 to 7.5.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Composition

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *teicoplanin for identification CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (c) Dissolve 50.0 mg of *mesityl oxide CRS* (impurity A) in *water R* and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 900 mL of a 3.0 g/L solution of *anhydrous sodium dihydrogen phosphate R*, adjusted to pH 6.0 with a 40 g/L solution of *sodium hydroxide R*, and 100 mL of *acetonitrile R*;

— *mobile phase B*: mix 300 mL of a 3.0 g/L solution of *anhydrous sodium dihydrogen phosphate R*, adjusted to pH 6.0 with a 40 g/L solution of *sodium hydroxide R*, and 700 mL of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 50	0 → 50
30 - 31	50 → 10	50 → 90
31 - 35	10	90

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Flow rate 2.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Identification Use the chromatogram supplied with *teicoplanin for identification CRS* and the chromatogram obtained with reference solution (a) to identify the groups and components.

Relative retention With reference to teicoplanin A_{2-2} (retention time = about 18 min):

— teicoplanin A_3 group ≤ 0.70:

— teicoplanin A_{3-1} = about 0.43.

— teicoplanin A_2 group > 0.70 including:

— teicoplanin A_{2-1} group > 0.70 and < 1.00:

— teicoplanin A_{2-1a} = about 0.85;

— teicoplanin A_{2-1b} = about 0.88;

— teicoplanin A_{2-1} = about 0.93;

— teicoplanin A_{2-2} = 1.00;

— teicoplanin A_{2-3} group > 1.00 and < 1.12:

— teicoplanin A_{2-3} = about 1.03;

— teicoplanin A_{2-4} = about 1.12;

— teicoplanin A_{2-5} group > 1.12 and < 1.25:

— teicoplanin A_{2-5} = about 1.15;

— teicoplanin A_{2-6} group ≥ 1.25:

— teicoplanin-like related substance RS A_{2-6a} = about 1.25;

— teicoplanin-like related substance RS A_{2-6b} = about 1.30;

— teicoplanin-like related substance RS A_{2-6c} = about 1.38.

System suitability:

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— the chromatogram obtained with reference solution (a) is similar to the chromatogram supplied with *teicoplanin for identification CRS*;

— *resolution*: minimum 1.0 between the peaks due to teicoplanin A_{2-4} and teicoplanin A_{2-5} in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 40 for the peak due to teicoplanin A_{2-2} in the chromatogram obtained with reference solution (b).

Calculate the percentage contents using the following equations:

teicoplanin A_3 group = $\frac{0.83 \times S_3}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_2 group = $\frac{S_2}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-1} group = $\frac{S_{2-1}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-1a} = $\frac{A_{2-1a}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-1b} = $\frac{A_{2-1b}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-1} = $\frac{A_{2-1}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-2} = $\frac{A_{2-2}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-3} group = $\frac{S_{2-3}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-3} = $\frac{A_{2-3}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-4} = $\frac{A_{2-4}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-5} group = $\frac{S_{2-5}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-5} = $\frac{A_{2-5}}{S_2 + 0.83 \times S_3} \times 100$

teicoplanin A_{2-6} group = $\frac{S_{2-6}}{S_2 + 0.83 \times S_3} \times 100$

S_2 = sum of the areas of the peaks due to teicoplanin A_2 group in the chromatogram obtained with the test solution;

S_3 = sum of the areas of the peaks due to teicoplanin A_3 group in the chromatogram obtained with the test solution; disregard any peak due to impurity A;

S_{2-6} = sum of the areas of the peaks with a relative retention greater than or equal to 1.25 in the chromatogram obtained with the test solution;

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$S_{2\text{-}1}$	=	sum of the areas of the peaks due to teicoplanin $A_{2\text{-}1}$ group in the chromatogram obtained with the test solution;
$A_{2\text{-}1a}$	=	area of the peak due to teicoplanin $A_{2\text{-}1a}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}1b}$	=	area of the peak due to teicoplanin $A_{2\text{-}1b}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}1}$	=	area of the peak due to teicoplanin $A_{2\text{-}1}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}2}$	=	area of the peak due to teicoplanin $A_{2\text{-}2}$ in the chromatogram obtained with the test solution;
$S_{2\text{-}3}$	=	sum of the areas of the peaks due to teicoplanin $A_{2\text{-}3}$ group in the chromatogram obtained with the test solution;
$A_{2\text{-}3}$	=	area of the peak due to teicoplanin $A_{2\text{-}3}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}4}$	=	area of the peak due to teicoplanin $A_{2\text{-}4}$ in the chromatogram obtained with the test solution;
$S_{2\text{-}5}$	=	sum of the areas of the peaks due to teicoplanin $A_{2\text{-}5}$ group in the chromatogram obtained with the test solution;
$A_{2\text{-}5}$	=	area of the peak due to teicoplanin $A_{2\text{-}5}$ in the chromatogram obtained with the test solution.

Limits:

— *teicoplanin A_2 group*: 84.0 per cent to 98.0 per cent;

— *teicoplanin $A_{2\text{-}2}$*: 37.0 per cent to 50.0 per cent;

— *teicoplanin $A_{2\text{-}1}$ group*: 10.0 per cent to 19.0 per cent;

— *teicoplanin $A_{2\text{-}5}$ group*: 7.0 per cent to 17.0 per cent;

— *teicoplanin $A_{2\text{-}4}$*: 7.0 per cent to 15.0 per cent;

— *teicoplanin $A_{2\text{-}5}$*: 7.0 per cent to 15.0 per cent;

— *teicoplanin $A_{2\text{-}3}$ group*: 5.0 per cent to 11.0 per cent;

— *teicoplanin A_3 group*: 4.0 per cent to 12.0 per cent;

— *teicoplanin $A_{2\text{-}3}$*: 4.0 per cent to 8.5 per cent;

— *teicoplanin $A_{2\text{-}1}$*: 2.0 per cent to 7.0 per cent;

— *teicoplanin $A_{2\text{-}1a}$*: 0.5 per cent to 5.5 per cent;

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— *teicoplanin $A_{2\text{-}1b}$*: 0.5 per cent to 4.0 per cent;

— *teicoplanin $A_{2\text{-}6}$ group*: maximum 5.0 per cent;

— *disregard limit*: 0.25 per cent.

Related substances

Liquid chromatography (2.2.29) as described in the test for composition. Use the normalisation procedure.

Use the chromatogram obtained with reference solution (a) to identify all peaks present above the disregard limit as teicoplanin-like related substances. Any peak present in any part of the chromatogram obtained with the test solution that cannot be correlated to a peak above the disregard limit in reference solution (a) should be considered as a non-teicoplanin-like impurity, unless it is characterized by other means.

A teicoplanin-like related substance is defined as a substance that shares the same glycopeptide core structure of the parent molecule, composed of a linear heptapeptide aglycone, an α-D-mannose and an acetyl-β-D-glucosamine.

The R′ side chains in the teicoplanin-like related substances RS $A_{2\text{-}6a}$, RS $A_{2\text{-}6b}$ and RS $A_{2\text{-}6c}$ are unknown.

Calculate the percentage contents using the following equations:

teicoplanin-like related substance (x) = $\frac{A_{\mathrm{RSTLx}}}{\left(S2 + 0.83 \times S_3\right)} \times 100$

A_{RSTLx} = area of the peak due to the teicoplanin-like related substance (x) in the chromatogram obtained with the test solution;

non-teicoplanin-like impurity (x) = $\frac{A_{\mathrm{Ix}}}{\left(S2 + 0.83 \times S_3\right)} \times 100$

A_{Ix} = area of the peak due to the non-teicoplanin-like impurity (x) in the chromatogram obtained with the test solution.

Limits:

— *teicoplanin-like related substance RS $A_{2\text{-}6c}$*: maximum 2.5 per cent;

— *teicoplanin-like related substance RS $A_{2\text{-}6a}$*: maximum 1.5 per cent;

— *teicoplanin-like related substance RS $A_{2\text{-}6b}$*: maximum 1.5 per cent;

— *any non-teicoplanin-like impurity other than impurity A*: maximum 0.5 per cent;

— *total non-teicoplanin-like impurities other than impurity A*: maximum 1.5 per cent.

Impurity A

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Liquid chromatography (2.2.29) as described in the test for composition with the following modifications.

Injection 20 µL of the test solution and reference solution (c).

Relative retention With reference to teicoplanin A_{2-2} (retention time = about 18 min): impurity A = about 0.6.

Calculation of percentage content:

— for impurity A, use the concentration of impurity A in reference solution (c).

Limit:

— *impurity A*: maximum 0.2 per cent.

Chlorides

Maximum 5.0 per cent, expressed as sodium chloride (anhydrous substance).

Dissolve 1.000 g in 300 mL of *water R*, stir and acidify with 2 mL of *nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Water (2.5.12)

Maximum 15.0 per cent, determined on 0.300 g.

ASSAY

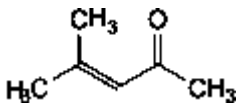
Carry out the microbiological assay of antibiotics (2.7.2), using the diffusion method. Use *teicoplanin CRS* as the reference substance.

STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A.*



A. 4-methylpent-3-en-2-one (mesityl oxide).

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Teicoplanin for Injection

General Notices

Action and use

Glycopeptide antibacterial.

DEFINITION

Teicoplanin for Injection is a sterile material consisting of Teicoplanin with or without excipients. It is supplied in a sealed container.

The contents of the sealed container complies with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the reference spectrum of teicoplanin *(RS 510)*.

TESTS

Acidity or alkalinity

pH of the injection reconstituted according to the manufacturer's instructions, 6.0 to 8.0, Appendix V L.

Composition

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation* procedure.

(1) Dissolve a quantity of the contents of a sealed container in sufficient *water* to produce a solution containing 200,000 IU of Teicoplanin per mL.

(2) 0.2% w/v *teicoplanin for identification EPCRS*.

(3) Dilute 1 volume of solution (2) to 20 volumes.

(4) 0.002% w/v *mesityl oxide EPCRS* (impurity A).

(5) Dilute 1 volume of solution (1) to 100 volumes. Further dilute 1 volume of this solution to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS-RP 18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2.3 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

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(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *acetonitrile* and 9 volumes of a 0.3% w/v solution of *sodium dihydrogen orthophosphate* previously adjusted to pH 6.0 with 1M *sodium hydroxide*.

Mobile phase B 300 volumes of a 0.3% w/v solution of *sodium dihydrogen orthophosphate* previously adjusted to pH 6.0 with 1M *sodium hydroxide* and 700 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	100→50	0→50	linear gradient
30-31	50→10	50→90	linear gradient
31-35	10	90	isocratic
35-36	10→100	90→0	linear gradient
36-40	100	0	re-equilibration

Use the chromatogram supplied with *teicoplanin for identification EPCRS* and the chromatogram obtained with solution (2) to identify the groups and components of teicoplanin.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to teicoplanin A_{2-2} (retention time about 18 minutes) are detailed in the following table.

Group	Subgroup	Component	Relative retention
teicoplanin A_3 group			≤0.70
		teicoplanin A_{3-1}	about 0.43
teicoplanin A_2 group			>0.70
	teicoplanin A_{2-1} group		>0.70 and <1.00
		teicoplanin A_{2-1a}	about 0.85
		teicoplanin A_{2-1b}	about 0.88
		teicoplanin A_{2-1}	about 0.93
		teicoplanin A_{2-2}	1.00
	teicoplanin A_{2-3} group		>1.00 and <1.12
		teicoplanin A_{2-3}	about 1.03

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Group	Subgroup	Component	Relative retention
		teicoplanin A_{2-4}	about 1.12
	teicoplanin A_{2-5} group		>1.12 and <1.25
		teicoplanin A_{2-5}	about 1.15
	teicoplanin A_{2-6} group		≥1.12
		teicoplanin-like related substance RS A_{2-6a}	about 1.25
		teicoplanin-like related substance RS A_{2-6b}	about 1.30
		teicoplanin-like related substance RS A_{2-6c}	about 1.38

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to teicoplanin A_{2-4} and teicoplanin A_{2-5} is at least 1.0;

in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of the peak due to teicoplanin A_{2-2} is at least 40.

CALCULATION OF IMPURITIES

In the chromatogram obtained with solution (1), integrate all peaks present with an area greater than the area of the principal peak in the chromatogram obtained with solution (5) and use the following equation to determine total peak area. Use the chromatogram obtained with solution (4) to identify any peak present due to impurity A.

$S_2 + (0.83 \times S_3)$

where:

S_2 = sum of the areas of the peaks due to teicoplanin A_2 group;

S_3 = sum of the areas of the peaks due to teicoplanin A_3 group disregarding any peak due to impurity A;

Calculate the percentage content for each teicoplanin groups and components in the injection by *normalisation*.

LIMITS

The proportions are within the following limits:

— teicoplanin A_2 group: not less than 78%;

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— teicoplanin A_3 group: not more than 17%.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, as described in the test for Composition.

CALCULATION OF IMPURITIES

Use the chromatogram obtained with solution (2) to identify all peaks present above the disregard limit as teicoplanin-like related substances. Any peak present in any part of the chromatogram obtained with solution (1) that cannot be correlated to a peak above the disregard limit in solution (2) should be considered as a non-teicoplanin-like impurity, unless it is characterised by other means. Use the chromatogram obtained with solution (4) to identify any peak present due to impurity A.

A teicoplanin-like related substance is defined as a substance that shares the same glycopeptide core structure of the parent molecule, composed of a linear heptapeptide aglycone, an α-D-mannose and an acetyl-β-D-glucosamine.

The R' side chains in the teicoplanin-like related substances RS $A_{2\text{-}6a}$, RS $A_{2\text{-}6b}$ and RS $A_{2\text{-}6c}$ are unknown.

Calculate the percentage content of the impurities in the injection by *normalisation*.

LIMITS

— any non-teicoplanin-like impurity: not more than 0.5%;

— total non-teicoplanin-like impurities: not more than 1.5%;

— Disregard any peak due to impurity A.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Mix the contents of the 10 containers and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

For a container of average content weight, the upper fiducial limit of error is not less than 95.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU.

LABELLING

The label of the sealed container states (1) the total number of IU (Units) contained in it; (2) the number of IU (Units) per mg.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Teicoplanin.

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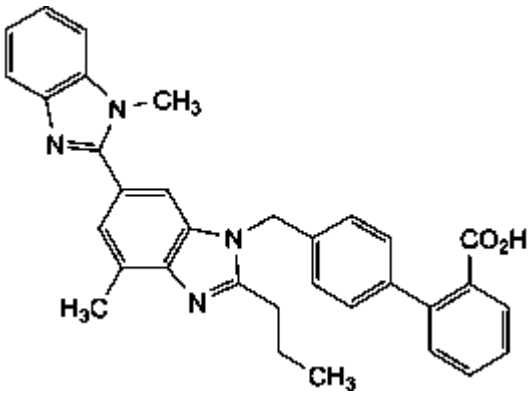
Telmisartan

General Notices

(Ph. Eur. monograph 2154)



$C_{33}H_{30}N_4O_2$ 514.6 *144701-48-4*

Action and use

Angiotensin II (AT_1) receptor antagonist.

Preparation

Telmisartan Tablets

Ph Eur

DEFINITION

4′-[[4-Methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

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Practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride. It dissolves in a 40 g/L solution of *sodium hydroxide R*.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *telmisartan CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in hot *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution Y_4 (*2.2.2, Method II*).

Dissolve 0.5 g in a 40 g/L solution of *sodium hydroxide R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution To 25 mg of the substance to be examined add about 5 mL of *methanol R* and 100 µL of a 40 g/L solution of *sodium hydroxide R*. Dissolve using sonication and dilute to 50.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve the contents of a vial of *telmisartan for system suitability CRS* (containing impurities A, B, C, E and F) in 2 mL of *methanol R*.

Reference solution (c) To 5 mg of *telmisartan for peak identification CRS* (containing impurity D) add about 5 mL of *methanol R* and 100 µL of a 40 g/L solution of *sodium hydroxide R*. Dissolve using sonication and dilute to 10 mL with *methanol R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm;

— *temperature*: 40 °C.

Mobile phase:

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— *mobile phase A*: dissolve 2.0 g of *potassium dihydrogen phosphate R* and 3.8 g of *sodium pentanesulfonate monohydrate R1* in 900 mL of *water for chromatography R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	70	30
3 - 28	70 → 20	30 → 80

Flow rate 1 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *telmisartan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, E and F; use the chromatogram supplied with *telmisartan for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to telmisartan (retention time = about 15 min): impurity A = about 0.2; impurity E = about 0.6; impurity F = about 0.7; impurity B = about 0.9; impurity C = about 1.5; impurity D = about 1.6.

System suitability Reference solution (b):

— the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with *telmisartan for system suitability CRS*;

— *resolution*: minimum 3.0 between the peaks due to impurity B and telmisartan.

Limits:

— *impurities C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities A, B*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

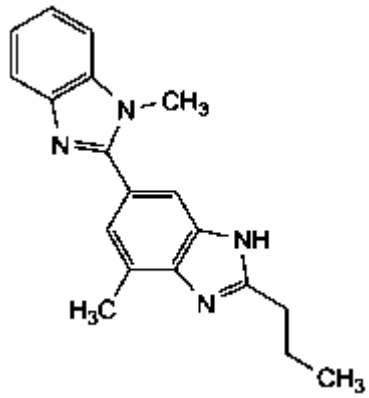
Dissolve 0.190 g in 5 mL of *anhydrous formic acid R*. Add 75 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.73 mg of $C_{33}H_{30}N_4O_2$.

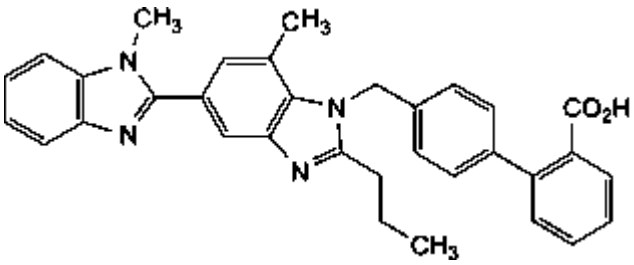
IMPURITIES

Specified impurities *A, B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, G, H, I, J.*



A. 4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazole,



B. 4′-[[7-methyl-5-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl][1,1′-biphenyl]-2-carboxylic acid,

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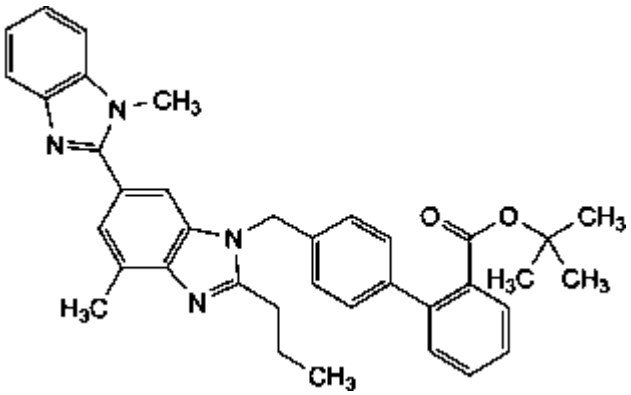
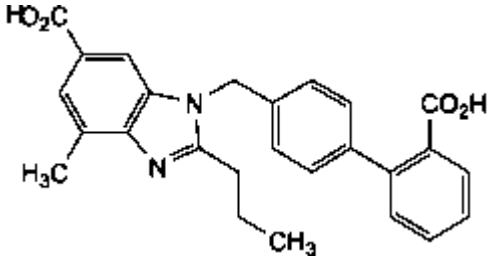
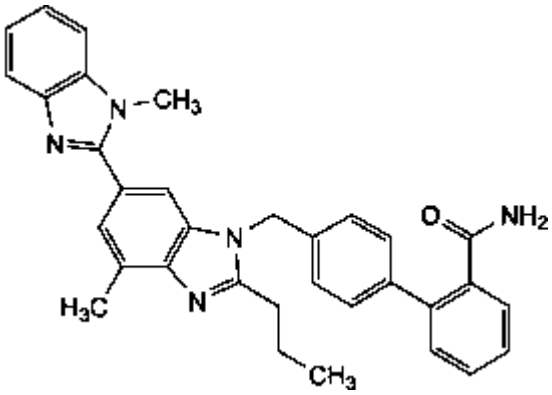


C. *tert*-butyl 4′-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl][1,1′-biphenyl]-2-carboxylate,

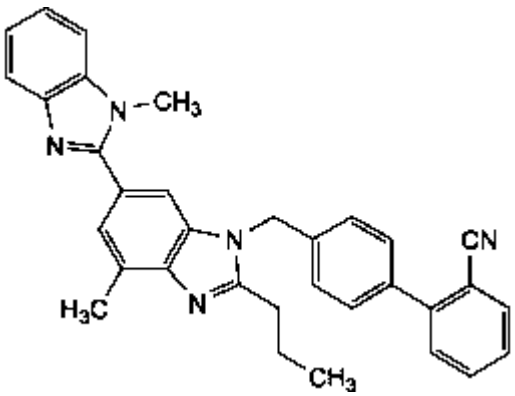
D. unknown structure,



E. 1-[(2′-carboxy[1,1′-biphenyl]-4-yl)methyl]-4-methyl-2-propyl-1*H*-benzimidazole-6-carboxylic acid,



F. 4′-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl][1,1′-biphenyl]-2-carboxamide,



G. 4′-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl][1,1′-biphenyl]-2-carbonitrile,

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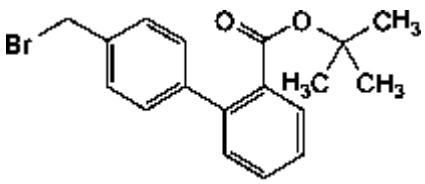
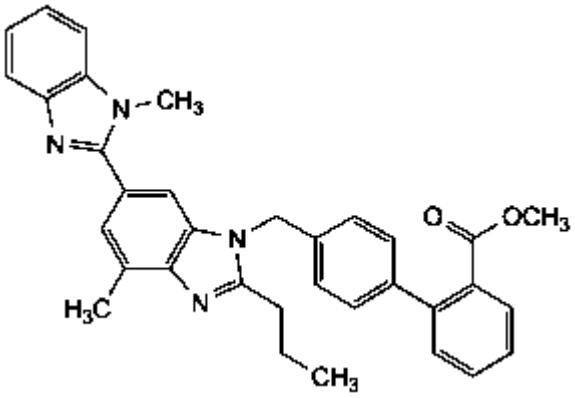
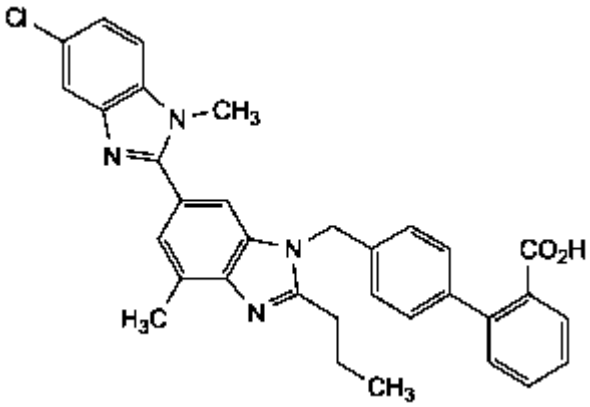


H. *tert*-butyl 4′-(bromomethyl)[1,1′-biphenyl]-2-carboxylate,



I. methyl 4′-[(1,7′-dimethyl-2′-propyl-1*H*,3′*H*-[2,5′-bibenzimidazol]-3′-yl)methyl][1,1′-biphenyl]-2-carboxylate,



J. 4′-[(5-chloro-1,7′-dimethyl-2′-propyl-1*H*,3′*H*-[2,5′-bibenzimidazol]-3′-yl)methyl][1,1′-biphenyl]-2-carboxylic acid.

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Telmisartan Tablets

General Notices

Action and use

Angiotensin II (AT_1) receptor antagonist.

DEFINITION

Telmisartan Tablets contain Telmisartan.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of telmisartan, $C_{33}H_{30}N_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of powdered tablets containing 80 mg of Telmisartan with 15 mL of *water*, filter and discard the filtrate. Extract the residue from the filter with 15 mL of *dichloromethane* in a flask and with the aid of ultrasound. Transfer this solution to a separating funnel, add 15 mL of *water* and shake. Separate the dichloromethane layer and evaporate to dryness under a stream of nitrogen. To the residue, add 10 mL of *acetonitrile* and filter. Evaporate the filtrate to dryness under a stream of nitrogen and dry the residue at 105° for 1 hour. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of telmisartan (*RS 486*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, and rotate the paddle at 75 revolutions per minute.

(b) Use 900 mL of a pH 7.5 phosphate buffer solution, prepared by dissolving 13.61 g of *potassium dihydrogen orthophosphate* in 800 mL of *water*, adjusted to pH 7.5 using *2M sodium hydroxide* and diluted to 1000 mL, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10-mL sample of the medium and measure the *absorbance* of the filtered sample, diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.001% w/v of Telmisartan, at the maximum at 296 nm, Appendix II B using dissolution medium in the reference cell.

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(2) To about 40 mg of *telmisartan BPCRS* add 1 mL of *0.1M sodium hydroxide* and sufficient *methanol* to produce a solution containing 0.04% w/v of Telmisartan. Dilute 1 volume of this solution to 40 volumes with the dissolution medium. Measure the *absorbance* of this solution using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of telmisartan, $C_{33}H_{30}N_4O_2$, in the medium from the absorbances obtained and using the declared content of $C_{33}H_{30}N_4O_2$ in *telmisartan BPCRS*.

LIMITS

The amount of telmisartan released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the powdered tablets containing 25 mg of Telmisartan in 5 mL of *methanol* and 100 µL of a 4% w/v solution of *sodium hydroxide* and mix with the aid of ultrasound. Add sufficient *methanol* to produce a solution containing 0.05% w/v of Telmisartan.
(2) Dilute 1 volume of solution (1) to 10 volumes with *methanol*. Dilute 1 volume of this solution to 100 volumes with *methanol*.
(3) Dissolve the contents of a vial of *telmisartan for system suitability EPCRS* in 2 mL of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 2.0 g of *potassium dihydrogen orthophosphate* and 3.8 g of *sodium pentanesulfonate monohydrate* in 950 mL *water*, adjust to pH 3.0 with *dilute orthophosphoric acid* and dilute to 1000 mL with *water*.

Mobile phase B 20 volumes of *methanol* and 80 volumes of *acetonitrile*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	70	30	isocratic
3-28	70→20	30→80	linear gradient
28-30	20→70	80→30	linear gradient
30-35	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to telmisartan (retention time about 15 minutes) are: impurity A, about 0.2; impurity E, about 0.6; impurity F, about 0.7; impurity B, about 0.9; impurity C, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) is similar to the chromatogram supplied with *telmisartan for system suitability EPCRS* and the *resolution* between the peaks due to impurity B and telmisartan is at least 3.0.

LIMITS

Use the chromatogram supplied with *telmisartan for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B, C, E and F. In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any peak corresponding to impurity A or B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the powdered tablets containing 25 mg of Telmisartan in 5 mL of *methanol* and 100 µL of a 4% w/v solution of *sodium hydroxide*. Mix with the aid of ultrasound, dilute to 50 mL with *methanol* and filter. To the filtrate, add sufficient *methanol* to produce a solution containing 0.0005% w/v of Telmisartan.

(2) 0.0005% w/v of *telmisartan BPCRS* in *methanol*.

(3) Dissolve the contents of a vial of *telmisartan for system suitability EPCRS* in 2 mL of *methanol*.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) is similar to the chromatogram supplied with *telmisartan for system suitability EPCRS* and the *resolution* between the peaks due to impurity B and telmisartan is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{33}H_{30}N_4O_2$ in the tablets using the declared content of $C_{33}H_{30}N_4O_2$ in *telmisartan BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, E and F listed under Telmisartan.

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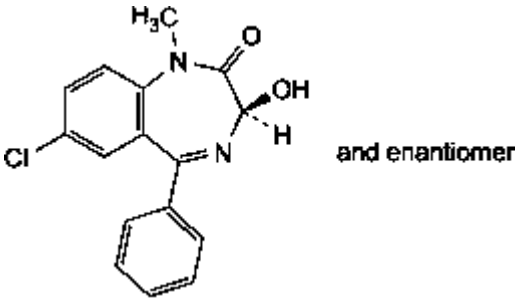
Temazepam

General Notices

(Ph. Eur. monograph 0954)



$C_{16}H_{13}ClN_2O_2$ 300.7 *846-50-4*

Action and use

Benzodiazepine.

Preparations

Temazepam Oral Solution

Temazepam Tablets

Ph Eur

DEFINITION

(3*RS*)-7-Chloro-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison temazepam CRS.

TESTS

Impurity A

Maximum 0.05 per cent.

Dissolve 0.400 g in methylene chloride R and dilute to 20.0 mL with the same solvent. The absorbance (2.2.25) is not greater than 0.30 at 409 nm.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 1 volume of water R and 9 volumes of methanol R and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of 1 volume of water R and 9 volumes of methanol R. Dilute 2.0 mL of this solution to 10.0 mL with a mixture of 1 volume of water R and 9 volumes of methanol R.

Reference solution (b) Dissolve 1 mg of oxazepam R, 1 mg of temazepam impurity F CRS and 1 mg of temazepam impurity G CRS in a mixture of 1 volume of water R and 9 volumes of methanol R and dilute to 25 mL with the same mixture of solvents.

Reference solution (c) Dissolve 1 mg of temazepam impurity C CRS and 1 mg of temazepam impurity D CRS with a mixture of 1 volume of water R and 9 volumes of methanol R and dilute to 25 mL with the same mixture of solvents.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3.5 µm).

Mobile phase:

— *mobile phase A*: solution containing 4.9 g/L of sodium dihydrogen phosphate R and 0.63 g/L of disodium hydrogen phosphate dodecahydrate R (pH 5.6);

— *mobile phase B*: methanol R;

— *mobile phase C*: acetonitrile R;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 18	54	39	7
18 - 25	54 → 22	39 → 63	7 → 15
25 - 31	22	63	15
31 - 37	22 → 54	63 → 39	15 → 7

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to temazepam (retention time = about 16 min): impurity E = about 0.55; impurity F = about 0.67; impurity G = about 0.73; impurity B = about 0.8; impurity D = about 1.2; impurity C = about 1.3; impurity A = about 1.5.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity F and impurity G;

— *peak-to-valley ratio*: minimum 1.7, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity F = 3.2; impurity G = 3.1;

— *impurities B, C, D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.250 g in 50 mL of *nitroethane R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

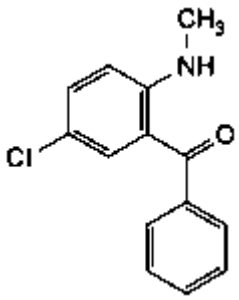
1 mL of *0.1 M perchloric acid* is equivalent to 30.07 mg of $C_{16}H_{13}ClN_2O_2$.

STORAGE

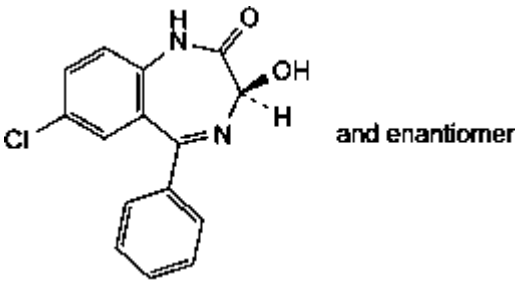
Protected from light.

IMPURITIES

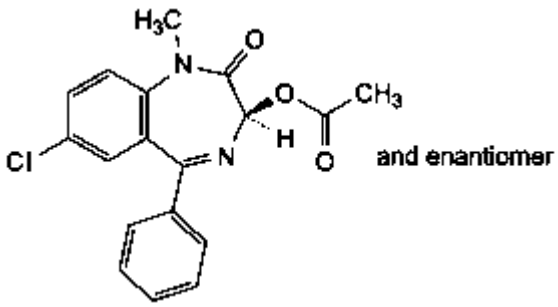
Specified impurities *A, B, C, D, E, F, G.*



A. [5-chloro-2-(methylamino)phenyl]phenylmethanone,



B. (3*RS*)-7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (oxazepam),



C. (3*RS*)-7-chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl acetate,

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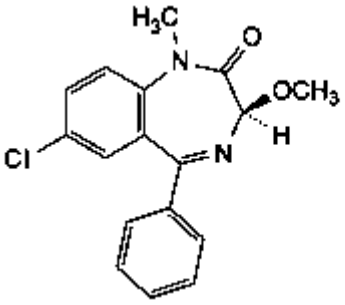
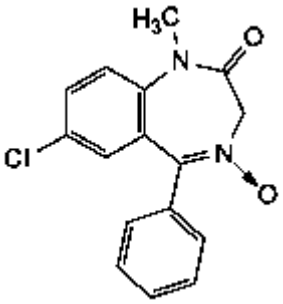
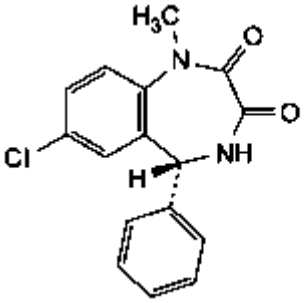


and enantiomer

D. (3*RS*)-7-chloro-3-methoxy-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,

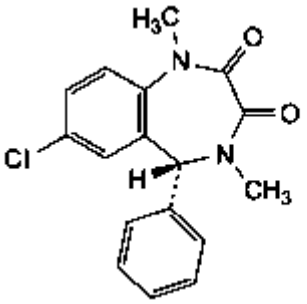


E. 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,



and enantiomer

F. (5*RS*)-7-chloro-1-methyl-5-phenyl-4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione,



and enantiomer

G. (5*RS*)-7-chloro-1,4-dimethyl-5-phenyl-4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione.

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Temazepam Oral Solution

General Notices

Action and use

Benzodiazepine.

DEFINITION

Temazepam Oral Solution is a solution of Temazepam in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of temazepam, $C_{16}H_{13}ClN_2O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the oral solution with sufficient 0.1M *methanolic hydrochloric acid* to produce a solution containing 0.001% w/v of Temazepam. The *light absorption* of the resulting solution, Appendix II B, in the range 210 to 400 nm exhibits three maxima, at 238 nm, 283 nm and 358 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 50 volumes of *cyclohexane*, 40 volumes of *chloroform* and 10 volumes of *diethylamine* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) add 5 mL of *water* to a quantity of the oral solution containing 10 mg of Temazepam and extract with two 10-mL quantities of *ether*. Evaporate the combined ether extracts almost to dryness and dissolve the residue in 2 mL of *acetone*. Solution (2) contains 0.5% w/v of *temazepam BPCRS* in *acetone*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. In the Assay, the chromatogram obtained with solution (2) exhibits a peak with the same retention time as that due to temazepam in the chromatogram obtained with solution (1).

TESTS

Alkalinity

pH, 7.3 to 8.3, Appendix V L.

6-Chloro-1,4-dihydro-1-methyl-4-phenylquinazolin-4-ol

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Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 92.5 volumes of *chloroform* and 7.5 volumes of *methanol* as the mobile phase but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) add 5 mL of *water* to a quantity of the oral solution containing 10 mg of Temazepam and extract with two 10-mL quantities of *ether*. Evaporate the combined ether extracts almost to dryness and dissolve the residue in 1 mL of *acetone*. Solution (2) contains 0.010% w/v of *6-chloro-1,4-dihydro-1-methyl-4-phenylquinazolin-4-ol BPCRS*. After removal of the plate, allow it to dry in a current of warm air and examine under *ultraviolet light* (*365 nm*). In the chromatogram obtained with solution (1) any spot corresponding to 6-chloro-1,4-dihydro-1-methyl-4-phenylquinazolin-4-ol is not more intense than the spot in the chromatogram obtained with solution (2).

5-Chloro-2-methylaminobenzophenone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.00050% w/v of *5-chloro-2-methylaminobenzophenone BPCRS* in *methanol* (*50%*). For solution (2) dilute a quantity of the oral solution with sufficient *methanol* (*50%*) to produce a solution containing 0.020% w/v of Temazepam.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 5 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP-18 is suitable), (b) a mixture of 75 volumes of *methanol*, 25 volumes of *water* and 0.03 volume of *diethylamine* as the mobile phase with a flow rate of 1.5 mL per minute and (c) a detection wavelength of 254 nm.

In the chromatogram obtained with solution (2) the area of any peak corresponding to 5-chloro-2-methylaminobenzophenone is not greater than the area of the peak in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.02% w/v of *temazepam BPCRS* in *methanol* (*50%*). For solution (2) add sufficient *methanol* (*50%*) to a weighed quantity of the oral solution containing 20 mg of Temazepam to produce 100 mL.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable), (b) a mixture of 60 volumes of *methanol*, 40 volumes of *water* and 0.03 volumes of *diethylamine* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 254 nm.

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{16}H_{13}ClN_2O_2$, weight in volume, using the declared content of $C_{16}H_{13}ClN_2O_2$ in *temazepam BPCRS*.

STORAGE

Temazepam Oral Solution should be protected from light.

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Temazepam Tablets

General Notices

Action and use

Benzodiazepine.

DEFINITION

Temazepam Tablets contain Temazepam.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of temazepam, $C_{16}H_{13}ClN_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 400 nm of the final solution obtained in the Assay exhibits two maxima at 230 nm and at 315 nm and a shoulder at 250 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 10 volumes of *diethylamine* and 90 volumes of *ether* as the mobile phase. Apply separately to the plate 5 µl of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 20 mg of Temazepam for 5 minutes with 20 ml of *methanol* and filter. Solution (2) contains 0.10% w/v of *temazepam BPCRS* in *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The chromatogram obtained with solution (1) exhibits a spot which corresponds to the spot in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 ml of *0.1M hydrochloric acid* and rotate the paddle at 50 revolutions per minute. Measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted if necessary, with *0.1M hydrochloric acid*, at the maximum at 237 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell. Measure the *absorbance* of a suitable solution of *temazepam BPCRS* in the dissolution medium and calculate the total content of temazepam, $C_{16}H_{13}ClN_2O_2$, in the medium from the absorbances obtained and from the declared content of $C_{16}H_{13}ClN_2O_2$ in *temazepam BPCRS*.

Related substances

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Carry out the test protected from light. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 2 volumes of *methanol* and 98 volumes of *dichloromethane* as the mobile phase. Apply separately to the plate 20 µl of each of the following solutions, prepared immediately before use, in low-actinic glassware. For solution (1) shake a quantity of the powdered tablets containing 50 mg of Temazepam for 10 minutes with 5 ml of a mixture of equal volumes of *dichloromethane* and *methanol* and filter. For solution (2) dilute 1 volume of solution (1) to 200 volumes with the same solvent mixture. For solution (3) dilute 2 volumes of solution (2) to 5 volumes with the same solvent mixture. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing 20 mg of Temazepam with 75 ml of *methanol* for 20 minutes, dilute to 100 ml with the same solvent and filter. Dilute 10 ml of the resulting filtrate to 250 ml with *methanol* and measure the *absorbance* of the resulting solution at the maximum at about 230 nm, Appendix II B. Calculate the content of $C_{16}H_{13}ClN_2O_2$ in the tablets from the *absorbance* obtained using a 0.0008% w/v solution of *temazepam BPCRS* in *methanol* and using the declared content of $C_{16}H_{13}ClN_2O_2$ in *temazepam BPCRS*.

STORAGE

Temazepam Tablets should be protected from light.

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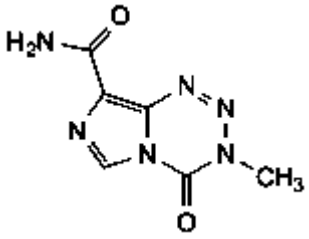
Temozolomide

General Notices

(Ph. Eur. monograph 2780)



$C_6H_6N_6O_2$ 194.2 *85622-93-1*

Action and use

Antineoplastic alkylating agent.

Preparations

Temozolomide Capsules

Temozolomide for Injection

Ph Eur

DEFINITION

3-Methyl-4-oxo-3,4-dihydroimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly brown or slightly pink powder.

Solubility

Sparingly soluble in water, soluble in dimethyl sulfoxide, very slightly soluble in ethanol (96 per cent), practically insoluble in toluene.

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison temozolomide CRS.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in dimethyl sulfoxide R and dilute to 25.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with dimethyl sulfoxide R.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with dimethyl sulfoxide R. Dilute 1.0 mL of this solution to 10.0 mL with dimethyl sulfoxide R.

Reference solution (b) In order to prepare impurities A, B and E *in situ*, mix 5 mL of a 10.3 g/L solution of hydrochloric acid R and 5 mL of test solution (a). Heat the mixture in a water-bath for 1 h.

Reference solution (c) Dissolve 2 mg of temozolomide for peak identification CRS (containing impurity D) in 2 mL of dimethyl sulfoxide R.

Reference solution (d) Dissolve 25.0 mg of temozolomide CRS in dimethyl sulfoxide R and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with dimethyl sulfoxide R.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase 0.94 g/L solution of sodium hexanesulfonate R in a mixture of 4 volumes of methanol R and 96 volumes of a 0.5 per cent *V/V* solution of glacial acetic acid R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time 3 times the retention time of temozolomide.

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Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and E; use the chromatogram supplied with *temozolomide for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to temozolomide (retention time = about 11 min): impurity E = about 0.4; impurity D = about 0.5; impurity B = about 0.9; impurity A = about 1.7. The peak due to impurity A in the chromatogram obtained with test solution (a) may be split.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity B and temozolomide.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.4; impurity E = 0.6;

— for each impurity, use the concentration of temozolomide in reference solution (a).

Limits:

— *impurity D*: maximum 0.5 per cent;

— *impurity A* (*sum of the peaks*): maximum 0.15 per cent;

— *impurities B, E*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.8 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 0.4 per cent, determined on 50.0 mg.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_6H_6N_6O_2$ taking into account the assigned content of *temozolomide CRS*.

IMPURITIES

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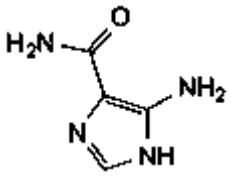
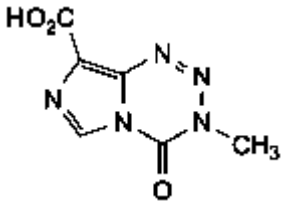
Specified impurities *A, B, D, E.*

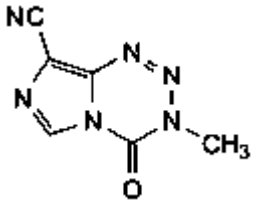
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



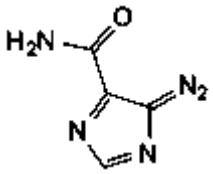
A. 5-amino-1*H*-imidazole-4-carboxamide,



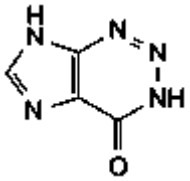
B. 3-methyl-4-oxo-3,4-dihydroimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylic acid,



C. 3-methyl-4-oxo-3,4-dihydroimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carbonitrile,



D. 4-diazo-4*H*-imidazole-5-carboxamide,



E. 3,7-dihydro-4*H*-imidazo[4,5-*d*][1,2,3]triazin-4-one (2-azahypoxanthine).

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Temozolomide Capsules

General Notices

Action and use

Antineoplastic alkylating agent.

DEFINITION

Temozolomide Capsules contain Temozolomide.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of temozolomide, $C_6H_6N_6O_2$

For capsules containing 5 mg or less of Temozolomide

93.0 to 105.0% of the stated amount.

For capsules containing more than 5 mg of Temozolomide

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

(1) Stir, using a magnetic stirrer, a quantity of capsule contents with sufficient *acetonitrile* to produce a solution expected to contain 0.1% w/v of Temozolomide. Mix with the aid of ultrasound and allow to settle.

(2) 0.1% w/v of *temozolomide EPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

15 volumes of *toluene* and 90 volumes of *acetone*.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) For capsules containing more than 5 mg of Temozolomide, use 900 mL of *water*, at a temperature of 37°, as the medium.

(c) For capsules containing 5 mg of Temozolomide, use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the absorbance of the filtered sample, suitably diluted with the dissolution medium if necessary to produce a solution expected to contain 0.001% w/v of Temozolomide, at the maximum at 328 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the absorbance of a 0.001% w/v solution of *temozolomide EPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of Temozolomide, $C_6H_6N_6O_2$, in the medium from the absorbances obtained and using the declared content of $C_6H_6N_6O_2$, in *temozolomide EPCRS*.

LIMITS

The amount of Temozolomide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. *Store the solutions at 4°.*

(1) Shake 10 whole capsules with the mobile phase. Mix, centrifuge and filter (a 0.45-µm PVDF filter is suitable). Dilute with sufficient mobile phase to produce a solution containing 0.01% w/v of Temozolomide.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.1% w/v of *temozolomide for peak identification EPCRS* in the mobile phase.

(4) Dissolve 10 mg of *temozolomide EPCRS* in 25 mL of mobile phase and 25 mL of 0.1M *hydrochloric acid*. Mix and heat the solution at 80° for 4 hours (generation of impurities A, B and E).

(5) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS-2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of temozolomide.

MOBILE PHASE

A 0.094% w/v solution of *sodium hexanesulfonate* in a mixture of 4 volumes of *methanol* and 96 volumes of 0.5% v/v *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to temozolomide (retention time, about 9 minutes) are: impurity E, about 0.4; impurity D, about 0.5; impurity 1, about 0.8; impurity B, about 0.9 and impurity A, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to temozolomide and impurity A is at least than 2.5.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks due to impurity D using the chromatogram obtained using solution (3) and identify any peaks due to impurities A and E using the chromatogram obtained using solution (4). Multiply the areas of any peaks due to impurities A and E with the corresponding correction factors: impurity A, 0.4 and impurity E, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.2 times the area of the principal peak due in the chromatogram obtained with solution (2) (1.2%);

the area of any peak corresponding to impurity D is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all *secondary peaks*, excluding impurities A and D, is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

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Carry out the method for liquid chromatography, Appendix III D, using the following solutions. *Store the solutions at 4°.*

(1) Shake 10 whole capsules with the mobile phase. Mix, centrifuge and filter (a 0.45-µm PVDF filter is suitable). Dilute with sufficient mobile phase to produce a solution containing 0.01% w/v of Temozolomide.

(2) 0.01% w/v of *temozolomide EPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described in the test for Related substances may be used.

SYSTEM SUITABILITY

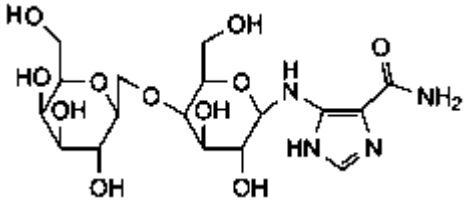
The test is not valid unless in the chromatogram obtained with solution (2), the symmetry factor is not greater than 1.9.

DETERMINATION OF CONTENT

Calculate the content of temozolomide, $C_6H_6N_6O_2$, in the capsules from the chromatograms obtained and using the declared content of $C_6H_6N_6O_2$ in *temozolomide EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Temozolomide* and:



1. 4-[(β-D-galactopyranoyl-(1→4)-β-D-glucopyranosyl)amino]-1*H*-imidazole-4-carboxamide (AIC-lactose)

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Temozolomide for Injection

General Notices

Action and use

Antineoplastic alkylating agent.

DEFINITION

Temozolomide for Injection is a sterile material consisting of Temozolomide with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powder for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of temozolomide, $C_6H_6N_6O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To one vial, add 40 mL of *dichloromethane* and shake for 30 minutes. Invert and allow to stand until undissolved solids settle. Filter 15 mL of the clear solution (a 0.45-µm PTFE filter is suitable). Discard the first 5 mL and evaporate the remaining filtrate to dryness under a stream of *nitrogen*. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of temozolomide *(RS 500)*.

TESTS

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient water to produce a solution containing 0.2% w/v of Temozolomide. Dilute 1 volume of this solution to 20 volumes with mobile phase and mix.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.1% w/v of *temozolomide for peak identification EPCRS* in the mobile phase.

(4) Dissolve 10 mg of *temozolomide EPCRS* in 25 mL of mobile phase and 25 mL of 0.1M *hydrochloric acid*. Mix and heat the solution at 80° for 4 hours (generation of impurities A, B and E).

(5) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS-2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 75 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of temozolomide.

MOBILE PHASE

A 0.094% w/v solution of *sodium hexanesulfonate* in a mixture of 4 volumes of *methanol* and 96 volumes of a 0.5% v/v*glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to temozolomide (retention time, about 9 minutes) are: impurity E, about 0.4; impurity D, about 0.5, impurity B, about 0.9 and impurity A, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to temozolomide and impurity A is not less than 2.5.

LIMITS

In the chromatogram obtained with solution (1), identify any peak due to impurity D using the chromatogram obtained using solution (3) and any peaks due to impurities A and E using the chromatogram obtained using solution (4). Multiply the areas of any peaks due to impurities A and E by the corresponding correction factors: impurity A, 0.4 and impurity E, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity D is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all *secondary peaks*, excluding impurities A and D, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

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Carry out the method for liquid chromatography, Appendix III D, using the following solutions. *Store the solutions at 4°.*

(1) Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing 0.2% w/v of Temozolomide. Dilute 1 volume of this solution to 20 volumes with mobile phase and mix.

(2) 0.01% w/v of *temozolomide EPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described in the test for Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (2), the symmetry factor is not greater than 1.9.

DETERMINATION OF CONTENT

Calculate the content of temozolomide, $C_6H_6N_6O_2$, in the sealed container from the chromatograms obtained and using the declared content of $C_6H_6N_6O_2$, in *temozolomide EPCRS*. Repeat the procedure with a further nine sealed containers. Calculate the average content of $C_6H_6N_6O_2$ per container from the 10 individual results thus obtained.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Temozolomide*.

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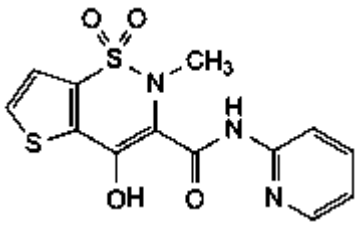
Tenoxicam

General Notices

(Ph. Eur. monograph 1156)



$C_{13}H_{11}N_3O_4S_2$ 337.4 *59804-37-4*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Tenoxicam Injection

Tenoxicam Tablets

Ph Eur

DEFINITION

4-Hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-thieno[2,3-*e*]1,2-thiazine-3-carboxamide 1,1-dioxide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in anhydrous ethanol. It dissolves in solutions of acids and alkalis.

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It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *tenoxicam CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 0.10 g in *methylene chloride R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture Mix equal volumes of *acetonitrile R* and *water R*. Adjust to apparent pH 3.2 with *dilute phosphoric acid R1*.

Test solution Dissolve 35 mg of the substance to be examined in the solvent mixture, sonicate and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 7 mg of pyridin-2-amine R (impurity A) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *tenoxicam impurity mixture CRS* (impurities B, G and H) in 1.0 mL of the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: diisopropylcyanosilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 25 volumes of *methanol R2* and 75 volumes of *water for chromatography R* and adjust to apparent pH 3.2 with *dilute phosphoric acid R1*;

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— *mobile phase B*: mix 25 volumes of *water for chromatography R* and 75 volumes of *methanol R2* and adjust to apparent pH 3.2 with *dilute phosphoric acid R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	96	4
5 - 16	96 → 76	4 → 24
16 - 25	76	24

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Identification of impurities:

— use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A;

— use the chromatogram supplied with *tenoxicam impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, G and H; for identification of impurities G and H, which may be inverted in the elution order, take into account the heights of the corresponding peaks in the chromatogram supplied with *tenoxicam impurity mixture CRS*.

Relative retention With reference to tenoxicam (retention time = about 12 min): impurity A = about 0.1; impurity G = about 0.85; impurity H = about 0.9; impurity B = about 1.3.

System suitability Reference solution (c):

— *resolution*: minimum 1.3 between the peaks due to impurity H (or G if peaks are inverted) and tenoxicam, and between the peaks due to impurities G and H; if necessary, optimise the apparent pH of the mobile phases within the range 3.0-3.4.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.2; impurity B = 2.0;

— *impurities A, B*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 5 mL of *anhydrous formic acid R*. Add 70 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 33.74 mg of $C_{13}H_{11}N_3O_4S_2$.

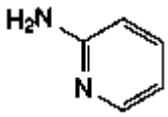
STORAGE

Protected from light.

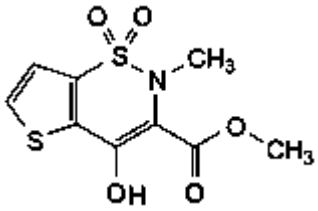
IMPURITIES

Specified impurities A, B.

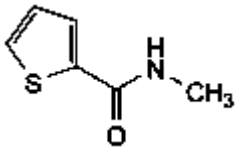
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E, F, G, H.



A. pyridin-2-amine,



B. methyl 4-hydroxy-2-methyl-2*H*-thieno[2,3-*e*]1,2-thiazine-3-carboxylate 1,1-dioxide,



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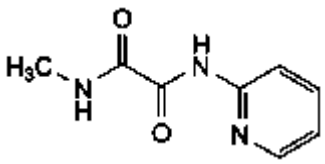
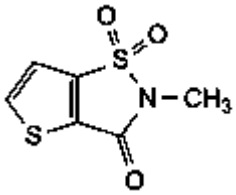
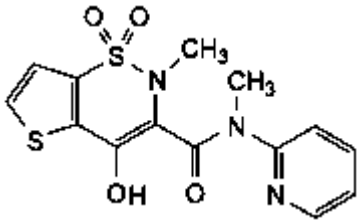
C. *N*-methylthiophene-2-carboxamide,



D. *N*-methyl-*N*′-(pyridin-2-yl)-ethanediamide,

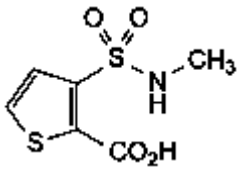


E. 2-methylthieno[2,3-*d*]isothiazol-3(2*H*)-one 1,1-dioxide,



F. 4-hydroxy-*N*,2-dimethyl-*N*-(pyridin-2-yl)-2*H*-thieno[2,3-*e*]1,2-thiazine-3-carboxamide 1,1-dioxide,

G. 4-hydroxy-2-methyl-2*H*-thieno[2,3-*e*]1,2-thiazine-3-carboxamide 1,1-dioxide,



H. 3-[(methylamino)sulfonyl]thiophene-2-carboxylic acid.

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Tenoxicam Injection

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Tenoxicam Injection is a sterile solution of Tenoxicam in Water for Injections. It is prepared by dissolving Tenoxicam for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

STORAGE

Tenoxicam Injection should be used immediately after preparation.

TENOXICAM FOR INJECTION

DEFINITION

Tenoxicam for Injection is a sterile material consisting of Tenoxicam with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of tenoxicam, $C_{13}H_{11}N_3O_4S_2$

104.5 to 115.5% of the stated amount.

IDENTIFICATION

A. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak in the chromatogram obtained with solution (4).

B. The *light absorption*, Appendix II B, in the range 230 to 400 nm of the solution prepared in the Assay exhibits three maxima at 257 nm, 285 nm and 368 nm.

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the sealed container containing 20 mg of Tenoxicam with 10 mL of a mixture containing equal volumes of *dichloromethane* and *methanol* for 5 minutes, centrifuge and use the supernatant liquid.

(2) 0.2% w/v of *tenoxicam BPCRS* in a mixture of equal volumes of *dichloromethane* and *methanol*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*. Spray the plate with *acid potassium iodobismuthate solution* and examine again.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 45 volumes of *acetone* and 55 volumes of *toluene*.

CONFIRMATION

Using each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH of the injection when constituted in accordance with the manufacturer's instructions, 9.0 to 10.0, Appendix V L.

Clarity of solution

The injection, constituted in accordance with the manufacturer's instructions, is *clear*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the contents of the sealed container containing 20 mg of Tenoxicam in 20 mL of *acetonitrile* (*50%*) and dilute 1 volume of the resulting solution to 4 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.0000625% w/v of *2-pyridylamine* (impurity A) in *acetonitrile* (*50%*).

(4) Dilute 5 mL of a 0.1% w/v solution of *tenoxicam BPCRS* to 20 mL with the mobile phase.

(5) Dilute 1 volume of a 0.1% w/v solution of *tenoxicam degradation impurity standard BPCRS* in *acetonitrile* (*50%*) to 4 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil C8 is suitable) and a pre-column packed with *octylsilyl silica gel for chromatography* (10 µm) (Spheri-10 RP8, RP-GU pre-column is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use an ambient column temperature.

(e) Use detection wavelengths of 254 nm and 290 nm.

(f) Inject 20 µL of each solution.

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(g) Condition the column with the mobile phase for 3 hours.

MOBILE PHASE

Dissolve 0.12 g of *sodium dodecyl sulfate* in 700 mL of *methanol*, mix with 1000 mL of 0.05M *potassium dihydrogen orthophosphate* and adjust the pH to 2.8 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (5) closely resembles the reference chromatogram provided with *tenoxicam degradation impurity standard BPCRS*.

LIMITS

At a detection wavelength of 290 nm In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-pyridylamine (impurity A) is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.25%).

At a detection wavelength of 254 nm In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Water

Not more than 4.0% w/w, Appendix IX C. Use 0.3 g.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Dissolve the contents of 10 containers in 0.1M *sodium hydroxide* and dilute to 1000 mL with 0.1M *sodium hydroxide*. Dilute the resulting solution with 0.1M *sodium hydroxide* to contain 0.0016% of Tenoxicam. Mix well, filter and measure the *absorbance* of the resulting solution at the maximum at 368 nm, Appendix II B.

Calculate the total content of $C_{13}H_{11}N_3O_4S_2$ in a container of average content weight in the injection from the *absorbance* of a 0.0016% w/v solution of *tenoxicam BPCRS* in 0.1M *sodium hydroxide* using the declared content of $C_{13}H_{11}N_3O_4S_2$ in *tenoxicam BPCRS*.

STORAGE

Where the sealed container is supplied with an ampoule of Water for Injections, this should not be allowed to freeze.

IMPURITIES

The impurities limited by the requirements of this monograph include those impurities listed under Tenoxicam.

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Tenoxicam Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Tenoxicam Tablets contain Tenoxicam.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tenoxicam, $C_{13}H_{11}N_3O_4S_2$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 20 mg of Tenoxicam with 20 mL of *dichloromethane* for 15 minutes, centrifuge and use the supernatant liquid.

(2) 0.1% w/v of *tenoxicam BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

4 volumes of *anhydrous formic acid*, 30 volumes of *acetone* and 70 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of phosphate buffer pH 6.8 prepared in the following manner: dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 500 mL of *water*, add 23 mL of 1M *sodium hydroxide*, dilute to 1000 mL and, if necessary, adjust the pH to 6.8 using either 1M *sodium hydroxide* or a 10% w/v solution of *orthophosphoric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 368 nm, Appendix II B.

(2) Measure the *absorbance* of a suitable solution of *tenoxicam BPCRS*.

DETERMINATION OF CONTENT

Calculate the total content of tenoxicam, $C_{13}H_{11}N_3O_4S_2$, in the medium from the absorbances obtained and using the declared content of $C_{13}H_{11}N_3O_4S_2$ in *tenoxicam BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a number of whole tablets containing 0.1 g of Tenoxicam with 100 mL of *acetonitrile* (*50%*) for 70 minutes, mixing occasionally with the aid of ultrasound. Allow to stand for 10 minutes, dilute 5 volumes of the clear supernatant liquid to 20 volumes with the mobile phase and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.0000625% w/v of *2-pyridylamine* (impurity A) in *acetonitrile* (*50%*).

(4) Dilute 1 volume of a 0.1% w/v solution of *tenoxicam degradation impurity standard BPCRS* in *acetonitrile* (*50%*) to 4 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil C8 5µ is suitable) and a pre-column packed with *octylsilyl silica gel for chromatography* (10 µm) (Spheri-10 RP8, RP-GU pre-column is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use an ambient column temperature.

(e) Use detection wavelengths of 254 nm and 290 nm.

(f) Inject 20 µL of each solution.

Condition the column with the mobile phase for 3 hours.

MOBILE PHASE

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Dissolve 0.12 g of *sodium dodecyl sulfate* in 700 mL of *methanol*, mix with 1000 mL of 0.05M *potassium dihydrogen orthophosphate* and adjust the pH to 2.8 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *tenoxicam degradation impurity standard BPCRS*.

LIMITS

At a detection wavelength of 290 nm In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-pyridylamine (impurity A) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.25%).

At a detection wavelength of 254 nm In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than four times the principal peak in the chromatogram obtained with solution (2) (2%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 whole tablets with 200 mL of *acetonitrile* (*50%*) for 70 minutes, mixing occasionally with the aid of ultrasound. Allow to stand for 10 minutes, dilute a volume of the clear supernatant liquid with sufficient mobile phase to produce a solution containing 0.025% w/v of Tenoxicam and filter through a 0.45-µm membrane filter.

(2) Dilute 5 mL of a 0.1% w/v solution of *tenoxicam BPCRS* in *acetonitrile* (*50%*) to 20 mL with the mobile phase.

(3) Dilute 1 volume of a 0.1% w/v solution of *tenoxicam degradation impurity standard BPCRS* in *acetonitrile* (*50%*) to 4 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a detection wavelength of 290 nm.

MOBILE PHASE

Dissolve 0.12 g of *sodium dodecyl sulfate* in 700 mL of *methanol*, mix with 1000 mL of 0.05M *potassium dihydrogen orthophosphate* and adjust the pH to 2.8 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *tenoxicam degradation impurity standard BPCRS*.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{11}N_3O_4S_2$ in the tablets using the declared content of $C_{13}H_{11}N_3O_4S_2$ in *tenoxicam BPCRS*.

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IMPURITIES

The impurities limited by the requirements of this monograph include those impurities listed under Tenoxicam.

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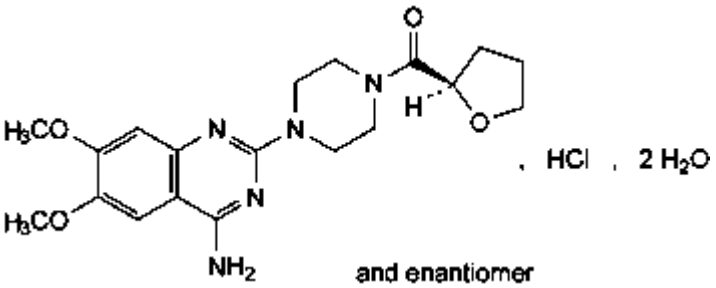
Terazosin Hydrochloride Dihydrate

General Notices

(Ph. Eur. monograph 2021)



$C_{19}H_{26}ClN_5O_4,2H_2O$ 459.9 *70024-40-7*

Action and use

Alpha1-adrenoceptor antagonist.

Ph Eur

DEFINITION

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl][(2*RS*)-oxolan-2-yl]methanone hydrochloride dihydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *terazosin hydrochloride dihydrate CRS*.

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B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Dilute 10 mL of solution S to 20 mL with *water R*.

pH (2.2.3)

3.0 to 5.0 for solution S.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *methanol R* (30:70 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *terazosin for system suitability A CRS* (containing impurities A, B and C) in 2.5 mL of the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of *terazosin impurity N CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *terazosin impurity E CRS* in the solvent mixture, sonicate for about 5 min and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 25 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped solid core pentafluorophenylpropylsilyl silica gel for chromatography R* (2.6 µm).

Mobile phase:

— *mobile phase A*: dilute 1.0 mL of *perchloric acid R* to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R* (10:90 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	95	5
1 - 21	95 → 65	5 → 35

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 0.5 µL.

Identification of impurities Use the chromatogram supplied with *terazosin for system suitability A CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity N.

Relative retention With reference to terazosin (retention time = about 13 min): impurity N = about 0.1; impurity C = about 0.6; impurity A = about 0.78; impurity B = about 0.81; impurity E = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.5; impurity C = 0.7;

— for impurity N, use the concentration of the impurity N in reference solution (c);

— for impurities other than N, use the concentration of terazosin hydrochloride dihydrate in reference solution (a).

Limits:

— *impurities A, C, E*: for each impurity, maximum 0.2 per cent;

— *impurity N*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

7.0 per cent to 8.6 per cent, determined on 0.200 g.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 42.39 mg of $C_{19}H_{26}ClN_5O_4$.

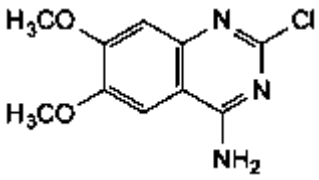
STORAGE

Protected from light.

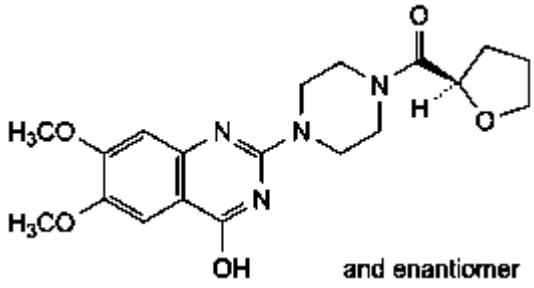
IMPURITIES

Specified impurities A, C, E, N.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D, F, G, H, I, J, K, L, M, O, P.



A. 2-chloro-6,7-dimethoxyquinazolin-4-amine,



B. [4-(4-hydroxy-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl][(2*RS*)-oxolan-2-yl]methanone,

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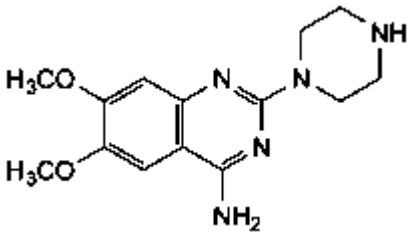
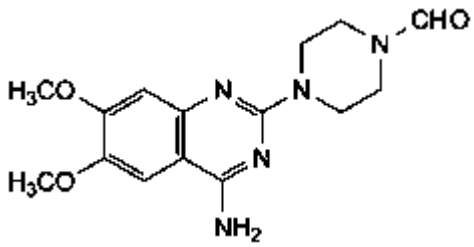
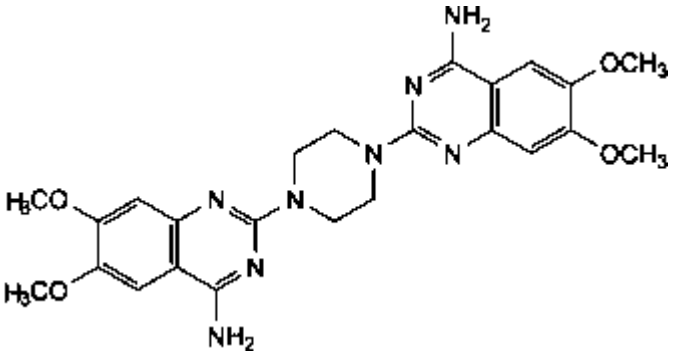


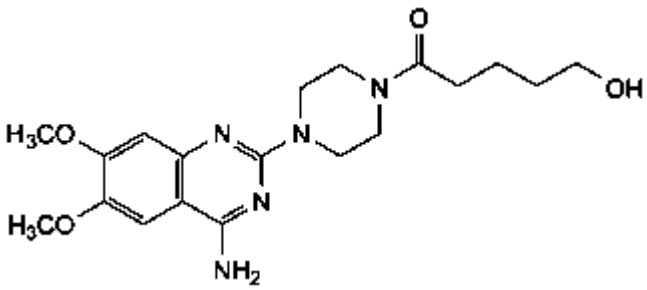
C. 6,7-dimethoxy-2-(piperazin-1-yl)quinazolin-4-amine,



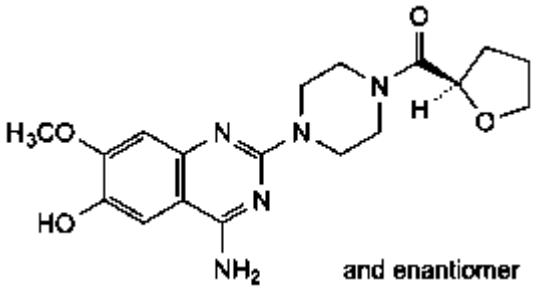
D. [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]formaldehyde,



E. 2,2′-(piperazine-1,4-diyl)bis(6,7-dimethoxyquinazolin-4-amine),



F. 1-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-5-hydroxypentan-1-one,



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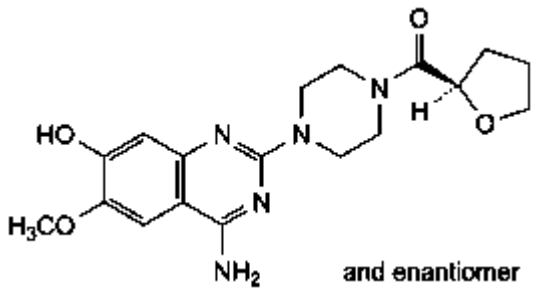
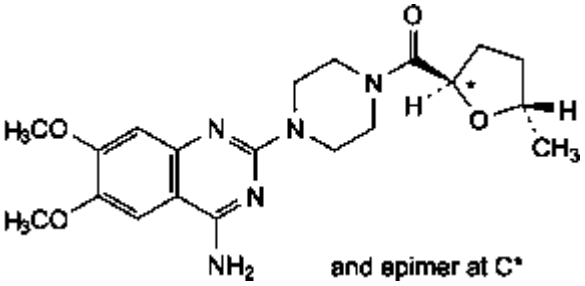
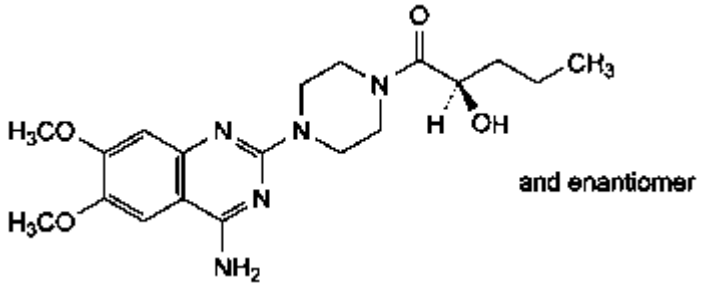
G. [4-(4-amino-6-hydroxy-7-methoxyquinazolin-2-yl)piperazin-1-yl][(2*RS*)-oxolan-2-yl]methanone,



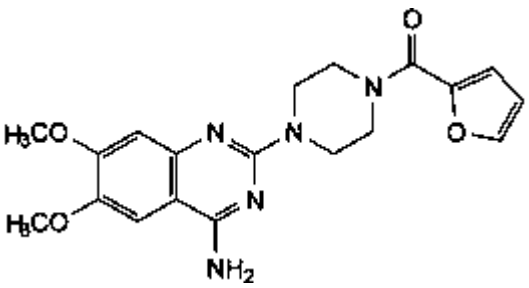
H. [4-(4-amino-7-hydroxy-6-methoxyquinazolin-2-yl)piperazin-1-yl][(2*RS*)-oxolan-2-yl]methanone,



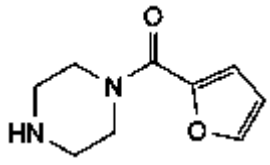
I. [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl][(2*RS*,5*S*)-5-methyloxolan-2-yl]methanone,



J. (2*RS*)-1-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-2-hydroxypentan-1-one,



K. [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl](furan-2-yl)methanone (prazosin),



L. (furan-2-yl)(piperazin-1-yl)methanone,

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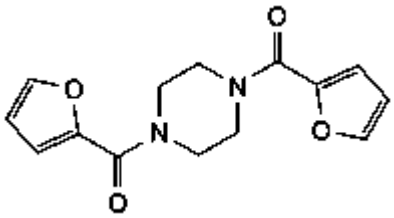
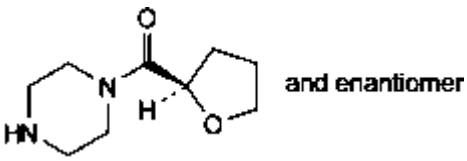
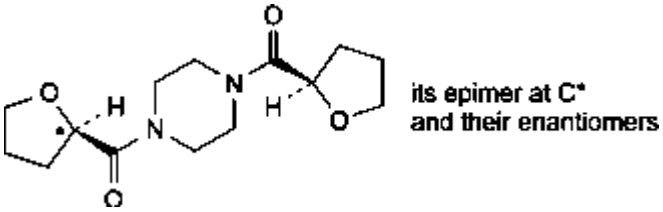


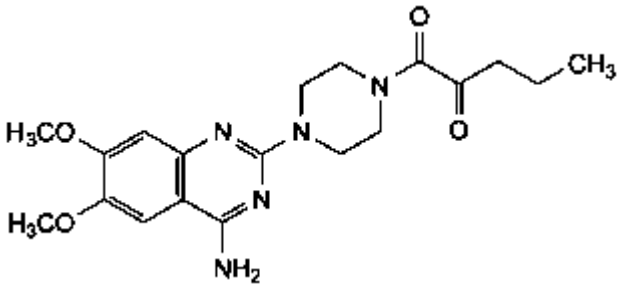
M. (piperazine-1,4-diyl)bis[(furan-2-yl)methanone],



N. [(2*RS*)-oxolan-2-yl](piperazin-1-yl)methanone,



O. mixture of [4-[(2*R*)-oxolane-2-carbonyl]piperazin-1-yl][(2*S*)-oxolan-2-yl]methanone and (piperazine-1,4-diyl)bis[[(2*RS*)-oxolan-2-yl]methanone],



P. 1-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]pentane-1,2-dione.

Ph Eur

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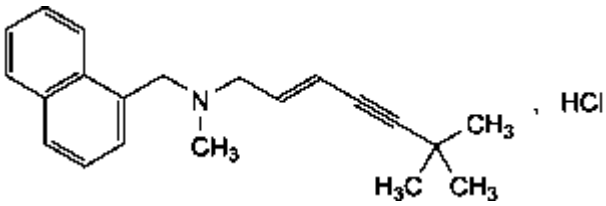
Terbinafine Hydrochloride

General Notices

(Ph. Eur. monograph 1734)



$C_{21}H_{26}ClN$ 327.9 *78628-80-5*

Action and use

Antifungal.

Preparation

Terbinafine Tablets

Ph Eur

DEFINITION

(2*E*)-*N*,6,6-Trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *terbinafine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*) using *anhydrous ethanol R* as solvent.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture A *acetonitrile R*, *water R* (50:50 *V/V*).

Solvent mixture B *acetonitrile R*, *methanol R* (40:60 *V/V*).

Buffer solution Dilute 2.0 mL of *triethylamine R1* to 950 mL with *water R*. Adjust to pH 7.5 with a mixture of 5 volumes of *glacial acetic acid R* and 95 volumes of *water R* and dilute to 1000.0 mL with *water R*.

Test solution Dissolve 25 mg of the substance to be examined in solvent mixture A and dilute to 50.0 mL with solvent mixture A.

Reference solution (a) Dissolve 5 mg of *terbinafine for system suitability CRS* (containing impurities B and E) in 10.0 mL of solvent mixture A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with solvent mixture A. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: buffer solution, solvent mixture B (30:70 *V/V*);

— *mobile phase B*: buffer solution, solvent mixture B (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 25	100 → 0	0 → 100
25 - 30	0	100

Flow rate 0.8 mL/min.

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Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *terbinafine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and E.

Relative retention With reference to terbinafine (retention time = about 15 min): impurity B = about 0.9; impurity E = about 1.7.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity B and terbinafine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.5;

— *impurity B*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity E*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R*, add 5 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.79 mg of $C_{21}H_{26}ClN$.

STORAGE

Protected from light.

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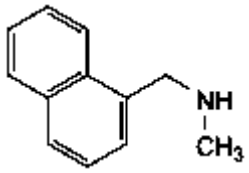
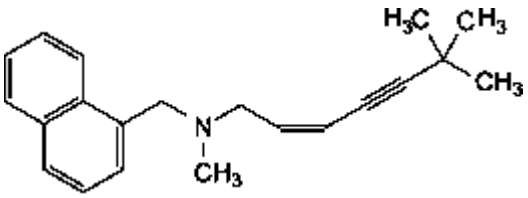
IMPURITIES

Specified impurities B, E.

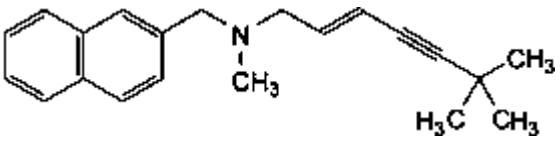
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D, F.



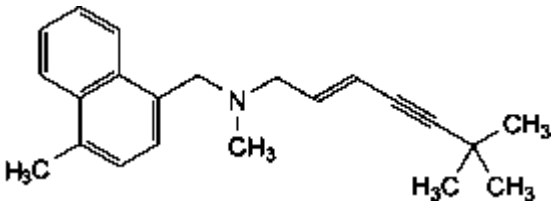
A. *N*-methyl-*C*-(naphthalen-1-yl)methanamine,



B. (2*Z*)-*N*,6,6-trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine (*cis*-terbinafine),



C. (2*E*)-*N*,6,6-trimethyl-*N*-(naphthalen-2-ylmethyl)hept-2-en-4-yn-1-amine (*trans*-isoterbinafine),



D. (2*E*)-*N*,6,6-trimethyl-*N*-[(4-methylnaphthalen-1-yl)methyl]hept-2-en-4-yn-1-amine (4-methylterbinafine),

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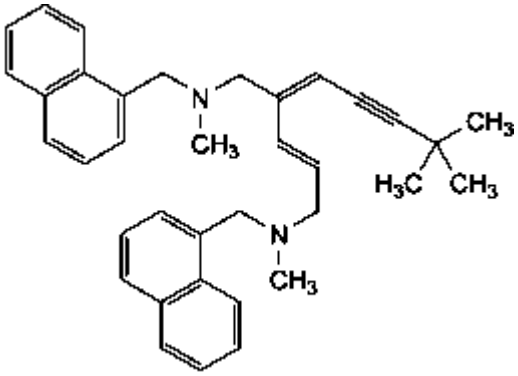
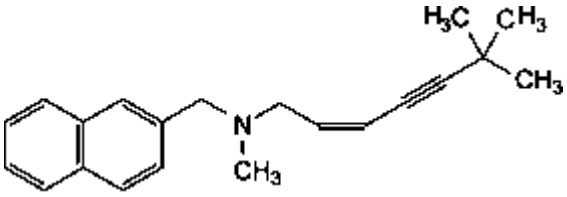


E. (2*E*,4*E*)-4-(4,4-dimethylpent-2-yn-1-ylidene)-*N*,*N*′-dimethyl-*N*,*N*′-bis(naphthalen-1-ylmethyl)pent-2-ene-1,5-diamine,



F. (2*Z*)-*N*,6,6-trimethyl-*N*-(naphthalen-2-ylmethyl)hept-2-en-4-yn-1-amine (*cis*-isoterbinafine).

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Terbinafine Tablets

General Notices

Action and use

Antifungal.

DEFINITION

Terbinafine Tablets contain Terbinafine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of terbinafine, $C_{21}H_{25}N$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of terbinafine with 10 mL of *anhydrous ethanol* and centrifuge. Filter the supernatant liquid and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of terbinafine hydrochloride (*RS 475*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of a solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* in sufficient *water* to produce 1000 mL and adjusting the pH to 2.0 with an 85% w/v solution of *orthophosphoric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of 20 mL of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, to give a solution expected to contain the equivalent of 0.00139% w/v of terbinafine, at the maximum at 274 nm, Appendix II B using dissolution medium in the reference cell.

(2) Dilute 1 volume of a 0.156% w/v solution of *terbinafine hydrochloride BPCRS* in *methanol* to 100 volumes with dissolution medium. Measure the *absorbance* of the resulting solution using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of terbinafine, $C_{21}H_{25}N$, in the medium from the *absorbances* obtained and using the declared content of $C_{21}H_{25}N$ in *terbinafine hydrochloride BPCRS*.

LIMITS

The amount of terbinafine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a 50% v/v solution of *acetonitrile*.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing the equivalent of 0.25 g of terbinafine in 80 mL, cool and dilute to 100 mL. Centrifuge and filter the supernatant liquid through a 0.45-µm filter (PTFE is suitable). Dilute 1 volume to 5 volumes.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume of the resulting solution to 10 volumes.

(3) 0.05% w/v of *terbinafine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.0 mm) packed with *spherical end-capped octadecylsilyl silica gel for chromatography* (5µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Buffer solution To 2.0 mL *of triethylamine R2,* add 950 mL of *water*. Adjust to pH 7.5 with a mixture of 5 volumes of *glacial acetic acid* and 95 volumes of *water* and dilute to 1000 mL with *water*.

Mobile phase A 30 volumes of the buffer solution and 70 volumes of a mixture of 40 volumes of *acetonitrile* and 60 volumes of *methanol*.

Mobile phase B 5 volumes of the buffer solution and 95 volumes of a mixture of 40 volumes of *acetonitrile* and 60 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0–4	100	0	isocratic
4–25	100→0	0→100	linear gradient
25–30	0	100	isocratic
30–31	0→100	100→0	linear gradient
31–35	100	0	re-equilibration

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and terbinafine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity E and multiply the area of this peak by a correction factor of 0.5;

the area of any peak corresponding to impurity E is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak, excluding impurity E, with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions dissolved in a 50% v/v solution of *acetonitrile*.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing the equivalent of 0.25 g of terbinafine in 80 mL, cool and dilute to 100 mL. Centrifuge and filter the supernatant liquid through a 0.45-µm filter (PTFE is suitable). Dilute 1 volume to 5 volumes.
(2) 0.056% w/v of *terbinafine hydrochloride BPCRS*.
(3) 0.05% w/v of *terbinafine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and terbinafine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{25}N$ in the tablets from the chromatogram obtained using the declared content of $C_{21}H_{25}N$ in *terbinafine hydrochloride BPCRS*.

STORAGE

Terbinafine Tablets should be protected from light.

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LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of terbinafine.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Terbinafine Hydrochloride.

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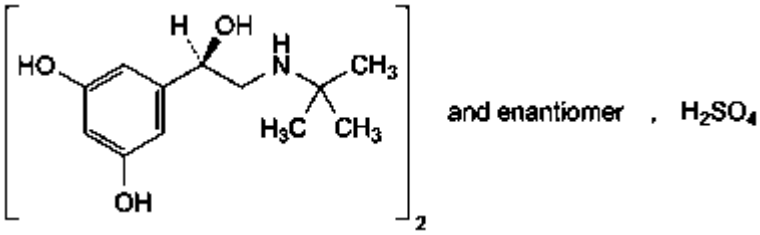
Terbutaline Sulfate

General Notices

Terbutaline Sulphate

(Ph. Eur. monograph 0690)



$C_{24}H_{40}N_2O_{10}S$ 548.6 *23031-32-5*

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

Preparation

Terbutaline Tablets

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DEFINITION

Bis[5-[(1*RS*)-2-(*tert*-butylamino)-1-hydroxyethyl]benzene-1,3-diol] sulfate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

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It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *terbutaline sulfate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *aldehyde-free methanol R*, evaporate to dryness and record new spectra using the residues.

B. 5 mL of solution S (see Tests) gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 400 nm in a 2 cm cell is not greater than 0.11.

Acidity

To 10 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 1.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 75.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 7.5 mg of *terbutaline impurity C CRS* and 22.5 mg of *terbutaline sulfate CRS* in the mobile phase and dilute to 50 mL with the mobile phase. Dilute 1 mL of the solution to 100 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

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Mobile phase Prepare a 0.050 M ammonium formate solution as follows: dissolve 3.15 g of *ammonium formate R* in about 980 mL of *water for chromatography R*, adjust to pH 3.0 by adding about 8 mL of *anhydrous formic acid R* and dilute to 1000 mL with *water for chromatography R*. Dissolve 4.23 g of *sodium hexanesulfonate R* in 770 mL of the 0.050 M ammonium formate solution, then add 230 mL of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 20 µL.

Run time 6 times the retention time of terbutaline.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to terbutaline (retention time = about 10 min): impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity C and terbutaline.

Calculation of percentage contents:

— for each impurity, use the concentration of terbutaline sulfate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.400 g in 70 mL of *anhydrous acetic acid R* with heating. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 54.86 mg of $C_{24}H_{40}N_2O_{10}S$.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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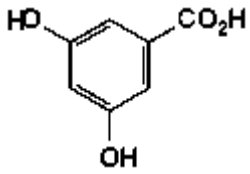
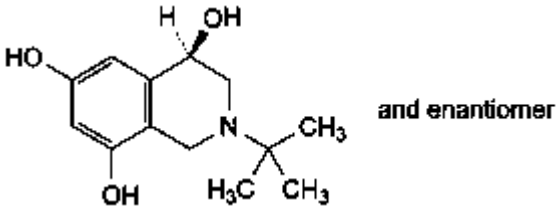
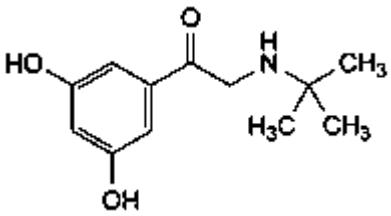
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



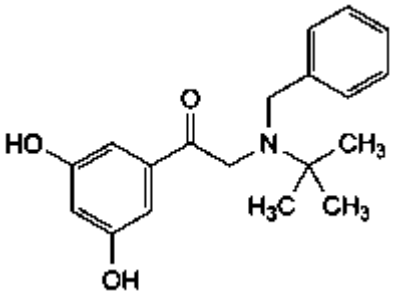
A. 3,5-dihydroxybenzoic acid (α-resorcylic acid),



B. (4*RS*)-2-*tert*-butyl-1,2,3,4-tetrahydroisoquinoline-4,6,8-triol,



C. 2-(*tert*-butylamino)-1-(3,5-dihydroxyphenyl)ethan-1-one,



D. 2-[benzyl(*tert*-butyl)amino]-1-(3,5-dihydroxyphenyl)ethan-1-one.

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Terbutaline Tablets

General Notices

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Terbutaline Tablets contain Terbutaline Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of terbutaline sulfate $(C_{12}H_{19}NO_3)_2,H_2SO_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Terbutaline Sulfate with 50 mL of 0.1M *sodium hydroxide* for 10 minutes, dilute to 100 mL with 0.1M *sodium hydroxide* and filter. Dilute 20 mL of the filtrate to 50 mL with 0.1M *sodium hydroxide*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum only at 296 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 10 mg of Terbutaline Sulfate with 4 mL of a mixture of equal volumes of *ethanol* (*96%*) and *water* for 10 minutes, centrifuge and use the clear solution.

(2) 0.25% w/v of *terbutaline sulfate BPCRS* in *water*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*, (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, allow to stand for a few minutes in an atmosphere saturated with *diethylamine* and spray with *diazotised nitroaniline solution*.

MOBILE PHASE

5 volumes of *formic acid*, 25 volumes of *cyclohexane* and 65 volumes of *propan-2-ol*.

CONFIRMATION

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The spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) and the principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 75 mg of Terbutaline Sulfate with 35 mL of the mobile phase for 15 minutes, add sufficient of the mobile phase to produce 50 mL, mix and filter (Whatman GF/C paper is suitable).
(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and further dilute 1 volume to 10 volumes with the mobile phase.
(3) 0.00045% w/v of *terbutaline sulfate BPCRS* and 0.00015% w/v of *terbutaline impurity C BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 5µm is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 276 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for 6 times the retention time of the principal peak.

MOBILE PHASE

Prepare a 0.05M solution of *ammonium formate* by dissolving 3.15 g of *ammonium formate* in 980 mL of *water*, adjust the pH to 3.0 by the addition of about 8 mL of *anhydrous formic acid* and add sufficient *water* to produce 1000 mL. Dissolve 4.23 g of *sodium hexanesulfonate* in 770 mL of the ammonium formate solution and add 230 mL of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times are about 9 minutes for terbutaline impurity C and about 11 minutes for terbutaline sulfate.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to terbutaline sulfate and terbutaline impurity C is at least 2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to terbutaline impurity C is not greater than twice the area of the peak due to terbutaline impurity C in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

Disregard any peaks with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.02%) and any peaks with a retention time of less than 2.5 minutes.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 15 mg of Terbutaline Sulfate with 20 mL of 0.05M *sulfuric acid* for 15 minutes, add 1.6 mL of 1.5M *sodium acetate* and sufficient *water* to produce 25 mL and filter (Whatman GF/C paper is suitable).

(2) Dissolve 30 mg of *terbutaline sulfate BPCRS* in 40 mL of 0.05M *sulfuric acid*, add 3.2 mL of 1.5M *sodium acetate* and add sufficient *water* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $(C_{12}H_{19}NO_3)_2,H_2SO_4$ in the tablets from the chromatograms obtained and using the declared content of $(C_{12}H_{19}NO_3)_2,H_2SO_4$ in *terbutaline sulfate BPCRS*.

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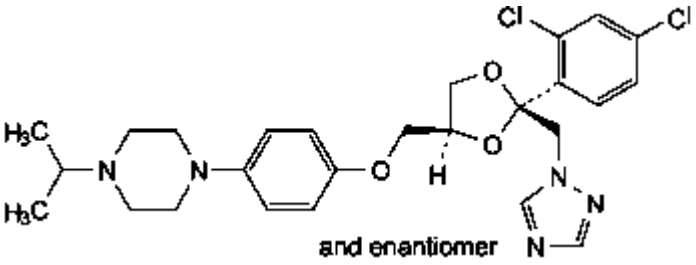
Terconazole

General Notices

(Ph. Eur. monograph 1270)



$C_{26}H_{31}Cl_2N_5O_3$ 532.5 *67915-31-5*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[4-[[(2*RS*,4*SR*)-2-(2,4-Dichlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, sparingly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

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Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *terconazole CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness in a current of air and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 30 mg of *terconazole CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 30 mg of *ketoconazole CRS* and 30 mg of *terconazole CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel plate R*.

Mobile phase *ammonium acetate solution R*, *dioxan R*, *methanol R* (20:40:40 *V/V/V*).

Application 5 µL.

Development In an unsaturated tank over half of the plate.

Drying In a current of warm air for 15 min.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 30 mg in a porcelain crucible add 0.3 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 1.0 g in *methylene chloride R* and dilute to 10 mL with the same solvent.

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Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in methanol R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2.0 mg of ketoconazole CRS and 2.5 mg of terconazole CRS in methanol R and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with methanol R. Dilute 5.0 mL of this solution to 20.0 mL with methanol R.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase:

— *mobile phase A*: 3.4 g/L solution of tetrabutylammonium hydrogen sulfate R;

— *mobile phase B*: acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	95 → 50	5 → 50
10 - 15	50	50

Flow rate 2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Relative retention With reference to terconazole (retention time = about 7.5 min): ketoconazole = about 0.8; impurity A = about 0.85; impurity B = about 0.9.

System suitability Reference solution (a):

— resolution: minimum 13 between the peaks due to ketoconazole and terconazole.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

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— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 70 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically at the 2nd point of inflexion (2.2.20).

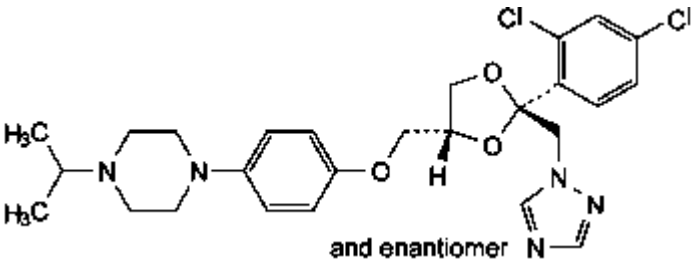
1 mL of *0.1 M perchloric acid* is equivalent to 17.75 mg of $C_{26}H_{31}Cl_2N_5O_3$.

STORAGE

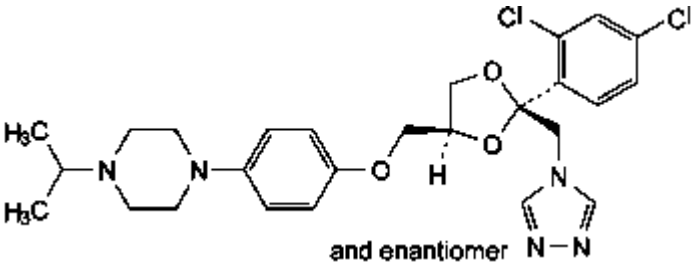
Protected from light.

IMPURITIES

Specified impurities A, B.



A. 1-[4-[[(2*RS*,4*RS*)-2-(2,4-dichlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine,



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B. 1-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-[(4*H*-1,2,4-triazol-4-yl)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine.

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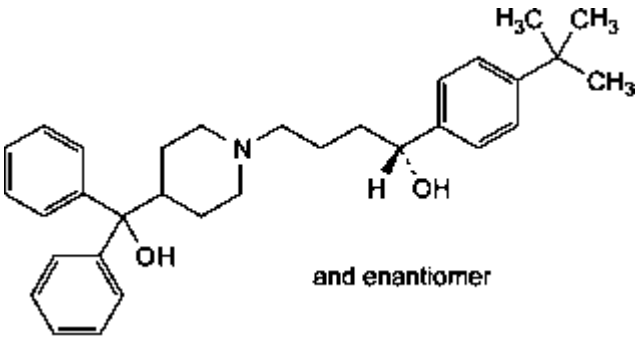
Terfenadine

General Notices

(Ph. Eur. monograph 0955)



$C_{32}H_{41}NO_2$ 471.7 *50679-08-8*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

(1*RS*)-1-[4-(1,1-Dimethylethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butan-1-ol.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol. It is very slightly soluble in dilute hydrochloric acid.

It shows polymorphism (*5.9*).

IDENTIFICATION

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First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 146 °C to 152 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent.

Spectral range 230-350 nm.

Absorption maximum At 259 nm.

Shoulders At 253 nm and 270 nm.

Specific absorbance at the absorption maximum 13.5 to 14.9.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *terfenadine CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *terfenadine CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 15 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

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Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 15 mg of *terfenadine impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. To 5.0 mL of this solution, add 5.0 mL of the test solution and dilute to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 10.0 mL of reference solution (a) to 25.0 mL with the mobile phase.

Reference solution (d) Dissolve 0.1 g of *potassium iodide R* in the mobile phase and dilute to 100 mL with the mobile phase. Dilute 1 mL of this solution to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dilute 600 mL of *acetonitrile R1* to 1 L with *diethylammonium phosphate buffer solution pH 6.0 R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 217 nm.

Injection 20 µL.

Run time 5 times the retention time of terfenadine.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to terfenadine and impurity A;

— *mass distribution ratio*: minimum 2.0 for the peak due to terfenadine; use *potassium iodide R* as the unretained compound (reference solution (d)).

Limits:

— *impurities A, B, C, D, E, F, G, H, I, J*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.005 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.5 kPa.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

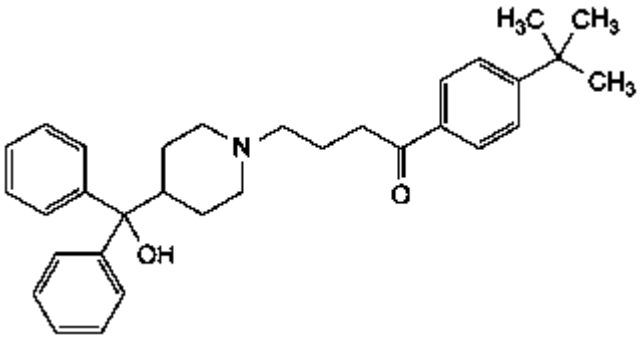
1 mL of *0.1 M perchloric acid* is equivalent to 47.17 mg of $C_{32}H_{41}NO_2$.

STORAGE

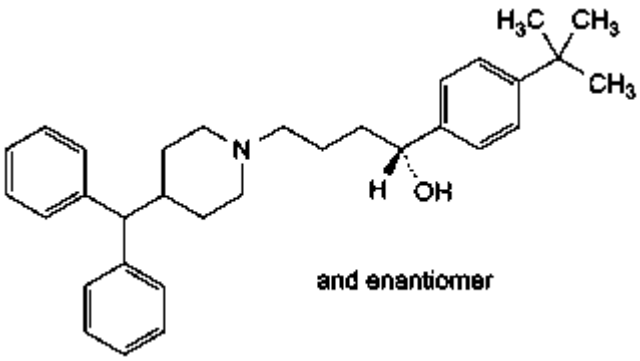
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J.*



A. 1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butan-1-one,



B. (1*RS*)-1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(diphenylmethyl)piperidin-1-yl]butan-1-ol,

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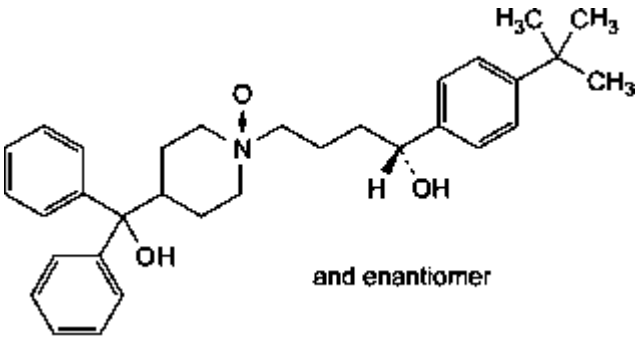
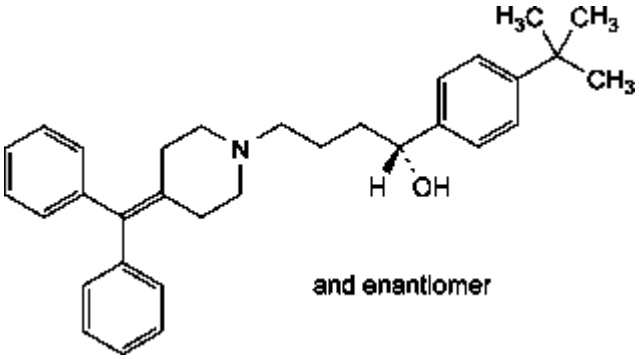
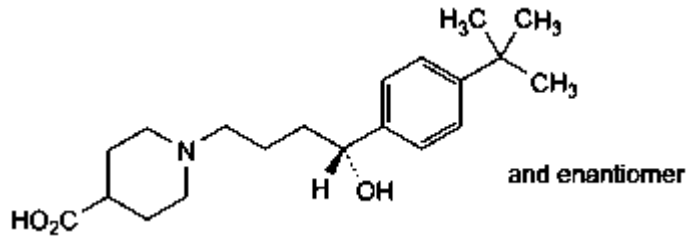


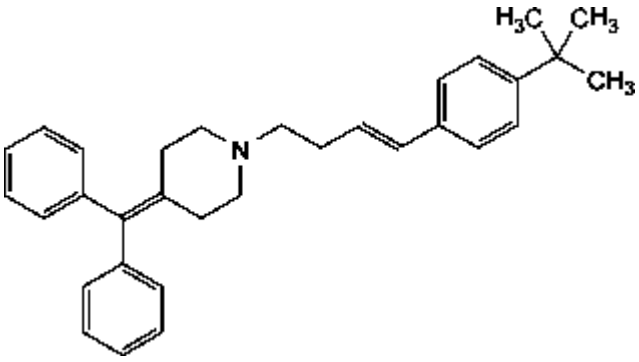
C. 1-[(4*RS*)-4-[4-(1,1-dimethylethyl)phenyl]-4-hydroxybutyl]-4-(hydroxydiphenylmethyl)piperidine 1-oxide,



D. (1*RS*)-1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(diphenylmethylene)piperidin-1-yl]butan-1-ol,



E. 1-[(4*RS*)-4-[4-(1,1-dimethylethyl)phenyl]-4-hydroxybutyl]piperidine-4-carboxylic acid,



F. 1-[4-[4-(1,1-dimethylethyl)phenyl]but-3-enyl]-4-(diphenylmethylene)piperidine,

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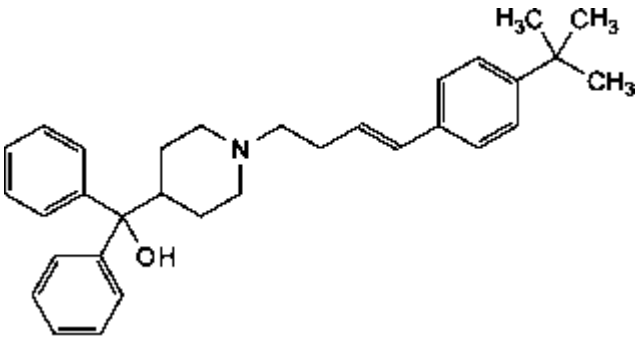
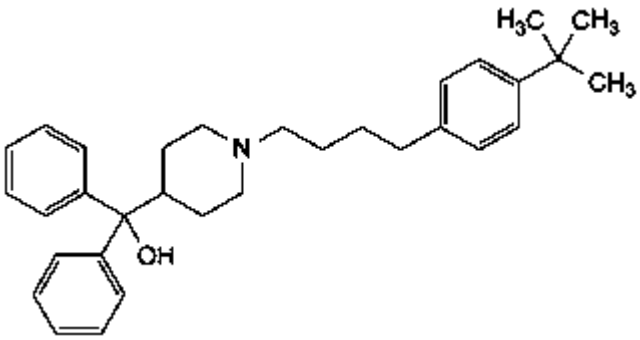
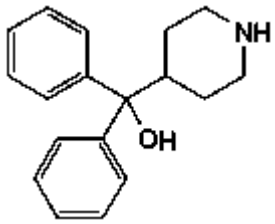


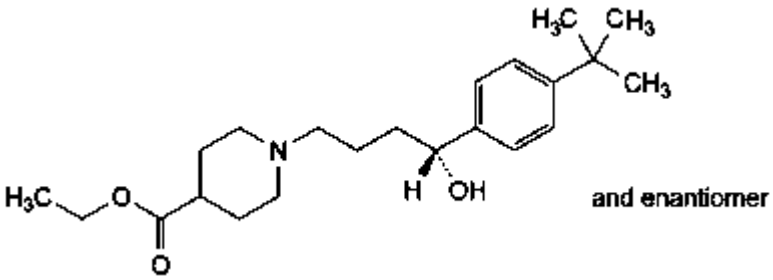
G. [1-[4-[4-(1,1-dimethylethyl)phenyl]but-3-enyl]piperidin-4-yl]diphenylmethanol,



H. [1-[4-[4-(1,1-dimethylethyl)phenyl]butyl]piperidin-4-yl]diphenylmethanol,



I. diphenyl(piperidin-4-yl)methanol,



J. ethyl 1-[(4*RS*)-4-[4-(1,1-dimethylethyl)phenyl]-4-hydroxybutyl]piperidine-4-carboxylate.

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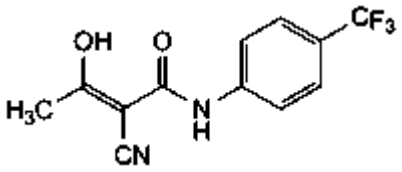
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Teriflunomide

General Notices

(Ph. Eur. monograph 3036)



$C_{12}H_9F_3N_2O_2$ 270.2 *163451-81-8*

Action and use

Immunomodulator; treatment of multiple sclerosis.

Preparation

Teriflunomide Tablets

Ph Eur

DEFINITION

(2*Z*)-2-Cyano-3-hydroxy-*N*-[4-(trifluoromethyl)phenyl]but-2-enamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison teriflunomide CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions.*

Buffer solution 3.85 g/L solution of ammonium acetate R in water for chromatography R adjusted to pH 5.5 with glacial acetic acid R.

Solvent mixture Buffer solution, acetonitrile R (20:80 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 40 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of leflunomide impurity A CRS (teriflunomide impurity A) in acetonitrile R and dilute to 250 mL with the same solvent. Dilute 1 mL of the solution to 200 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of teriflunomide impurity B CRS in acetonitrile R and dilute to 100 mL with the same solvent. Dilute 2 mL of the solution to 50 mL with the solvent mixture. To 1 mL of this solution add 1 mL of reference solution (b) and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of teriflunomide for assay CRS in 40 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped solid core octadecylsilyl silica gel for chromatography R (2.7 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile for chromatography R, buffer solution (10:90 *V/V*);

— *mobile phase B*: buffer solution, acetonitrile for chromatography R (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	76	24

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
2 - 12	76 → 23	24 → 77

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 249 nm.

Injection 5 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to teriflunomide (retention time = about 5 min): impurity B = about 1.5; impurity A = about 1.6.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities B and A;

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of teriflunomide in reference solution (a).

Limits:

— *impurity A*: maximum 0.01 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent; do not disregard the peak due to impurity A.

Water (2.5.32)

Maximum 0.5 per cent, determined on 0.100 g by direct sample introduction.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (d).

System suitability Reference solution (d):

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— *symmetry factor*: maximum 2.0 for the peak due to teriflunomide;

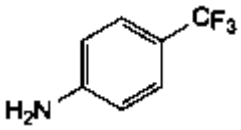
— *repeatability*: maximum relative standard deviation of 1.2 per cent determined on 6 injections.

Calculate the percentage content of $C_{12}H_9F_3N_2O_2$ taking into account the assigned content of *teriflunomide for assay CRS*.

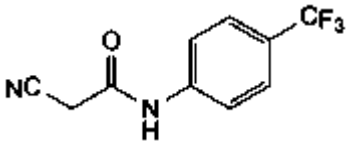
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. 4-(trifluoromethyl)aniline (leflunomide impurity A),



B. 2-cyano-*N*-[4-(trifluoromethyl)phenyl]acetamide.

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Teriflunomide Tablets

General Notices

(Ph. Eur. monograph 3037)

Action and use

Immunomodulator; treatment of multiple sclerosis.

Ph Eur

DEFINITION

Tablets containing *Teriflunomide (3036)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of teriflunomide ($C_{12}H_9F_3N_2O_2$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector, in the range of 200-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (d).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution 3.85 g/L solution of *ammonium acetate R* adjusted to pH 5.5 with *glacial acetic acid R*.

Solvent mixture Buffer solution, *acetonitrile R* (20:80 *V/V*).

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Test solution To 10 tablets, add a volume of the solvent mixture equivalent to about half of the final volume. Dissolve the tablets by shaking for approximately 20 min and sonicating for about 3 min. Dilute to volume with the solvent mixture to obtain a concentration of teriflunomide of 0.7 mg/mL and filter. Dilute 3.0 mL of the filtrate to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *leflunomide impurity A CRS* (teriflunomide impurity A) in *acetonitrile R* and dilute to 250 mL with the same solvent. Dilute 1 mL of the solution to 200 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *teriflunomide impurity B CRS* in *acetonitrile R* and dilute to 100 mL with the same solvent. Dilute 2 mL of the solution to 50 mL with the solvent mixture. To 1 mL of this solution add 1 mL of reference solution (b) and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 21.0 mg of *teriflunomide for assay CRS* in 40 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (e) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (2.7 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, buffer solution (10:90 *V/V*);

— *mobile phase B*: buffer solution, *acetonitrile for chromatography R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	76	24
2 - 12	76 → 23	24 → 77

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 249 nm.

Injection 5 µL of the test solution and reference solutions (c) and (e).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to teriflunomide (retention time = about 5 min): impurity B = about 1.5; impurity A = about 1.6.

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System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities B and A;

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of teriflunomide in reference solution (e).

Limits:

— *impurity A*: maximum 0.01 per cent;

— *impurity B*: maximum 0.30 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.40 per cent;

— *reporting threshold*: 0.05 per cent; do not disregard the peak due to impurity A.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium 6.8 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 6.8 with a 200 g/L solution of *sodium hydroxide R*. Use 1000 mL of the medium.

Rotation speed 50 r/min.

Time 30 min.

Analysis Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution Samples withdrawn from the dissolution vessel and filtered.

Measure the absorbance of the solutions at the absorption maximum at 292 nm.

Calculate the amount of dissolved teriflunomide ($C_{12}H_9F_3N_2O_2$), expressed as a percentage of the content stated on the label, taking the specific absorbance to be 854.

Acceptance criterion:

— *Q* = 75 per cent after 30 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (d).

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System suitability Reference solution (d):

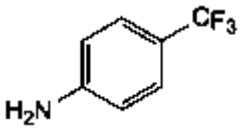
— *symmetry factor*: maximum 2.0 for the peak due to teriflunomide;

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

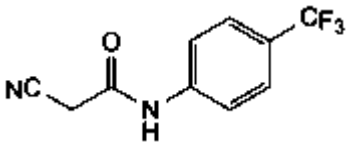
Calculate the percentage content of teriflunomide ($C_{12}H_9F_3N_2O_2$) taking into account the assigned content of *teriflunomide for assay CRS*.

IMPURITIES

Specified impurities *A, B.*



A. 4-(trifluoromethyl)aniline (leflunomide impurity A),



B. 2-cyano-*N*-[4-(trifluoromethyl)phenyl]acetamide.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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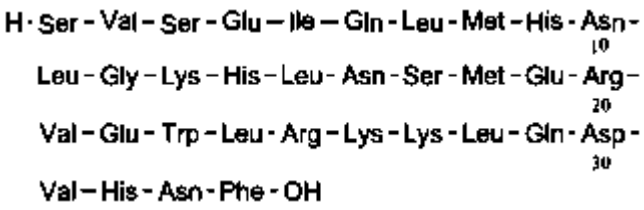
Teriparatide

General Notices

(Ph. Eur. monograph 2829)



$C_{181}H_{291}N_{55}O_{51}S_2$ 4118 *52232-67-4*

Action and use

Parathyroid hormone analogue; treatment of osteoporosis.

Ph Eur

DEFINITION

Tetratriacontapeptide in which the sequence of amino acids is the same as that of the 1-34 *N*-terminal fragment of endogeneous human parathyroid hormone (rhPTH).

Content

95.0 per cent to 105.0 per cent (anhydrous, acetic acid- and chloride-free substance).

PRODUCTION

Teriparatide is produced by a method based on recombinant DNA (rDNA) technology. During the course of product development it must be demonstrated that the manufacturing process produces a biologically active protein using a suitable bioassay as approved by the competent authority.

Prior to release, the following tests are carried out on each batch of teriparatide, unless exemption has been granted by the competent authority.

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell- and vector-derived DNA

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The limit is approved by the competent authority.

CHARACTERS

Appearance

White or almost white, very hygroscopic powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in acetonitrile.

IDENTIFICATION

A. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Solution A Dissolve 230 mg of *anhydrous disodium hydrogen phosphate R* and 60 mg of *sodium dihydrogen phosphate monohydrate R* in 100 mL of *water R* and adjust to pH 7.8 with *sodium hydroxide solution R*.

Test solution Dissolve the substance to be examined in solution A to obtain a concentration of 1.5 mg/mL and transfer 150 µL of the solution to a clean tube. Add 90 µL of a 0.25 mg/mL solution of *glutamyl endopeptidase for peptide mapping R* in solution A. Mix and incubate at 37 °C for 18-24 h. Stop the reaction by adding 660 µL of mobile phase A to reach a final digested protein concentration of about 0.25 mg/mL.

NOTE: if a teriparatide concentration of 1.5 mg/mL is not obtainable, a similar ratio of micrograms of endopeptidase per milligram of teriparatide may be used.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *teriparatide CRS* instead of the substance to be examined.

Blank solution Prepare at the same time and in the same manner as for the test solution but omitting the substance to be examined.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (2.2.29). *Store the solutions at 2-8 °C and use them within 72 h.*

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm) with a pore size of 30 nm;

— *temperature*: 40 °C.

Mobile phase:

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— *mobile phase A*: mix 1 mL of *trifluoroacetic acid R* and 1000 mL of *water R*; filter and degas;

— *mobile phase B*: mix 1 mL of *trifluoroacetic acid R*, 400 mL of *water R* and 600 mL of *acetonitrile for chromatography R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	96	4
6 - 20	96 → 45	4 → 55
20 - 25	45 → 0	55 → 100

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Autosampler Set at 2-8 °C.

Injection 20 µL.

System suitability:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of teriparatide digest supplied with *teriparatide CRS*;

— in the chromatogram obtained with the reference solution, identify the peaks due to digest fragments I, II, III, IV and V:

symmetry factor Maximum 2.3 for the peak due to fragment IV;

resolution Minimum 1.5 between the peaks due to fragments I and III.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Impurities with molecular masses greater than that of teriparatide

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure. *Store the solutions at 2-8 °C and use them within 72 h.*

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of 1 mg/mL.

Reference solution Dissolve the contents of a vial of *teriparatide CRS* in *water R* to obtain a concentration of 1 mg/mL.

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Blank solution *water R*.

Resolution solution Incubate a vial of *teriparatide CRS* at 75 °C for 16-24 h. After incubation, dissolve the contents of the vial in *water R* to obtain a concentration of 1 mg/mL of degraded teriparatide.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5-10 µm) with a pore size of 12.5 nm, of a grade suitable for fractionation of globular proteins of relative molecular mass up to 150 000.

Mobile phase Add 1 mL of *trifluoroacetic acid R* to 750 mL of *water R*, mix with 250 mL of *acetonitrile for chromatography R* and degas.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 214 nm.

Autosampler Set at 2-8 °C.

Injection 20 µL.

Run time 1.5 times the retention time of teriparatide monomer.

Retention time Teriparatide monomer = about 17 min.

System suitability:

— the chromatogram obtained with the reference solution is similar to the chromatogram supplied with *teriparatide CRS*;

— *resolution*: minimum 2.0 between the peaks due to teriparatide dimer and monomer in the chromatogram obtained with the resolution solution.

Limit:

— *sum of the peaks eluted before the principal peak*: maximum 0.3 per cent; disregard any peak with a retention time greater than that of the peak due to teriparatide monomer.

Related proteins

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Store the solutions at 2-8 °C and use them within 48 h.*

Buffer solution Dissolve 28.4 g of *anhydrous sodium sulfate R* in 900 mL of *water R* and adjust to pH 2.3 with *phosphoric acid R*. Dilute to 1000 mL with *water for chromatography R* and filter.

Test solution Dissolve the substance to be examined in mobile phase A to obtain a concentration of 0.7 mg/mL.

Reference solution Dissolve the contents of a vial of *teriparatide CRS* in mobile phase A to obtain a concentration of 0.7 mg/mL.

Blank solution Mobile phase A.

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Resolution solution Dissolve the contents of a vial of *teriparatide for system suitability CRS* in mobile phase A to obtain a concentration of 1 mg/mL.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm) with a pore size of 30 nm;

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 10 volumes of *acetonitrile for chromatography R* and 90 volumes of the buffer solution and degas; apply mild heating at 20-25 °C while stirring continuously during analysis;

— *mobile phase B*: mix equal volumes of *acetonitrile for chromatography R* and the buffer solution and degas; apply mild heating at 20-25 °C while stirring continuously during analysis;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100 → 65	0 → 35
5 - 35	65 → 60	35 → 40
35 - 45	60 → 0	40 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Autosampler Set at 2-8 °C.

Injection 20 µL.

Relative retention With reference to teriparatide (retention time = 20-25 min): related protein A ([$MetO^{8}$,$MetO^{18}$]teriparatide) = about 0.40; related protein B ([$MetO^{8}$]teriparatide) = about 0.49; related protein C ([$MetO^{18}$]teriparatide) = about 0.57; related protein D = about 1.06; related protein E = about 1.14.

System suitability Resolution solution:

— the chromatogram obtained is similar to the chromatogram supplied with *teriparatide for system suitability CRS*;

— *resolution*: minimum 1.5 between the peaks due to teriparatide and related protein D;

— *symmetry factor*: 0.8 to 2.0 for the peak due to teriparatide;

Results:

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— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

Limits:

— *sum of related proteins A, B and C*: maximum 0.5 per cent;

— *any other related protein*: maximum 0.5 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

Maximum 7.0 per cent, determined on 10 mg using the evaporation technique:

— *temperature*: 100 °C;

— *heating time*: 8 min.

Bacterial endotoxins (*2.6.14*)

Less than 50 IU/mg.

ASSAY

Acetate

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Store the solutions at 2-8 °C and use them within 72 h.*

Test solution Dissolve the substance to be examined in the mobile phase to obtain a concentration of 5 mg/mL.

Reference solutions Dissolve separately 100 mg, 200 mg and 300 mg of *anhydrous sodium acetate R* in the mobile phase and dilute to 100 mL with the mobile phase. Further dilute 1.0 mL of each solution to 10.0 mL with the mobile phase to prepare a standard curve with acetate concentrations in the range of 0.072-0.216 mg/mL.

Plot peak areas versus injected acetate content and perform linear regression to create a standard curve.

Column:

— *size*: *l* = 0.25 m, Ø = 9.0 mm;

— *stationary phase*: *ion-exclusion resin for chromatography R* (7.5 µm).

Mobile phase 0.5 per cent *V/V* solution of *dilute sulfuric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

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Autosampler Set at 2-8 °C.

Injection 100 µL.

Run time 1.5 times the retention time of acetate.

Retention time Acetate = about 10 min.

System suitability:

— *repeatability*: maximum relative standard deviation of 1.25 per cent for the area of the principal peak, determined on 3 injections of the middle reference solution;

— the correlation coefficient (*r*) calculated for the standard curve is not less than 0.999.

Calculate the acetate content using the standard curve and the area of the peak due to acetate in the chromatogram obtained with the test solution.

Chloride

Liquid chromatography (2.2.29): use the normalisation procedure. *Use the solutions within 72 h.*

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of 1 mg/mL.

Reference solution (a) Dissolve 165.9 mg of *sodium chloride R*, previously dried at 105 °C for 30 min, in *water R* and dilute to 100 mL with the same solvent.

Reference solution (b) Dissolve 150 mg of *sodium nitrite R* in *water R* and dilute to 100 mL with the same solvent. Mix 1.0 mL of the solution and 2.5 mL of reference solution (a) and dilute to 100 mL with *water R*.

Reference solutions Dilute reference solution (a) with *water R* to prepare a standard curve with at least 4 concentrations in the range of 10-40 µg/mL.

Plot peak areas versus injected chloride content and perform linear regression to create a standard curve.

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (15 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (15 µm).

Mobile phase Dissolve 285.7 mg of *sodium hydrogen carbonate R* and 381.6 mg of *anhydrous sodium carbonate R* in *water R* and dilute to 2000 mL with the same solvent.

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Flow rate 2.0 mL/min.

Detection Conductivity detector; use a self-regenerating anion suppressor at 100 mA.

Injection 50 µL.

Run time 6 times the retention time of chloride.

Retention time Chloride = about 1.6 min; nitrite = about 1.8 min.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to chloride and nitrite;

— *symmetry factor*: maximum 2.0 for the peaks due to chloride and nitrite;

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the areas of the peaks due to chloride and nitrite, determined on 5 injections;

— the correlation coefficient (*r*) calculated for the standard curve is not less than 0.999.

Calculate the chloride content using the standard curve and the area of the peak due to chloride in the chromatogram obtained with the test solution.

Content

Liquid chromatography (2.2.29) as described in the test for related proteins with the following modifications.

Test solution Dissolve the substance to be examined in the mobile phase to obtain a concentration of 0.25 mg/mL.

Reference solution Dissolve the contents of a vial of *teriparatide CRS* in the mobile phase to obtain a concentration of 0.25 mg/mL.

Mobile phase Mobile phase A, mobile phase B (63:37 *V/V*); apply mild heating at 20-25 °C while stirring continuously during analysis.

Run time 1.5 times the retention time of teriparatide.

Retention time Teriparatide = about 10 min.

System suitability Reference solution:

— *symmetry factor*: 0.8 to 1.5 for the peak due to teriparatide;

— *repeatability*: maximum relative standard deviation of 1.25 per cent for the area of the peak due to teriparatide, determined on 3 injections.

Calculate the percentage content of teriparatide ($C_{181}H_{291}N_{55}O_{51}S_2$) taking into account the assigned content of *teriparatide CRS*.

STORAGE

In an airtight container, protected from light, at -10 °C or below.

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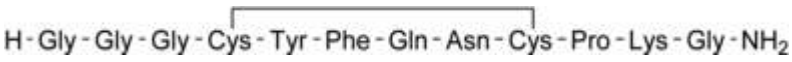
Terlipressin

General Notices

(Ph. Eur. monograph 2646)



$C_{52}H_{74}N_{16}O_{15}S_2$ 1227 *14636-12-5*

Action and use

Vasopressin analogue; treatment of diabetes insipidus, bleeding from varices, dialysis.

Ph Eur

DEFINITION

Glycyl-glycyl-glycyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysylglycinamide cyclic (4→9)-disulfide.

Synthetic dodecapeptide analogue of the natural hormone vasopressin. It is available as an acetate.

Content

95.0 per cent to 105.0 per cent (anhydrous, acetic acid-free substance).

CHARACTERS

Appearance

White or almost white fluffy powder, hygroscopic.

IDENTIFICATION

Carry out either tests A, B or tests A, C.

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

B. Nuclear magnetic resonance spectrometry (*2.2.64*).

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Preparation 2.9 mg/mL solution in *deuterium oxide R* containing 20 µg/mL of *deuterated sodium trimethylsilylpropionate R*, adjusted to pH 4 with *deuterated acetic acid R*.

Comparison Dissolve the contents of a vial of *terlipressin for NMR identification CRS* in *deuterium oxide R* containing 20 µg/mL of *deuterated sodium trimethylsilylpropionate R*, adjusted to pH 4 with *deuterated acetic acid R*, to obtain a concentration of 2.9 mg/mL.

Operating conditions:

— *field strength*: minimum 300 MHz;

— *temperature*: 23 °C.

Results Examine the ^{1}H NMR spectrum from 0 to 9 ppm. The ^{1}H NMR spectrum obtained is qualitatively similar to the ^{1}H NMR spectrum obtained with *terlipressin for NMR identification CRS*.

C. Amino acid analysis (*2.2.56*). Method 1 for hydrolysis and method 1 for analysis are suitable.

Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids, taking 1/9 of the sum of the number of moles of aspartic acid, glutamic acid, proline, glycine, phenylalanine and lysine as equal to 1. The values fall within the following limits: glycine 3.6 to 4.4; half-cystine 1.4 to 2.2; tyrosine 0.7 to 1.1; phenylalanine, glutamic acid, aspartic acid, proline and lysine 0.9 to 1.1. Not more than traces of other amino acids are present.

TESTS

Specific optical rotation (*2.2.7*)

-108 to -88 (anhydrous and acetic acid-free substance).

Dissolve 125.0 mg in 25.0 mL of a 1 per cent *V/V* solution of *glacial acetic acid R*.

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution Dissolve 3.30 g of *ammonium sulfate R* in *water for chromatography R* and dilute to 5000 mL with the same solvent. Add 1.0 mL of *sulfuric acid R* and mix well; filter through a membrane filter (nominal pore size 0.45 µm).

Test solution Dissolve 10.0 mg of the substance to be examined in 50.0 mL of a 9 g/L solution of *sodium chloride R*.

Solution A Dissolve the contents of a vial of *terlipressin impurity mixture CRS* (containing impurities A, D and L) in 1.0 mL of a 9 g/L solution of *sodium chloride R*.

Solution B Dissolve the contents of a vial of *terlipressin CRS* in a 9 g/L solution of *sodium chloride R* and dilute to 2.5 mL with the same solution.

Reference solution (a) Dilute 1.0 mL of solution B to 2.0 mL with a 9 g/L solution of *sodium chloride R*.

Reference solution (b) Mix 20 µL of solution A and 500 µL of solution B, and dilute to 1.0 mL with a 9 g/L solution of *sodium chloride R*.

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Reference solution (c) Mix 100 µL of solution A and 500 µL of solution B, and dilute to 1.0 mL with a 9 g/L solution of *sodium chloride R*.

Reference solution (d) Dilute 1.0 mL of the test solution to 100.0 mL with a 9 g/L solution of *sodium chloride R*. Dilute 1.0 mL of this solution to 10.0 mL with a 9 g/L solution of *sodium chloride R*.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, buffer solution (18.5:81.5 *V/V*);

— *mobile phase B*: *methanol R*, buffer solution (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	100	0
35 - 55	100 → 0	0 → 100
55 - 65	0	100

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 200 µL of the test solution and reference solutions (a), (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *terlipressin impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, D and L.

Relative retention With reference to terlipressin (retention time = about 21 min): impurity E = about 0.4; impurity C = about 0.5; impurity B = about 0.7; impurity A = about 0.85; impurity G = about 1.2; impurity H = about 1.4; impurities I and F = about 2.0; impurity L = about 2.2; impurity D = about 2.3; impurity K = about 2.5; impurity J = about 2.8.

System suitability:

— *resolution*: minimum 1.4 between the peak due to impurity A and the principal peak in the chromatogram obtained with reference solution (c); the peaks due to impurities L and D are separated as shown in the chromatogram supplied with *terlipressin impurity mixture CRS*.

— *signal-to-noise ratio*: minimum 50 for the peak due to impurity A in the chromatogram obtained with reference solution (b);

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— *symmetry factor*: maximum 2.0 for the peak due to terlipressin in the chromatogram obtained with reference solution (a);

— *repeatability*: maximum relative standard deviation of 2.0 per cent determined on 5 injections of reference solution (a).

Calculation of percentage contents:

— for each impurity, use the concentration of terlipressin in reference solution (d).

Limits:

— *impurity D*: maximum 0.6 per cent;

— *unspecified impurities*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.1 per cent.

Acetic acid (2.5.34)

8.0 per cent to 14.0 per cent.

Test solution Dissolve 20.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A, and dilute to 20.0 mL with the same mixture of solvents.

Water (2.5.32)

Maximum 10.0 per cent, determined on 10.0 mg using the evaporation technique at 120 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 200 µL of the test solution and reference solution (a).

Calculate the percentage content of terlipressin ($C_{52}H_{74}N_{16}O_{15}S_2$) taking into account the assigned content of $C_{52}H_{74}N_{16}O_{15}S_2$ in *terlipressin CRS*.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

LABELLING

The label states the terlipressin content ($C_{52}H_{74}N_{16}O_{15}S_2$).

IMPURITIES

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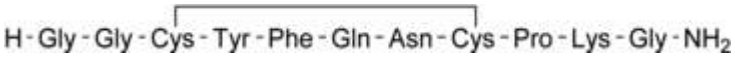
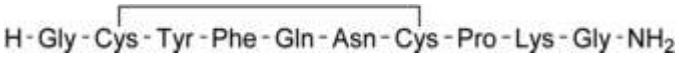
Specified impurities *D.*

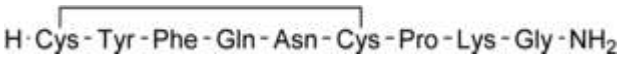
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, F, G, H, I, J, K, L.*



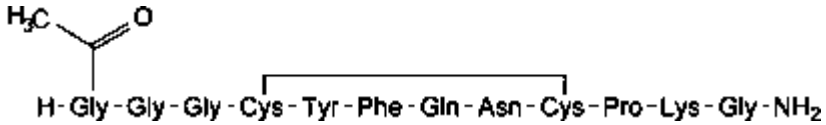
A. des-1-glycine-terlipressin,



B. des-1,2-diglycine-terlipressin,



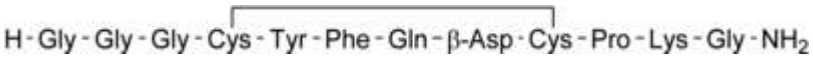
C. des-(1-3)-terlipressin,



D. N^1-acetylterlipressin,

E. [6-D-phenylalanine]terlipressin,

F. [7-L-glutamic acid]terlipressin,



G. [8-L-β-aspartic acid]terlipressin,

H. [8-L-α-aspartic acid]terlipressin,

I. [12-glycine]terlipressin,

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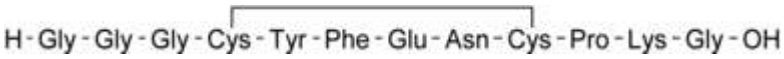
J. [12-glycine]terlipressin ethyl ester,



K. [7-L-glutamic acid,12-glycine]terlipressin,

L. [8-L-aspartic acid,12-glycine]terlipressin.

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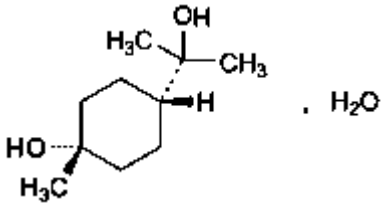
Terpin Monohydrate

General Notices

(Ph. Eur. monograph 2940)



$C_{10}H_{20}O_2,H_2O$ 190.3 *2451-01-6*

Action and use

Expectorant.

Ph Eur

DEFINITION

(1*s*,4*s*)-4-(2-Hydroxypropan-2-yl)-1-methylcyclohexan-1-ol monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

mp

About 117 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *terpin monohydrate CRS*.

B. Water (see Tests).

TESTS

Solution S

Dissolve 2.50 g in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.02 M sodium hydroxide* or *0.02 M hydrochloric acid* is required to change the colour of the indicator.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Internal standard solution Dissolve 0.500 g of *biphenyl R* in 1 mL of *methylene chloride R* and dilute to 25.0 mL with *methanol R*.

Test solution (a) Dissolve 0.375 g of the substance to be examined in *methanol R* and dilute to 25.0 mL with the same solvent.

Test solution (b) Dissolve 85.0 mg of the substance to be examined in *methanol R*, add 2.0 mL of the internal standard solution and dilute to 100.0 mL with *methanol R*.

Reference solution (a) Dissolve the contents of a vial of *terpin impurity D CRS* in 1 mL of test solution (a).

Reference solution (b) Dissolve 85.0 mg of *terpin monohydrate CRS* in *methanol R*, add 2.0 mL of the internal standard solution and dilute to 100.0 mL with *methanol R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 1.0 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:10.

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Temperature:

	Time (min)	Temperature (°C)
Column	0 - 11	180
	11 - 14	180 → 270
	14 - 15	270
Injection port		220
Detector		300

Detection Flame ionisation.

Injection 1 µL of test solution (a) and reference solution (a).

Relative retention With reference to terpin (retention time = about 6.3 min): impurity D = about 1.05; internal standard = about 1.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to terpin.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

8.0 per cent to 10.0 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (2.2.28) as described in the test for related substances with the following modification.

Injection 0.5 µL of test solution (b) and reference solution (b).

Calculate the percentage content of terpin using the following expression:

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$$\frac{A_1 \times m_2 \times A_4 \times 100}{A_2 \times m_1 \times A_3}$$

A_1 = area of the peak due to terpin in the chromatogram obtained with test solution (b);

A_2 = area of the peak due to terpin in the chromatogram obtained with reference solution (b);

A_3 = area of the peak due to the internal standard in the chromatogram obtained with test solution (b);

A_4 = area of the peak due to the internal standard in the chromatogram obtained with reference solution (b);

m_1 = mass of the substance to be examined used to prepare test solution (b), in milligrams;

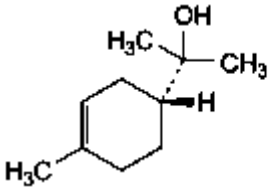
m_2 = mass of *terpin monohydrate CRS* used to prepare reference solution (b), in milligrams.

STORAGE

In an airtight container, protected from light.

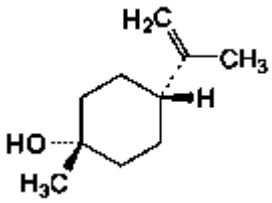
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D.*

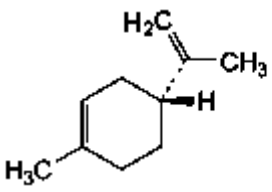


and enantiomer

A. 2-[(1*RS*)-4-methylcyclohex-3-en-1-yl]propan-2-ol (α-terpineol),



B. (1*s*,4*s*)-1-methyl-4-(prop-1-en-2-yl)cyclohexan-1-ol (*cis*-β-terpineol),



and enantiomer

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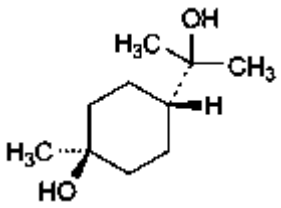
C. (4*RS*)-1-methyl-4-(prop-1-en-2-yl)cyclohex-1-ene (limonene),



D. (1*r*,4*r*)-4-(2-hydroxypropan-2-yl)-1-methylcyclohexan-1-ol (*trans*-terpin).

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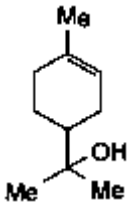
Terpineol

General Notices



$C_{10}H_{18}O$ 154.3 *98-55-5*

DEFINITION

Terpineol is a mixture of structural isomers in which *α-terpineol* predominates.

CHARACTERISTICS

A colourless, slightly viscous, liquid which may deposit crystals; odour, pleasant and characteristic.

Very slightly soluble in *water*; freely soluble in *ethanol (70%)*; soluble in *ether*.

TESTS

Refractive index

1.4800 to 1.4855, Appendix V E.

Weight per mL

0.931 to 0.935 g, Appendix V G.

Low-boiling substances

Not more than 4.0% v/v distils below 214°, Appendix V C.

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Testosterone

General Notices

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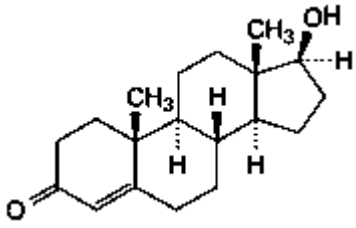

$C_{19}H_{28}O_2$ 288.4 *58-22-0*

Action and use

Androgen.

Preparation

Testosterone Implants

Ph Eur

DEFINITION

17β-Hydroxyandrost-4-en-3-one.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystalline powder, or colourless or yellowish-white crystals.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride, practically insoluble in fatty oils.

mp

About 155 °C.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *testosterone for ID and assay CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 106 to + 114 (dried substance).

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (30:70 *V/V*).

Test solution Dissolve 35.0 mg of the substance to be examined in 30 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*.

Reference solution (a) Dissolve 9 mg of *testosterone for system suitability A CRS* (containing impurities C, G and K) in 8 mL of *acetonitrile R* and dilute to 25 mL with *water R*.

Reference solution (b) Dissolve 7.0 mg of *testosterone impurity I CRS* in 30 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 35.0 mg of *testosterone for ID and assay CRS* in 30 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core phenylhexylsilyl silica gel for chromatography R* (2.7 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.7	65	35
2.7 - 7	65 → 63	35 → 37
7 - 10	63 → 10	37 → 90
10 - 12	10	90

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 242 nm, and for impurity I, at 290 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *testosterone for system suitability A CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C, G and K; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity I.

Relative retention With reference to testosterone (retention time = about 4 min): impurity I = about 0.84; impurity K = about 0.86; impurity G = about 1.1; impurity C = about 1.3.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to testosterone.

Calculation of percentage contents:

— for impurity I, use the concentration of impurity I in reference solution (b);

— for impurities other than I, use the concentration of testosterone in reference solution (c).

Limits:

— *impurity C*: maximum 0.3 per cent;

— *impurity I at 290 nm*: maximum 0.2 per cent;

— *impurity K*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

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Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 2 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 5 µL of the test solution and reference solution (d).

Calculate the percentage content of $C_{19}H_{28}O_2$ taking into account the assigned content of *testosterone for ID and assay CRS*.

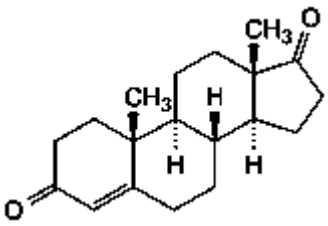
STORAGE

Protected from light.

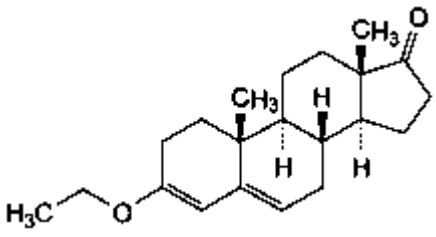
IMPURITIES

Specified impurities *C, I, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, E, G, H, J, L, M.*



A. androst-4-ene-3,17-dione (androstenedione),



B. 3-ethoxyandrosta-3,5-dien-17-one (androstenedione ethylenolether),

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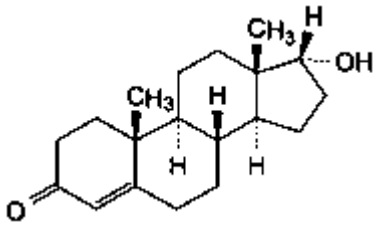
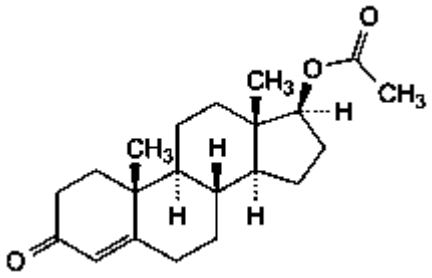
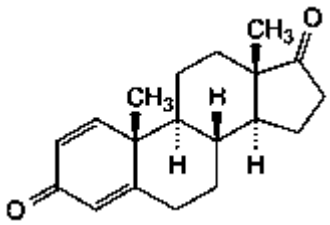


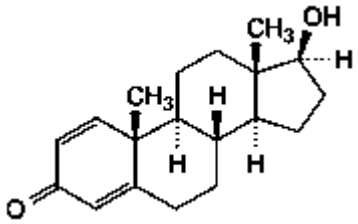
C. 17α-hydroxyandrost-4-en-3-one (17-*epi*-testosterone),



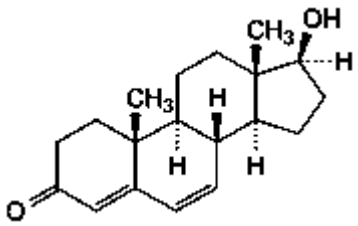
E. 3-oxoandrost-4-en-17β-yl acetate (testosterone acetate),



G. androsta-1,4-diene-3,17-dione (androstadienedione),



H. 17β-hydroxyandrosta-1,4-dien-3-one (boldenone),



I. 17β-hydroxyandrosta-4,6-dien-3-one (Δ6-testosterone),

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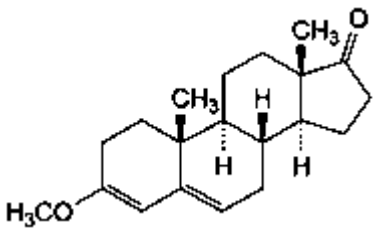
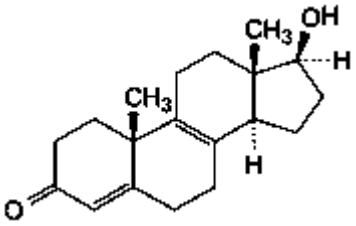
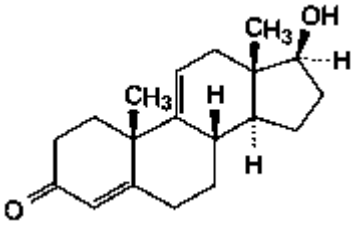


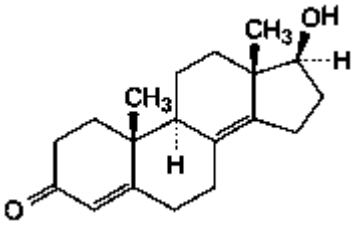
J. 3-methoxyandrosta-3,5-dien-17-one (androstenedione methylenolether),



K. 17β-hydroxyandrosta-4,8-dien-3-one,



L. 17β-hydroxyandrosta-4,9(11)-dien-3-one,



M. 17β-hydroxyandrosta-4,8(14)-dien-3-one.

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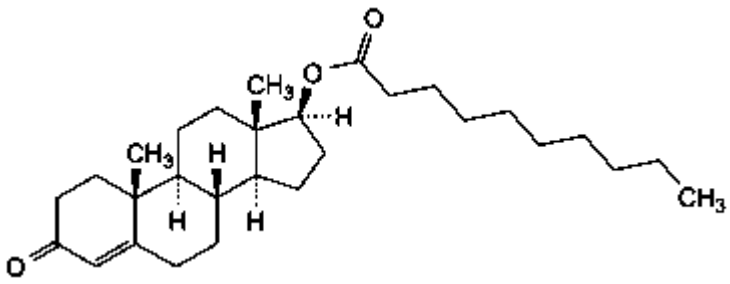
Testosterone Decanoate

General Notices

(Ph. Eur. monograph 1736)



$C_{29}H_{46}O_3$ 442.7

Action and use

Androgen.

Ph Eur

DEFINITION

3-Oxoandrost-4-en-17β-yl decanoate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, very soluble in acetone, in methylene chloride and in anhydrous ethanol, freely soluble in fatty oils.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *testosterone decanoate CRS*.

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B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 0.20 g in 20 mL of *methanol R*.

Specific optical rotation (*2.2.7*)

+ 75.0 to + 80.0 (dried substance).

Dissolve 0.200 g in *anhydrous ethanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *testosterone decanoate for system suitability CRS* (containing impurities A, B, C, D, E and F) in 1 mL of the mobile phase.

Reference solution (b) Dilute 10.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 20.0 mg of *testosterone decanoate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *water R*, *acetonitrile R* (5:95 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time Twice the retention time of testosterone decanoate.

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Identification of impurities Use the chromatogram supplied with *testosterone decanoate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention With reference to testosterone decanoate (retention time = about 20 min): impurity A = about 0.2; impurity B = about 0.6; impurities C and G = about 0.79; impurity D = about 0.83; impurity E = about 1.3; impurity F = about 1.7.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities C and D.

Limits:

— *correction factors*: for the calculation of content, multiply the peak area of impurity A by 0.7;

— *impurities A, B, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *sum of impurities C and G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Free acid

Dissolve 0.65 g in 10 mL of *ethanol (96 per cent) R*, previously neutralised to *bromothymol blue solution R3*, and titrate immediately with *0.01 M sodium hydroxide*, using 0.1 mL of *bromothymol blue solution R3* as indicator. Not more than 0.6 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at a pressure not exceeding 0.7 kPa.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 20 µL of the test solution and reference solution (c).

Calculate the percentage content of $C_{29}H_{46}O_3$ from the declared content of *testosterone decanoate CRS*.

STORAGE

At a temperature of 2 °C to 8 °C.

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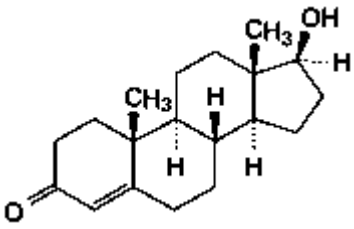
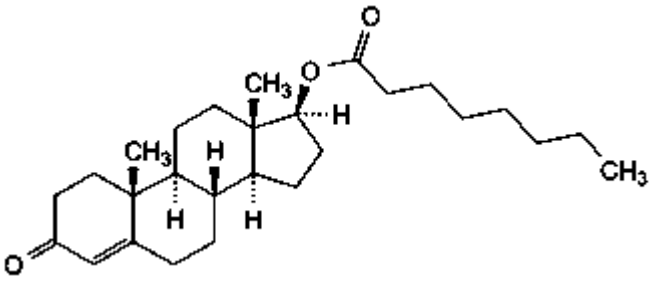
IMPURITIES

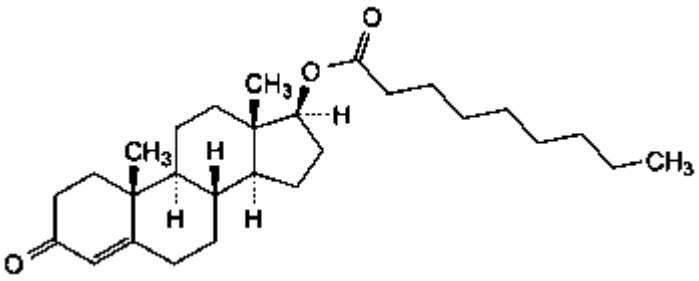
Specified impurities *A, B, C, D, E, F, G.*



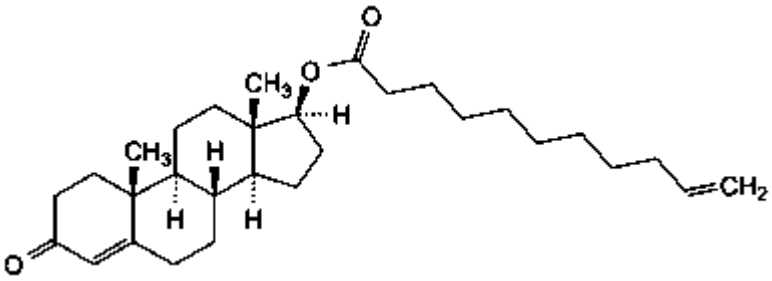
A. testosterone,



B. 3-oxoandrost-4-en-17β-yl octanoate (testosterone octanoate),



C. 3-oxoandrost-4-en-17β-yl nonanoate (testosterone nonanoate),



D. 3-oxoandrost-4-en-17β-yl undec-10-enoate (testosterone undecylenate),

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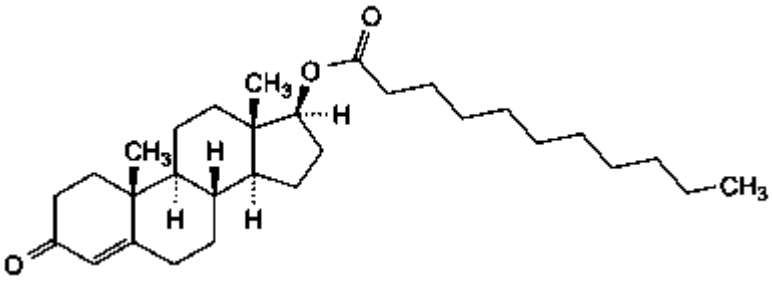
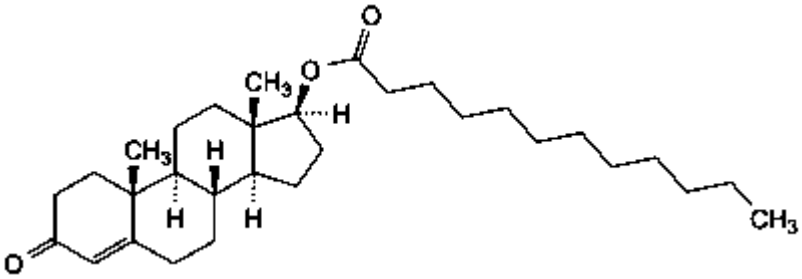
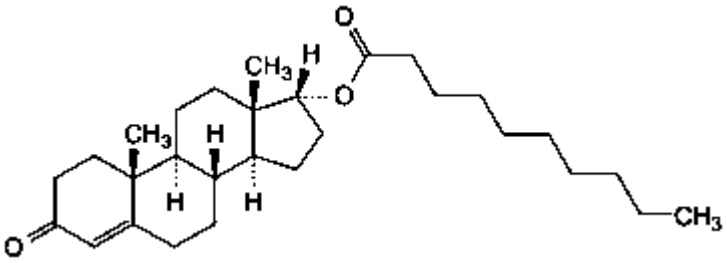


E. 3-oxoandrost-4-en-17β-yl undecanoate (testosterone undecanoate),



F. 3-oxoandrost-4-en-17β-yl dodecanoate (testosterone laurate),



G. 3-oxoandrost-4-en-17α-yl decanoate (epitestosterone decanoate).

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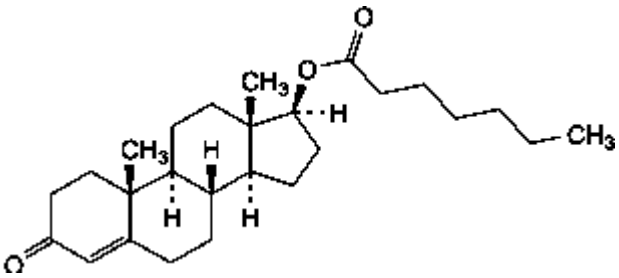
Testosterone Enantate

General Notices

(Ph. Eur. monograph 1048)



$C_{26}H_{40}O_3$ 400.6 *315-37-7*

Action and use

Androgen.

Ph Eur

DEFINITION

3-Oxoandrost-4-en-17β-yl heptanoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in anhydrous ethanol, freely soluble in fatty oils.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

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A. Melting point (2.2.14): 34 °C to 39 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison testosterone enantate CRS.

C. Thin-layer chromatography (2.2.27).

Solvent mixture methanol R, methylene chloride R (10:90 *V/V*).

Test solution Dissolve 5 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of testosterone enantate CRS in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of testosterone enantate CRS, 5 mg of testosterone decanoate CRS and 5 mg of testosterone isocaproate CRS in the solvent mixture and dilute to 10 mL with the solvent mixture.

Plate TLC octadecylsilyl silica gel F_{254} plate R.

Mobile phase water R, acetonitrile R, 2-propanol R (20:40:60 *V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air, then at 100 °C for 10 min; allow to cool.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with alcoholic solution of sulfuric acid R; heat at 120 °C for 10 min; allow to cool and examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is green and is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated principal spots by each method of visualisation.

D. To about 25 mg add 2 mL of a 10 g/L solution of potassium hydroxide R in methanol R and boil under a reflux condenser for 1 h. Cool. Add 10 mL of water R. Acidify with dilute hydrochloric acid R until blue litmus paper R turns red. Filter and wash the precipitate with a small quantity of water R. The residue, after drying at 60 °C at a pressure not exceeding 0.7 kPa for 3 h, melts (2.2.14) at 150 °C to 153 °C.

TESTS

Specific optical rotation (2.2.7)

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+ 81 to + 86 (dried substance).

Dissolve 0.100 g in *anhydrous ethanol R* and dilute to 10.0 mL with the same solvent.

Impurity A

Maximum 0.16 per cent.

Dissolve 0.50 g in 10 mL of *ethanol (96 per cent) R* previously neutralised to *bromothymol blue solution R3*. Titrate immediately with *0.01 M sodium hydroxide* using 0.1 mL of *bromothymol blue solution R3* as indicator. Not more than 0.6 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Impurity H

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.100 g of the substance to be examined in 1.0 mL of *ethanol (96 per cent) R*.

Reference solution Dissolve 3.0 mg of *testosterone enantate impurity H CRS* in 20.0 mL of *ethanol (96 per cent) R*.

Plate *TLC silica gel plate R*.

Mobile phase *ethyl acetate R*, *cyclohexane R1* (40:60 *V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 200 g/L solution of *toluenesulfonic acid R* in *ethanol (96 per cent) R* and heat at 120 °C for 10 min; examine in ultraviolet light at 366 nm.

System suitability Reference solution:

— the chromatogram shows a clearly visible spot due to impurity H.

Limit:

— *impurity H*: any spot due to impurity H is not more intense than the principal spot in the chromatogram obtained with the reference solution (0.15 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve with the aid of ultrasound the contents of a vial of *testosterone enantate for system suitability CRS* (containing impurities F and G) in the mobile phase and dilute to 1.0 mL with the mobile phase.

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Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 2 mg of *testosterone enantate for peak identification CRS* (containing impurity E) in 1.0 mL of the mobile phase.

Reference solution (d) Dissolve 2 mg of *testosterone caproate CRS* (impurity B) and 2 mg of *testosterone CRS* (impurity D) in the mobile phase and dilute to 5.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped dodecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase *water R*, *acetonitrile R* (30:70 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 10 µL.

Run time 1.5 times the retention time of testosterone enantate.

Identification of impurities Use the chromatogram supplied with *testosterone enantate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities F and G; use the chromatogram supplied with *testosterone enantate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B and D.

Relative retention With reference to testosterone enantate (retention time = about 22 min): impurity D = about 0.1; impurity B = about 0.7; impurity E = about 0.8; impurity F = about 0.85; impurity G = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 1.3 between the peaks due to impurities F and G.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 6.3;

— *impurity D*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurities E, F*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

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— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at a pressure not exceeding 0.7 kPa.

ASSAY

Dissolve 50.0 mg in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *anhydrous ethanol R*. Measure the absorbance (2.2.25) at the absorption maximum at 241 nm.

Calculate the content of $C_{26}H_{40}O_3$ taking the specific absorbance to be 422.

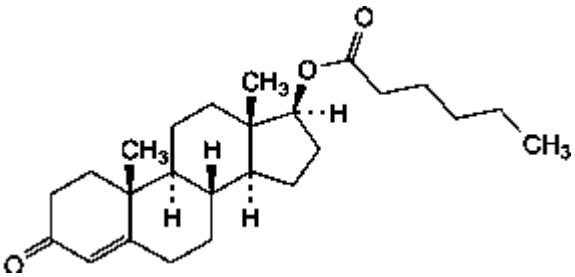
STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A, B, D, E, F, G, H.*

A. heptanoic acid,



B. 3-oxoandrost-4-en-17β-yl hexanoate (testosterone caproate),

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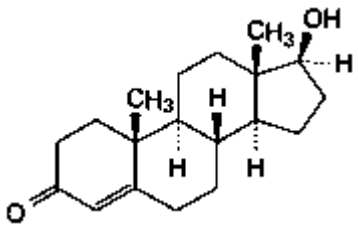
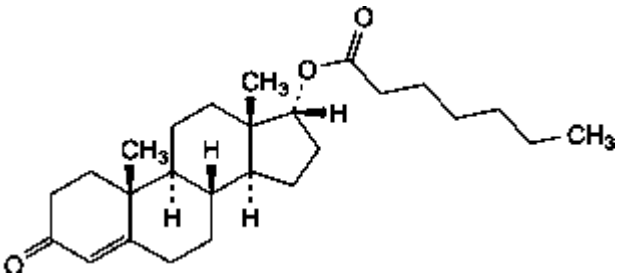
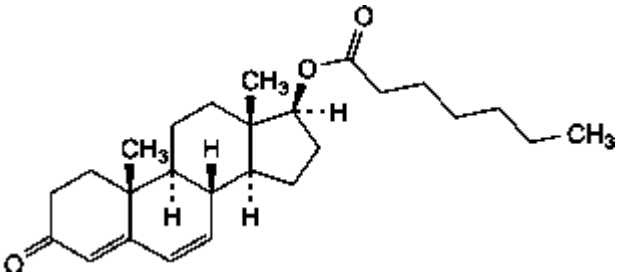


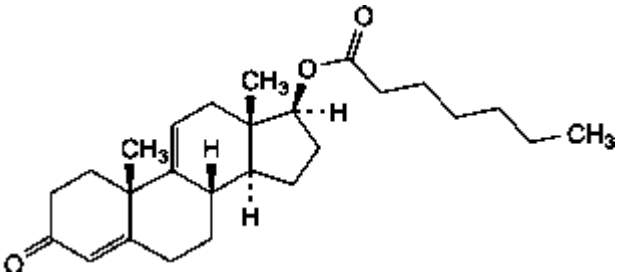
D. 17β-hydroxyandrost-4-en-3-one (testosterone),



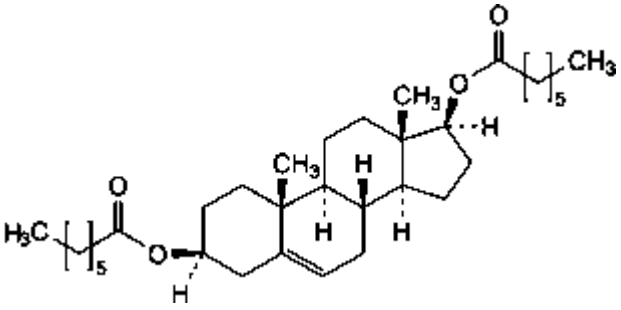
E. 3-oxoandrost-4-en-17α-yl heptanoate (17α-testosterone enantate),



F. 3-oxoandrosta-4,6-dien-17β-yl heptanoate (Δ6-testosterone enantate),



G. 3-oxoandrosta-4,9(11)-dien-17β-yl heptanoate (Δ9(11)-testosterone enantate),



H. androst-5-ene-3β,17β-diyl diheptanoate.

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Testosterone Implants

General Notices

Action and use

Androgen.

DEFINITION

Testosterone Implants are sterile cylinders prepared by the fusion or heavy compression of Testosterone without the addition of any other substance.

The implants comply with the requirements stated under Parenteral Preparations and with the following requirements.

Content of testosterone, $C_{19}H_{28}O_2$

97 to 103%, calculated with reference to the dried substance, and 90 to 110% of the stated amount.

Diameter

Implants containing less than 50 mg, 2.0 to 2.5 mm; implants containing 50 mg or more, 4.25 to 4.75 mm.

Where appropriate, powder the implants before carrying out the following tests.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of testosterone (*RS 329*).

B. Comply with the test for *identification of steroids*, Appendix III A, using *impregnating solvent II* and *mobile phase D*.

C. To 0.1 g in a stoppered tube add 3 mL of *anhydrous pyridine* and 0.6 mL of *acetic anhydride*. Heat on a waterbath for 3 hours, add *water* dropwise until crystals begin to form, then add slowly a further 15 mL of *water* and allow to stand until precipitation is complete. Filter the precipitate using a sintered-glass crucible and wash with *water* until the washings are neutral to *methyl red solution*. Recrystallise from *ethanol* (*96%*), adding a few drops of *water* if necessary to aid crystallisation, and dry at 105°. The *melting point* of the crystals is about 140°, Appendix V A.

TESTS

Melting point

152° to 156°, Appendix V A.

Specific optical rotation

In a 1% w/v solution in *absolute ethanol*, +106 to +112, Appendix V F, calculated with reference to the dried substance.

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Carbonisation

A 1% w/v solution in *ethanol* (*96%*) is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method I.

Loss on drying

When dried to constant weight at 105°, lose not more than 1.0% of their weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Weigh and powder a single implant. Dissolve 10 mg of the powdered implant in sufficient *absolute ethanol* to produce 100 mL, dilute 5 mL to 50 mL with *absolute ethanol* and measure the *absorbance* of the resulting solution at the maximum at 240 nm, Appendix II B. Calculate the content of $C_{19}H_{28}O_2$ taking 560 as the value of A(1%, 1 cm) at the maximum at 240 nm.

STORAGE

Testosterone Implants should be protected from light.

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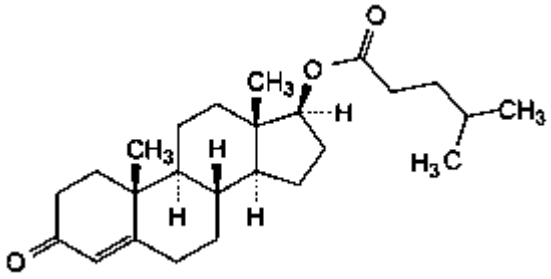
Testosterone Isocaproate

General Notices

(Ph. Eur. monograph 1737)



$C_{25}H_{38}O_3$ 386.6

Action and use

Androgen.

Ph Eur

DEFINITION

3-Oxoandrost-4-en-17β-yl 4-methylpentanoate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, very soluble in acetone and in methylene chloride, freely soluble in fatty oils.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *testosterone isocaproate CRS*.

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B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 0.20 g in 20 mL of *methanol R*.

Specific optical rotation (*2.2.7*)

+ 82.0 to + 88.0 (dried substance).

Dissolve 0.200 g in *anhydrous ethanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *testosterone isocaproate for system suitability CRS* (containing impurities A, B, C, D, E, F and G) in 10 mL of the mobile phase.

Reference solution (b) Dilute 10.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 20.0 mg of *testosterone isocaproate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *water R*, *acetonitrile R* (15:85 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

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Run time Twice the retention time of testosterone isocaproate.

Identification of impurities Use the chromatogram supplied with *testosterone isocaproate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E, F and G.

Relative retention With reference to testosterone isocaproate (retention time = about 14 min): impurity A = about 0.2; impurity B = about 0.4; impurity C = about 0.5; impurity D = about 0.7; impurity G = about 0.8; impurity E = about 1.1; impurity F = about 1.4.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to testosterone isocaproate.

Limits:

— *impurities A, B, C, D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Free acid

Dissolve 0.44 g in 10 mL of *ethanol (96 per cent) R*, previously neutralised to *bromothymol blue solution R3*, and titrate immediately with *0.01 M sodium hydroxide*, using 0.1 mL of *bromothymol blue solution R3* as indicator. Not more than 0.6 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at a pressure not exceeding 0.7 kPa.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 20 µL of the test solution and reference solution (c).

Calculate the percentage content of $C_{25}H_{38}O_3$ from the declared content of *testosterone isocaproate CRS*.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G*.

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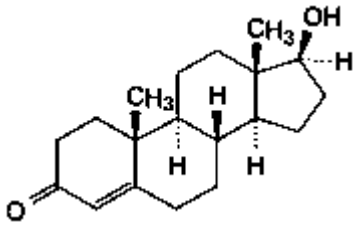
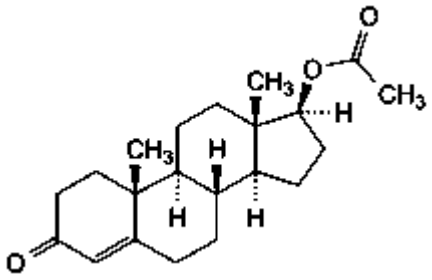
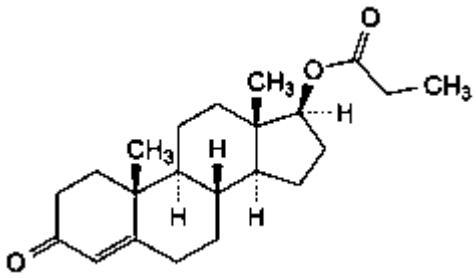


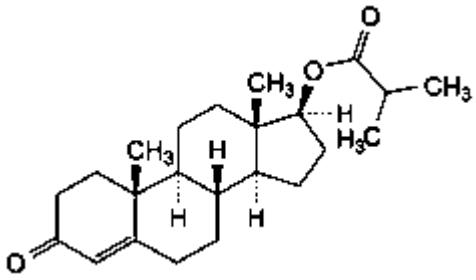
A. testosterone,



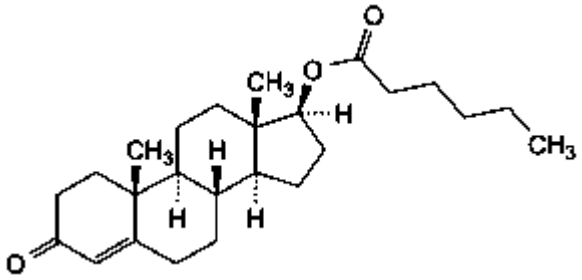
B. 3-oxoandrost-4-en-17β-yl acetate (testosterone acetate),



C. testosterone propionate,



D. 3-oxoandrost-4-en-17β-yl 2-methylpropanoate (testosterone isobutyrate),



E. 3-oxoandrost-4-en-17β-yl hexanoate (testosterone caproate),

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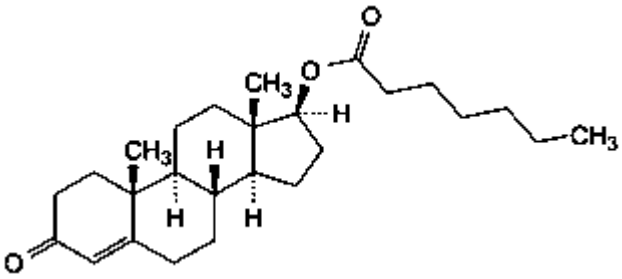
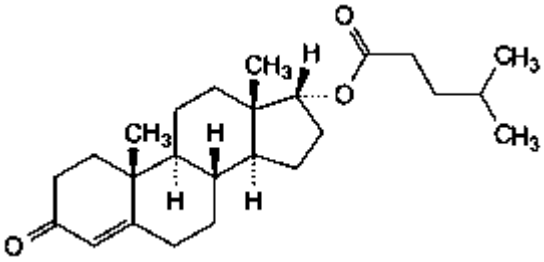


F. testosterone enantate,



G. 3-oxoandrost-4-en-17α-yl 4-methylpentanoate (epitestosterone isocaproate).

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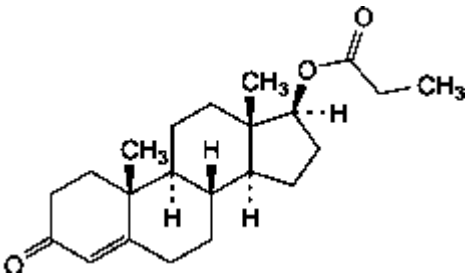
Testosterone Propionate

General Notices

(Ph. Eur. monograph 0297)



$C_{22}H_{32}O_3$ 344.5 *57-85-2*

Action and use

Androgen.

Preparation

Testosterone Propionate Injection

Ph Eur

DEFINITION

3-Oxoandrost-4-en-17β-yl propanoate.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals.

Solubility

Practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent), soluble in fatty oils.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *testosterone propionate CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 84 to + 90 (dried substance).

Dissolve 0.250 g in *ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 2 mg of *testosterone propionate for system suitability CRS* (containing impurities A, B and C) in 5.0 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 20.0 mg of *testosterone propionate CRS* in 50.0 mL of *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water R*, *methanol R* (20:80 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time Twice the retention time of testosterone propionate.

Identification of impurities Use the chromatogram supplied with *testosterone propionate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to testosterone propionate (retention time = about 8 min): impurity C = about 0.4; impurity A = about 0.7; impurity B = about 1.4.

System suitability Reference solution (a):

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— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to testosterone propionate.

Limits:

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

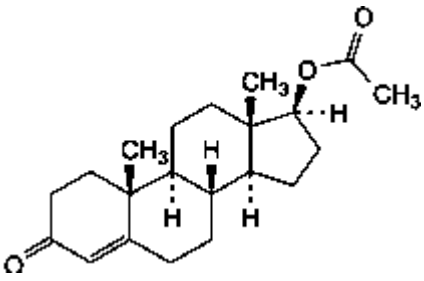
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{22}H_{32}O_3$ taking into account the assigned content of *testosterone propionate CRS*.

IMPURITIES

Specified impurities *A, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E.*



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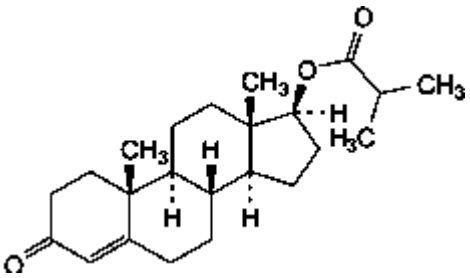
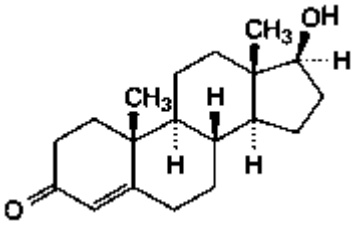
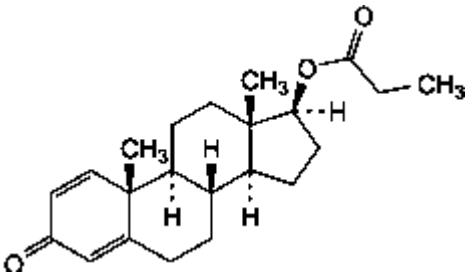
A. 3-oxoandrost-4-en-17β-yl acetate (testosterone acetate),



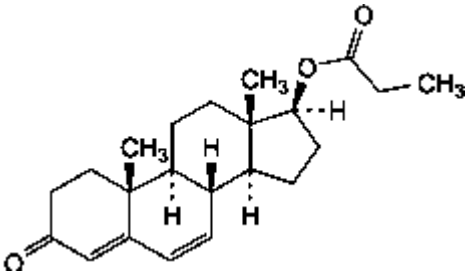
B. 3-oxoandrost-4-en-17β-yl 2-methylpropanoate (testosterone isobutyrate),



C. 17β-hydroxyandrost-4-en-3-one (testosterone),



D. 3-oxoandrosta-1,4-dien-17β-yl propanoate,



E. 3-oxoandrosta-4,6-dien-17β-yl propanoate.

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Testosterone Propionate Injection

General Notices

Action and use

Androgen.

DEFINITION

Testosterone Propionate Injection is a sterile solution of Testosterone Propionate in Ethyl Oleate or other suitable ester, in a suitable fixed oil or in any mixture of these.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of testosterone propionate, $C_{22}H_{32}O_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Dissolve a volume containing 50 mg of Testosterone Propionate in 8 mL of *petroleum spirit* (*boiling range, 40° to 60°*) and extract with three 8-mL quantities of a mixture of 7 volumes of *glacial acetic acid* and 3 volumes of *water*. Wash the combined extracts with 10 mL of *petroleum spirit* (*boiling range, 40° to 60°*), dilute with *water* until the solution becomes turbid, allow to stand for 2 hours in ice and filter. The precipitate, after washing with *water* and drying at 105°, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of testosterone propionate (*RS 332*).

B. Complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent III* and *mobile phase F*.

ASSAY

To a volume containing 0.1 g of Testosterone Propionate add sufficient *chloroform* to produce 100 mL. Dilute 3 mL to 50 mL with *chloroform* and to 5 mL of the solution add 10 mL of *isoniazid solution* and sufficient *methanol* to produce 20 mL. Allow to stand for 45 minutes and measure the *absorbance* of the resulting solution at the maximum at 380 nm, Appendix II B, using in the reference cell a solution prepared by treating 5 mL of *chloroform* in the same manner. Calculate the content of $C_{22}H_{32}O_3$ from the *absorbance* obtained by repeating the operation using a 0.006% w/v solution of *testosterone propionate BPCRS* in *chloroform*, beginning at the words ‘to 5 mL...’ and using the declared content of $C_{22}H_{32}O_3$ in *testosterone propionate BPCRS*.

STORAGE

Testosterone Propionate Injection should be protected from light.

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LABELLING

The label states that the preparation is intended for intramuscular injection only.

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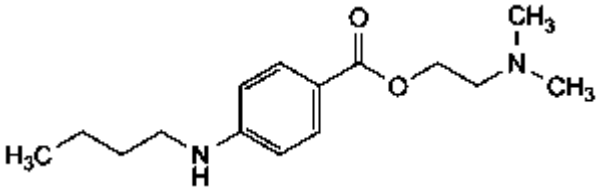
Tetracaine

General Notices

(Ph. Eur. monograph 2909)



$C_{15}H_{24}N_2O_2$ 264.4 *94-24-6*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

2-(Dimethylamino)ethyl 4-(butylamino)benzoate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent).

mp

About 44 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *tetracaine CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 2.0 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 10 mg of *4-aminobenzoic acid R* (impurity A), 10 mg of *4-(butylamino)benzoic acid R* (impurity B) and 10 mg of *methyl 4-(butylamino)benzoate R* (impurity C) in *acetonitrile R* and dilute to 50 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.36 g of *potassium dihydrogen phosphate R* in *water for chromatography R*, add 0.5 mL of *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	80	20
3 - 18	80 → 40	20 → 60
18 - 23	40	60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 300 nm.

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Injection 5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to tetracaine (retention time = about 7 min): impurity A = about 0.4; impurity B = about 1.6; impurity C = about 2.2.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to tetracaine and impurity B.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.7; impurity C = 0.7;

— for each impurity, use the concentration of tetracaine in reference solution (a).

Limits:

— *impurities B, C*: for each impurity, maximum 0.15 per cent;

— *impurity A*: maximum 0.05 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent, except for impurity A.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 30 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 25 volumes of *water R* and 75 volumes of *ethanol (96 per cent) R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 26.44 mg of $C_{15}H_{24}N_2O_2$.

STORAGE

In an airtight container, protected from light.

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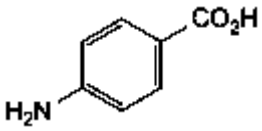
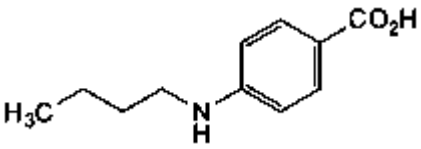
IMPURITIES

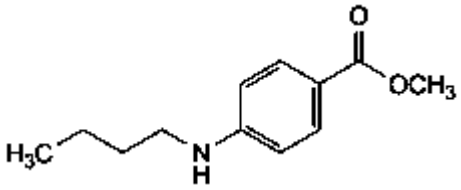
Specified impurities *A, B, C.*



A. 4-aminobenzoic acid,



B. 4-(butylamino)benzoic acid,



C. methyl 4-(butylamino)benzoate.

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Tetracaine Eye Drops

General Notices

Action and use

Local anaesthetic.

DEFINITION

Tetracaine Eye Drops are a sterile solution of Tetracaine Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of tetracaine hydrochloride, $C_{15}H_{24}N_2O_2$,HCl

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute the eye drops with *water*, if necessary, to produce a solution containing 0.01% w/v of Tetracaine Hydrochloride. To 5 mL of this solution, add 15 mL of *buffer (acetate) solution pH 5.0* and add sufficient *water* to produce a solution containing 0.00003% w/v of Tetracaine Hydrochloride. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution, exhibits a maximum only at 310 nm. The absorbance at 310 nm is about 0.35.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.3 to 4.4, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the eye drops, if necessary, with the mobile phase to produce a solution containing 0.5% w/v of Tetracaine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.05% w/v of *4-(butylamino)benzoic acid* (impurity B) in *methanol*. To 1 volume of this solution, add 2 volumes of a solution of 1.0% w/v of *tetracaine hydrochloride BPCRS* in 0.01M *hydrochloric acid* and dilute to 100 volumes with the mobile phase.

(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil GOLD C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 310 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

1 volume of *perchloric acid*, 35 volumes of *stabiliser-free tetrahydrofuran* and 100 volumes of *water*. Adjust this solution to pH 3.0 with *ammonia*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to tetracaine (retention time of about 4.5 minutes) are: impurity A, about 0.5 and impurity B, about 1.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to tetracaine and impurity B is at least 8.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity B using the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%)

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the eye drops, if necessary, with the mobile phase to produce a solution containing 0.01% w/v of Tetracaine Hydrochloride.

(2) 0.01% w/v of *tetracaine hydrochloride BPCRS* in 0.01M *hydrochloric acid*.

(3) 0.01% w/v of *4-(butylamino)benzoic acid* in *methanol*. To 1 volume of this solution, add 2 volumes of solution (2) and dilute to 100 volumes with the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Related substances can be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to tetracaine and impurity B is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{24}N_2O_2$,HCl in the eye drops using the declared content of $C_{15}H_{24}N_2O_2$,HCl in *tetracaine hydrochloride BPCRS*.

STORAGE

Tetracaine Eye Drops should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed under Tetracaine Hydrochloride.

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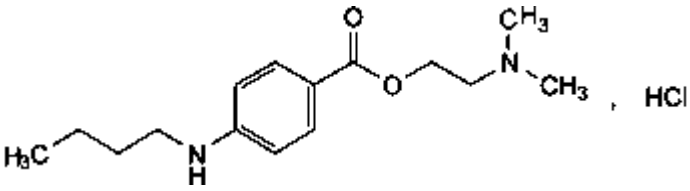
Tetracaine Hydrochloride

General Notices

(Ph. Eur. monograph 0057)



$C_{15}H_{25}ClN_2O_2$ 300.8 *136-47-0*

Action and use

Local anaesthetic.

Preparation

Tetracaine Eye Drops

Ph Eur

DEFINITION

2-(Dimethylamino)ethyl 4-(butylamino)benzoate hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in heptane.

It shows polymorphism (*5.9*).

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134 °C to 150 °C.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24), without recrystallisation.

Comparison *tetracaine hydrochloride CRS*.

B. To 10 mL of solution S (see Tests) add 1 mL of *ammonium thiocyanate solution R*. A white, crystalline precipitate is formed, which, after recrystallisation from *water R* and drying at 80 °C for 2 h, melts (2.2.14) at about 131 °C.

C. To about 5 mg add 0.5 mL of *fuming nitric acid R*. Evaporate to dryness on a water-bath, allow to cool and dissolve the residue in 5 mL of *acetone R*. Add 1 mL of *0.1 M alcoholic potassium hydroxide*. A violet colour develops.

D. Solution S gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dilute 2 mL of solution S to 10 mL with *water R*.

pH (2.2.3)

4.5 to 6.5.

Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R*, *water R* (20:80 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *tetracaine for system suitability CRS* (containing impurities A, B and C) in 2 mL of the solvent mixture.

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Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography, alkyl-bonded for use with highly aqueous mobile phases R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.36 g of *potassium dihydrogen phosphate R* in *water for chromatography R*, add 0.5 mL of *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	80	20
3 - 18	80 → 40	20 → 60
18 - 23	40	60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 300 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *tetracaine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to tetracaine (retention time = about 7 min): impurity A = about 0.3; impurity B = about 1.6; impurity C = about 2.2.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to tetracaine and impurity B.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.7; impurity C = 0.7;

— for each impurity, use the concentration of tetracaine hydrochloride in reference solution (a).

Limits:

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— *impurities B, C*: for each impurity, maximum 0.15 per cent;

— *impurity A*: maximum 0.05 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent, except for impurity A.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of a 1.03 g/L solution of *hydrochloric acid R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

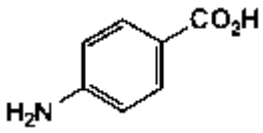
1 mL of *0.1 M sodium hydroxide* is equivalent to 30.08 mg of $C_{15}H_{25}ClN_2O_2$.

STORAGE

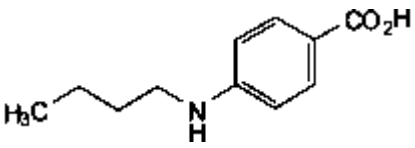
In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. 4-aminobenzoic acid,



B. 4-(butylamino)benzoic acid,

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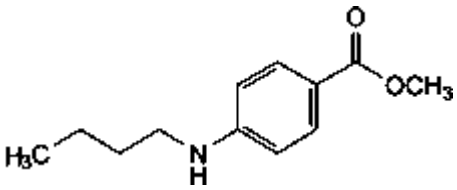

C. methyl 4-(butylamino)benzoate.

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Tetracosactide

General Notices

(Ph. Eur. monograph 0644)

H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-
Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-
Lys-Val-Tyr-Pro-OH

$C_{136}H_{210}N_{40}O_{31}S$ 2933 *16960-16-0*

Action and use

Corticotropic peptide.

Preparations

Tetracosactide Injection

Tetracosactide Zinc Injection

Ph Eur

DEFINITION

Synthetic tetracosapeptide, in which the sequence of amino acids is the same as that of the first 24 residues of human corticotropin. It increases the rate at which corticoid hormones are secreted by the adrenal glands. It is available as an acetate.

Content

90 per cent to 102 per cent (anhydrous and acetic acid-free substance). By convention, 1 µg of tetracosactide is equivalent to 1 IU of tetracosactide.

CHARACTERS

Appearance

White or yellow, amorphous powder.

Solubility

Sparingly soluble in water.

IDENTIFICATION

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A. Examine the chromatograms obtained in the test for related peptides.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

B. Amino acid analysis (2.2.56). For hydrolysis use Method 1 and for analysis use Method 1.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids, taking that of valine to be equivalent to 3. The values fall within the following limits: lysine 3.5 to 4.7; histidine 0.9 to 1.1; arginine 2.7 to 3.3; serine 1.1 to 2.2; glutamic acid 0.9 to 1.1; proline 2.5 to 3.5; glycine 1.8 to 2.2; methionine 0.9 to 1.1; tyrosine 1.7 to 2.2; phenylalanine 0.9 to 1.1. Not more than traces of other amino acids are present.

TESTS

Specific optical rotation (2.2.7)

-99 to -109 (anhydrous and acetic acid-free substance).

Dissolve 10.0 mg in 1.0 mL of a mixture of 1 volume of *glacial acetic acid R* and 99 volumes of *water R*.

Absorbance (2.2.25)

0.51 to 0.61 (anhydrous and acetic acid-free substance), determined at the absorption maximum between 240 nm and 280 nm, at 276 nm. The ratio of the absorbance at the maximum at 276 nm to the absorbance at 248 nm is 2.4 to 2.9.

Dissolve 1.0 mg in *0.1 M hydrochloric acid* and dilute to 5.0 mL with the same acid.

Related peptides

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve an accurately weighed quantity of the substance to be examined in *water R* to obtain the same concentration as in reference solution (a).

Reference solution (a) Dissolve the contents of a vial of *tetracosactide CRS* in *water R* to obtain a concentration of about 1 mg/mL, as indicated in the leaflet provided with the reference standard.

Reference solution (b) In order to prepare impurity A *in situ*, dissolve 1.0 mg of the substance to be examined in 1 mL of a 1 per cent *V/V* solution of *glacial acetic acid R*, add 50 µL of a mixture of 1 volume of *strong hydrogen peroxide solution R* and 999 volumes of *water R*, and allow to stand for 2 h.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 25 °C.

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Mobile phase:

— *mobile phase A*: mix 5.0 mL of *glacial acetic acid R*, 60 mL of *acetonitrile R* and 5.0 g of *ammonium sulfate R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: mix 5.0 mL of *glacial acetic acid R*, 310 mL of *acetonitrile R* and 5.0 g of *ammonium sulfate R* and dilute to 1000 mL with *water R*;

— *mobile phase C*: *acetonitrile R*.

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 50	55 → 40	45 → 60	0
50 - 50.1	40 → 0	60 → 15	0 → 85
50.1 - 55	0	15	85
55 - 55.1	0 → 55	15 → 45	85 → 0
55.1 - 60	55	45	0

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *tetracosactide CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to tetracosactide (retention time = about 26 min): impurity A = about 0.3; impurity B = about 0.95.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to tetracosactide.

Limits:

— *impurity A*: maximum 3 per cent;

— *impurity B*: maximum 4 per cent;

— *unspecified impurities*: for each impurity, maximum 2.5 per cent;

— *sum of impurities other than A*: maximum 9 per cent.

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Acetic acid (*2.5.34*)

8.0 per cent to 13.0 per cent.

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

Water (*2.5.32*)

Maximum 14.0 per cent, determined on 20.0-50.0 mg.

Bacterial endotoxins (*2.6.14*)

Less than 10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related peptides.

Calculate the content of $C_{136}H_{210}N_{40}O_{31}S$ using the declared content of *tetracosactide CRS*.

STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

LABELLING

The label states:

— the mass of peptide in the container;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, B.*

A. tetracosactide sulfoxide,

B. unknown structure.

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Tetracosactide Injection

General Notices

Action and use

Corticotropic peptide.

DEFINITION

Tetracosactide Injection is a sterile solution of Tetracosactide in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of tetracosactide, $C_{136}H_{210}N_{40}O_{31}S$

80.0 to 110.0% of the stated amount of the peptide.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

Mix 24 mL of *pyridine* and 16 mL of *glacial acetic acid* and add sufficient *water* to produce 100 mL (solution A). Carry out the method for *zone electrophoresis*, Appendix III F, using cellulose acetate foil as the support medium and an electrolyte solution containing 8% v/v of *glacial acetic acid* and 2% v/v of *pyridine*. Immerse the cellulose acetate foil in the electrolyte solution for 5 minutes and press dry between sheets of filter paper. Apply separately to the foil at points 1 cm from the anode edge and 2.5 cm apart 2 µL of each of the following solutions. For solution (1) evaporate to dryness a volume of the injection containing 0.5 mg of the peptide and dissolve the residue in 0.1 mL of solution A with the aid of gentle heat. For solution (2) dissolve 3.5 mg of *tetracosactide EPCRS* in 10 mL of *water* containing 10 µL of *glacial acetic acid*, 8.2 mg of *sodium acetate* and 81 mg of *sodium chloride*, evaporate 2 mL of the solution and dissolve the residue in 0.1 mL of solution A with the aid of gentle heat. Apply a voltage of 100 volts and allowing electrophoresis to proceed for 2 hours. Press the strips dry and immerse in a solution prepared by dissolving 1 g of *potassium hexacyanoferrate*(III) in 50 mL of *water* and adding 2 mL of a saturated solution of *iron*(III) *chloride hexahydrate*. Wash with a 5% v/v solution of *orthophosphoric acid* until the background is as pale as possible and finally wash with *water*. Examine the electrophoretograms while still moist. The principal spot in the electrophoretogram obtained with solution (1) corresponds to that in the electrophoretogram obtained with solution (2).

TESTS

Acidity

pH, 3.8 to 4.5, Appendix V L.

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Tetracosactide sulfoxide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared with de-aerated solvents. For solution (1) dilute the injection, if necessary, with *water* to give a final concentration of 0.025% w/v of the peptide. For solution (2) add 10 µL of a solution prepared by diluting 1 volume of *hydrogen peroxide solution* (*20 vol*) to 200 volumes with *water* to 1 mL of solution (1) and allow to stand for 2 hours.

The chromatographic conditions described under Assay may be used. Take care to ensure that the syringe used to inject solution (1) is not contaminated with peroxide.

The chromatogram obtained with solution (2) exhibits a peak due to tetracosactide corresponding to the principal peak in the chromatogram obtained with solution (1) and a peak with a shorter retention time, due to tetracosactide sulfoxide, of significantly greater area than any corresponding peak in the chromatogram obtained with solution (1). In the chromatogram obtained with solution (1) the relative amount of tetracosactide sulfoxide is not more than 10% by *normalisation*.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute the injection, if necessary, with *water* to give a final concentration of 0.025% w/v of the peptide. For solution (2) dissolve an amount of *tetracosactide EPCRS* in sufficient *water* to produce a solution containing 0.025% w/v of the peptide.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable), (b) a mixture of 10 mL of *glacial acetic acid*, 365 mL of *acetonitrile* and 10 g of *ammonium sulfate* diluted to 2000 mL with *water* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 280 nm.

Calculate the content of the peptide $C_{136}H_{210}N_{140}O_{31}S$ from the chromatograms obtained and using the declared content of $C_{136}H_{210}N_{140}O_{31}S$ in *tetracosactide EPCRS*.

The result obtained is not valid unless the *resolution factor* between the peaks due to tetracosactide and tetracosactide sulfoxide in the chromatogram obtained with solution (1) in the test for Tetracosactide sulfoxide is at least 7.

STORAGE

Tetracosactide Injection should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The strength is stated in terms of the equivalent amount of the peptide in micrograms per mL.

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Tetracosactide Zinc Injection

General Notices

Action and use

Corticotropic peptide.

DEFINITION

Tetracosactide Zinc Injection is a sterile aqueous suspension of Tetracosactide with zinc hydroxide.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of tetracosactide, $C_{136}H_{210}N_{40}O_{31}S$

80.0 to 110.0% of the stated amount of the peptide.

CHARACTERISTICS

A white, flocculent suspension which settles slowly and is readily resuspended. On examination under a microscope the majority of the particles are seen as amorphous or microcrystalline particles or aggregates thereof. The maximum dimension of single particles rarely exceeds 50 µm. Under high power magnification a considerable proportion of the particles can be seen to have no uniform shape.

IDENTIFICATION

A. Carry out the test for Identification described under Tetracosactide Injection using the following solutions. For solution (1) freeze dry a quantity of the well-shaken suspension containing 2 mg of the peptide and dissolve the residue in a mixture of 0.1 mL of *formic acid* and 0.1 mL of *water* with the aid of gentle heat. For solution (2) dissolve 10.45 g of *zinc chloride* in 20 mL of *water*, add 95 mL of *formic acid* followed by 4.2 g of *disodium hydrogen orthophosphate* and 4.0 g of *sodium chloride*. Dissolve 6.04 g of *sodium hydroxide* in 40 mL of *water*. Mix the two solutions carefully with cooling and add sufficient *water* to produce 200 mL. Dissolve 2.8 mg of *tetracosactide EPCRS* in 0.2 mL of the resulting solution. The principal spot in the electrophoretogram obtained with solution (1) corresponds to that in the electrophoretogram obtained with solution (2).

B. Evaporate 1 mL of the well-shaken suspension to dryness in a crucible and heat strongly until combustion of the organic material is complete. The residue is yellow while hot and becomes white on cooling.

TESTS

Alkalinity

pH, 7.8 to 9.2, Appendix V L.

Light absorption

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Centrifuge 7 mL of the well-shaken suspension for 10 minutes at about 2000 *g*. Shake the clear, supernatant liquid with five 5-mL quantities of *chloroform*, previously washed with *water*. Discard the chloroform and centrifuge the aqueous phase for 5 minutes at about 2000 g. The *absorbance* of the clear, supernatant liquid at 276 nm, Appendix II B, is not more than 0.38 for preparations containing 1 mg of the peptide per mL and not more than 0.19 for preparations containing 0.5 mg of the peptide per mL.

Sediment volume

Transfer 3.0 mL of the well-shaken suspension to a cuvette 10 mm × 10 mm in cross section. Allow to stand for 5 hours. The depth of the sediment is between 8 and 25 mm and the supernatant liquid is clear.

Zinc

To a volume of the well-shaken suspension containing 1 mg of the peptide add 5 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 1000 mL. Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, measuring at 214 nm and using *zinc standard solution* (*5 mg/mL Zn*), diluted if necessary with *water*, to prepare the standard solution. Preparations containing 1 mg of the peptide per mL contain 2.25 to 2.75 mg of zinc per mL; preparations containing 0.5 mg of the peptide per mL contain 1.35 to 1.65 mg of zinc per mL.

Tetracosactide sulfoxide

Carry out the test described under Tetracosactide Injection using the following solutions. For solution (1) mix a volume of the well-shaken suspension containing 1 mg of the peptide with 15 µL of *glacial acetic acid*. For solution (2) add 50 µL of a solution prepared by diluting 1 volume of *hydrogen peroxide solution* (*20 vol*) to 200 volumes to 1 mL of a 0.1% w/v solution of *tetracosactide EPCRS* in a 1% v/v solution of *glacial acetic acid* and allow to stand for 2 hours. The chromatogram obtained with solution (2) exhibits a peak due to tetracosactide and a significant peak with a shorter retention time, due to tetracosactide sulfoxide. In the chromatogram obtained with solution (1) the area of the peak due to tetracosactide sulfoxide is not more than 18% of the area of the peak due to tetracosactide. The peaks due to associated substances may be identified from the chromatogram obtained with solution (2) in the Assay.

ASSAY

Carry out the Assay described under Tetracosactide Injection using the following solutions. For solution (1) mix 1 mL of the well-shaken suspension with 15 µL of *glacial acetic acid*. For preparations containing 1 mg of the peptide per mL prepare solution (2) by dissolving quantities of *tetracosactide EPCRS* and *benzyl alcohol* in sufficient *water* to produce a solution containing the equivalent of 0.10% w/v of the peptide and 1.0% w/v of *benzyl alcohol* and adding 15 µL of *glacial acetic acid* per mL. For preparations containing 0.5 mg of the peptide per mL prepare solution (2) by dissolving quantities of *tetracosactide EPCRS* and *benzyl alcohol* in sufficient *water* to produce a solution containing the equivalent of 0.05% w/v of the peptide and 1.0% w/v of *benzyl alcohol* and adding 15 µL of *glacial acetic acid* per mL. If necessary, adjust the ratio of the volumes of *acetonitrile* and *water* in the mobile phase so that in the chromatogram obtained with solution (2) the *resolution factor* between the peaks due to benzyl alcohol (eluted before tetracosactide) and tetracosactide is between 1.5 and 2.0.

STORAGE

Tetracosactide Zinc Injection should be protected from light and stored at a temperature of 2° to 8°. It should not be allowed to freeze.

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LABELLING

The strength is stated in terms of the equivalent amount of the peptide in mg per mL.

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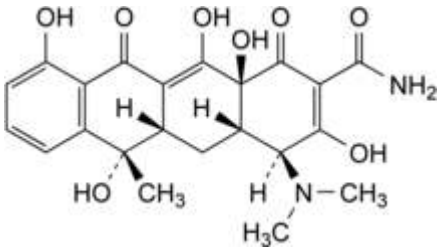
Tetracycline

General Notices

(Ph. Eur. monograph 0211)



$C_{22}H_{24}N_2O_8$ 444.4 *60-54-8*

Action and use

Tetracycline antibacterial.

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DEFINITION

(4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-(Dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.

Substance produced by certain strains of *Streptomyces aerofaciens* or obtained by any other means.

Content

88.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Very slightly soluble in water, soluble in ethanol (96 per cent) and in methanol, sparingly soluble in acetone. It dissolves in dilute acid and alkaline solutions.

IDENTIFICATION

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A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *tetracycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *tetracycline hydrochloride CRS*, 5 mg of *demeclocycline hydrochloride R* and 5 mg of *oxytetracycline hydrochloride R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

B. To about 2 mg add 5 mL of *sulfuric acid R*. A violet-red colour develops. Add the solution to 2.5 mL of *water R*. The colour becomes yellow.

C. Dissolve about 10 mg in a mixture of 1 mL of *dilute nitric acid R* and 5 mL of *water R*. Shake and add 1 mL of *silver nitrate solution R2*. Any opalescence in the solution is not more intense than that in a mixture of 1 mL of *dilute nitric acid R*, 5 mL of *water R* and 1 mL of *silver nitrate solution R2*.

TESTS

pH (2.2.3)

3.5 to 6.0.

Suspend 0.1 g in 10 mL of *carbon dioxide-free water R*.

Specific optical rotation (2.2.7)

-260 to -280 (dried substance).

Dissolve 0.250 g in *0.1 M hydrochloric acid* and dilute to 50.0 mL with the same acid.

Related substances

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Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 25.0 mg of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Reference solution (a) Dissolve 25.0 mg of *tetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Reference solution (b) Dissolve 12.5 mg of *4-epitetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 50.0 mL with the same acid.

Reference solution (c) Dissolve 10.0 mg of *anhydrotetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 100.0 mL with the same acid.

Reference solution (d) Dissolve 10.0 mg of *4-epianhydrotetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 50.0 mL with the same acid.

Reference solution (e) Mix 1.0 mL of reference solution (a), 2.0 mL of reference solution (b) and 5.0 mL of reference solution (d) and dilute to 25.0 mL with *0.01 M hydrochloric acid*.

Reference solution (f) Mix 40.0 mL of reference solution (b), 20.0 mL of reference solution (c) and 5.0 mL of reference solution (d) and dilute to 200.0 mL with *0.01 M hydrochloric acid*.

Reference solution (g) Dilute 1.0 mL of reference solution (c) to 50.0 mL with *0.01 M hydrochloric acid*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm);

— *temperature*: 60 °C.

Mobile phase Weigh 80.0 g of *2-methyl-2-propanol R* and transfer to a 1000 mL volumetric flask with the aid of 200 mL of *water R*; add 100 mL of a 35 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 9.0 with *dilute phosphoric acid R*, 200 mL of a 10 g/L solution of *tetrabutylammonium hydrogen sulfate R* adjusted to pH 9.0 with *dilute sodium hydroxide solution R* and 10 mL of a 40 g/L solution of *sodium edetate R* adjusted to pH 9.0 with *dilute sodium hydroxide solution R*; dilute to 1000.0 mL with *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL; inject the test solution and reference solutions (e), (f) and (g).

System suitability:

— *resolution*: minimum 2.5 between the peaks due to impurity A (1st peak) and tetracycline (2nd peak) and minimum 8.0 between the peaks due to tetracycline and impurity D (3rd peak) in the chromatogram obtained with reference solution (e); if necessary, adjust the

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concentration of 2-methyl-2-propanol in the mobile phase;

— *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (g);

— *symmetry factor*: maximum 1.25 for the peak due to tetracycline in the chromatogram obtained with reference solution (e).

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (5.0 per cent);

— *impurity B* (eluting on the tail of the principal peak): not more than 0.4 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (2.0 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (1.0 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.5 per cent).

Loss on drying (*2.2.32*)

Maximum 13.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

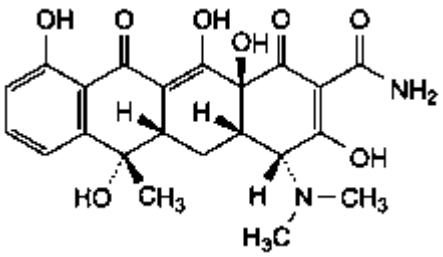
Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{22}H_{24}N_2O_8$.

STORAGE

Protected from light.

IMPURITIES



A. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epitetracycline),

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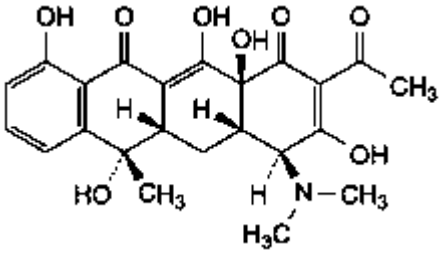
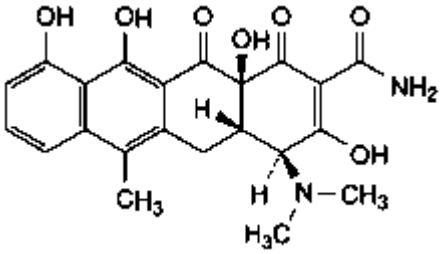
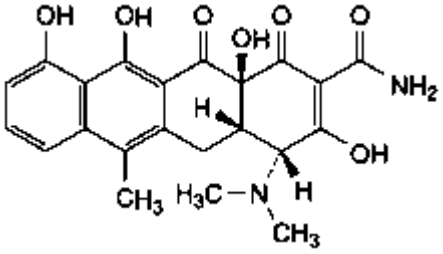


B. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-2-acetyl-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarbamoyltetracycline),



C. (4*S*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-6-methyl-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (anhydrotetracycline),



D. (4*R*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-6-methyl-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (4-epianhydrotetracycline).

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Tetracycline Capsules

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Tetracycline Capsules contain Tetracycline Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of tetracycline hydrochloride, $C_{22}H_{24}N_2O_8$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel H* as the coating substance. Adjust the pH of a 10% w/v solution of *disodium edetate* to 8.0 with 10M *sodium hydroxide* and spray the solution evenly onto the plate (about 10 mL for a plate 100 mm × 200 mm). Allow the plate to dry in a horizontal position at room temperature for at least 1 hour. Before use, dry the plate in an oven at 110° for 1 hour. Use a mixture of 6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane* as the mobile phase. Apply separately to the plate 1 µL of each of the following solutions. For solution (1) extract a quantity of the contents of the capsules containing 10 mg of Tetracycline Hydrochloride with 20 mL of *methanol* and centrifuge. Solution (2) contains 0.05% w/v of *tetracycline hydrochloride BPCRS* in *methanol*. Solution (3) contains 0.05% w/v of each of *tetracycline hydrochloride BPCRS*, *chlortetracycline hydrochloride BPCRS* and *doxycycline hyclate BPCRS* in *methanol*. Dry the plate in a current of air and examine under *ultraviolet light* (*365 nm*). The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to the principal spot in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

B. To a quantity of the contents of the capsules containing 10 mg of Tetracycline Hydrochloride add 20 mL of warm *ethanol* (*96%*), allow to stand for 20 minutes, filter and evaporate the filtrate to dryness on a water bath. To 0.5 mg of the residue add 2 mL of *sulfuric acid*; a deep crimson colour is produced. Add 1 mL of *water*; the colour changes to deep yellow.

C. The residue obtained in test B yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *0.1M hydrochloric acid* and rotating the basket at 100 revolutions per minute. Withdraw a sample of

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10 mL of the medium. Measure the *absorbance* of the filtered sample, suitably diluted if necessary, at the maximum at 353 nm, Appendix II B. Calculate the total content of tetracycline hydrochloride, $C_{22}H_{24}N_2O_8$,HCl, in the medium taking 310 as the value of A(1%, 1 cm) at the maximum at 353 nm.

4-Epitetracycline hydrochloride

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the mixed contents of 20 capsules containing 25 mg of Tetracycline Hydrochloride in 80 mL of 0.01M *methanolic hydrochloric acid* for 10 minutes, dilute to 100 mL with the same solvent, mix and filter if necessary. Solution (2) contains 0.0020% w/v of *4-epitetracycline hydrochloride EPCRS* in 0.01M *methanolic hydrochloric acid*. Solution (3) contains 0.0015% w/v each of *4-epitetracycline hydrochloride EPCRS* and *tetracycline hydrochloride BPCRS* in 0.01M *methanolic hydrochloric acid*.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable) and maintained at 40°, (b) as the mobile phase with a flow rate of 2 mL per minute a mixture of 5 volumes of *dimethylformamide* and 95 volumes of 0.1M *oxalic acid* the pH of which has been adjusted to 3.9 with *triethylamine* and (c) a detection wavelength of 280 nm.

The test is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (3) is at least 2.0.

In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-epitetracycline is not greater than the area of the principal peak in the chromatogram obtained with solution (2).

Anhydrotetracycline hydrochloride and 4-epi-anhydrotetracycline hydrochloride

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the mixed contents of 20 capsules containing 25 mg of Tetracycline Hydrochloride in 20 mL of 0.01M *methanolic hydrochloric acid* for 10 minutes, dilute to 25 mL with the same solvent, mix and filter if necessary. Solution (2) contains 0.0010% w/v each of *anhydrotetracycline hydrochloride EPCRS* and *4-epianhydrotetracycline hydrochloride EPCRS* in 0.01M *methanolic hydrochloric acid*. Solution (3) contains 0.0010% w/v each of *4-epianhydrotetracycline hydrochloride EPCRS* and *tetracycline hydrochloride BPCRS*.

The chromatographic conditions described under Epitetracycline hydrochloride may be used but use as the mobile phase a mixture of 10 volumes of *dimethylformamide*, 12 volumes of *acetonitrile* and 78 volumes of 0.1M *oxalic acid* the pH of which has been adjusted to 3.9 with *triethylamine*. The order of emergence of the peaks is tetracycline, 4-epianhydrotetracycline and anhydrotetracycline.

The test is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (3) is at least 6.0.

In the chromatogram obtained with solution (1) the area of any peaks corresponding to anhydrotetracycline hydrochloride and 4-epianhydrotetracycline hydrochloride is not greater than the area of the respective principal peak in the chromatogram obtained with solution (2).

Loss on drying

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When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, the contents of the capsules lose not more than 3.0% of their weight.

Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the mixed contents of 20 capsules containing 25 mg of Tetracycline Hydrochloride in 80 mL of 0.01M *methanolic hydrochloric acid* for 10 minutes, dilute to 100 mL with the same solvent, mix and filter if necessary. Solution (2) contains 0.025% w/v of *tetracycline hydrochloride BPCRS* in 0.01M *methanolic hydrochloric acid*. Solution (3) contains 0.025% w/v each of *4-epitetracycline hydrochloride EPCRS* and *tetracycline hydrochloride BPCRS* in 0.01M *methanolic hydrochloric acid*.

The chromatographic conditions described under 4-Epitetracycline hydrochloride may be used.

The assay is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (3) is at least 2.0.

Calculate the content of $C_{22}H_{24}N_2O_8$,HCl in the capsules using the declared content of $C_{22}H_{24}N_2O_8$,HCl in *tetracycline hydrochloride BPCRS*.

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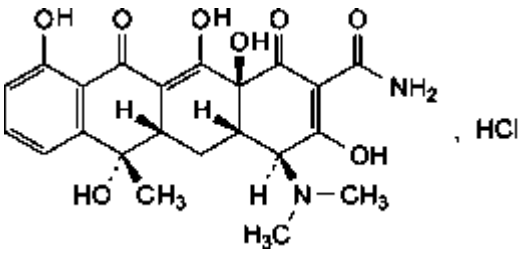
Tetracycline Hydrochloride

General Notices

(Ph. Eur. monograph 0210)



$C_{22}H_{25}ClN_2O_8$ 480.9 *64-75-5*

Action and use

Tetracycline antibacterial.

Preparations

Tetracycline Capsules

Tetracycline Tablets

Ph Eur

DEFINITION

(4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-(Dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride.

Substance produced by certain strains of *Streptomyces aerofaciens* or obtained by any other means.

Content

95.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

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Soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. Solutions in water become turbid on standing, owing to the precipitation of tetracycline.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *tetracycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *tetracycline hydrochloride CRS*, 5 mg of *demeclocycline hydrochloride R* and 5 mg of *oxytetracycline hydrochloride R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

B. To about 2 mg add 5 mL of *sulfuric acid R*. A violet-red colour develops. Add the solution to 2.5 mL of *water R*. The colour becomes yellow.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

1.8 to 2.8.

Dissolve 0.1 g in 10 mL of *carbon dioxide-free water R*.

Specific optical rotation (2.2.7)

-240 to -255 (dried substance).

Dissolve 0.250 g in *0.1 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

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Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 25.0 mg of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Reference solution (a) Dissolve 25.0 mg of *tetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 25.0 mL with the same acid.

Reference solution (b) Dissolve 15.0 mg of *4-epitetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 50.0 mL with the same acid.

Reference solution (c) Dissolve 10.0 mg of *anhydrotetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 100.0 mL with the same acid.

Reference solution (d) Dissolve 10.0 mg of *4-epianhydrotetracycline hydrochloride CRS* in *0.01 M hydrochloric acid* and dilute to 50.0 mL with the same acid.

Reference solution (e) Mix 1.0 mL of reference solution (a), 2.0 mL of reference solution (b) and 5.0 mL of reference solution (d) and dilute to 25.0 mL with *0.01 M hydrochloric acid*.

Reference solution (f) Mix 20.0 mL of reference solution (b), 10.0 mL of reference solution (c) and 5.0 mL of reference solution (d) and dilute to 200.0 mL using *0.01 M hydrochloric acid*.

Reference solution (g) Dilute 1.0 mL of reference solution (c) to 50.0 mL with *0.01 M hydrochloric acid*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm);

— *temperature*: 60 °C.

Mobile phase Weigh 80.0 g of *2-methyl-2-propanol R* and transfer to a 1000 mL volumetric flask with the aid of 200 mL of *water R*; add 100 mL of a 35 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 9.0 with *dilute phosphoric acid R*, 200 mL of a 10 g/L solution of *tetrabutylammonium hydrogen sulfate R* adjusted to pH 9.0 with *dilute sodium hydroxide solution R* and 10 mL of a 40 g/L solution of *sodium edetate R* adjusted to pH 9.0 with *dilute sodium hydroxide solution R*; dilute to 1000.0 mL with *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL; inject the test solution and reference solutions (e), (f) and (g).

System suitability:

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— *resolution*: minimum 2.5 between the peaks due to impurity A (1st peak) and tetracycline (2nd peak) and minimum 8.0 between the peaks due to tetracycline and impurity D (3rd peak) in the chromatogram obtained with reference solution (e); if necessary, adjust the concentration of 2-methyl-2-propanol in the mobile phase;

— *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (g);

— *symmetry factor*: maximum 1.25 for the peak due to tetracycline in the chromatogram obtained with reference solution (e).

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (3.0 per cent);

— *impurity B* (eluting on the tail of the principal peak): not more than 0.5 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (1.5 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.5 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.5 per cent).

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{22}H_{25}ClN_2O_8$.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, tamper-evident container.

IMPURITIES

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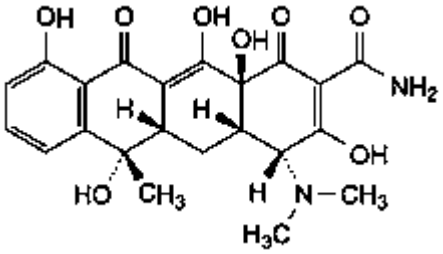
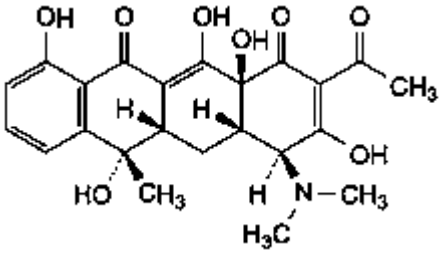
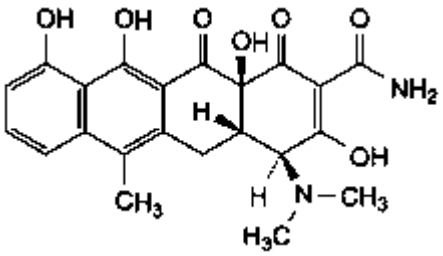


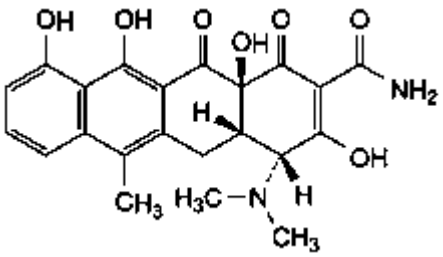
A. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epitetracycline),



B. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-2-acetyl-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarbamoyltetracycline),



C. (4*S*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-6-methyl-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (anhydrotetracycline),



D. (4*R*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-6-methyl-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (4-epianhydrotetracycline).

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Tetracycline Tablets

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Tetracycline Tablets contain Tetracycline Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tetracycline hydrochloride, $C_{22}H_{24}N_2O_8$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Comply with test A described under Tetracycline Capsules using the following solution as solution (1). Extract a quantity of the powdered tablets containing 10 mg of Tetracycline Hydrochloride with 20 mL of *methanol*, centrifuge and use the supernatant liquid.

B. Extract a quantity of the powdered tablets containing 25 mg of Tetracycline Hydrochloride with 25 mL of *methanol* for 20 minutes, filter and evaporate the filtrate to dryness on a water bath. To 0.5 mg of the residue add 2 mL of *sulfuric acid*; a purplish red colour is produced. Add 1 mL of *water*; the colour changes to deep yellow.

C. The residue obtained in test B yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *0.1M hydrochloric acid* and rotating the basket at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium. Measure the *absorbance* of the filtered sample, suitably diluted if necessary, at the maximum at 353 nm, Appendix II B. Calculate the total content of tetracycline hydrochloride, $C_{22}H_{24}N_2O_8$,HCl, in the medium taking 310 as the value of A(1%, 1 cm) at the maximum at 353 nm.

4-Epitetracycline hydrochloride

Complies with test described under Tetracycline Capsules. For solution (1) shake a quantity of the powdered tablets containing 25 mg of Tetracycline Hydrochloride with 80 mL of 0.01M *methanolic hydrochloric acid*, dilute to 100 mL with the same solvent, mix and filter if necessary.

Anhydrotetracycline hydrochloride and 4-epianhydrotetracycline hydrochloride

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Anhydrotetracycline hydrochloride and 4-epianhydro-tetracycline hydrochloride

Complies with the test described under Tetracycline Capsules. For solution (1) shake a quantity of the powdered tablets containing 25 mg of Tetracycline Hydrochloride with 20 mL of 0.01M *methanolic hydrochloric acid*, dilute to 25 mL with the same solvent, mix and filter if necessary.

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, the powdered tablets lose not more than 3.0% of their weight. Use 1 g.

ASSAY

Weigh and powder 20 tablets and carry out the Assay described under Tetracycline Capsules. For solution (1) shake a quantity of the powdered tablets containing 25 mg of Tetracycline Hydrochloride with 80 mL of 0.01M *methanolic hydrochloric acid*, dilute to 100 mL with the same solvent, mix and filter if necessary.

Calculate the content of $C_{22}H_{24}N_2O_8$,HCl in the tablets using the declared content of $C_{22}H_{24}N_2O_8$,HCl in *tetracycline hydrochloride BPCRS*.

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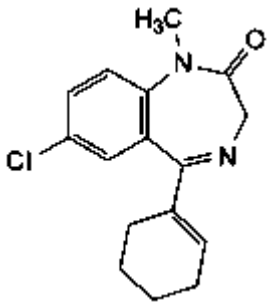
Tetrazepam

General Notices

(Ph. Eur. monograph 1738)



$C_{16}H_{17}ClN_2O$ 288.8 *10379-14-3*

Action and use

Benzodiazepine; hypnotic.

Ph Eur

DEFINITION

7-Chloro-5-(cyclohex-1-enyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Light yellow or yellow crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in acetonitrile.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

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Comparison *Ph. Eur. reference spectrum of tetrazepam*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of the substance to be examined and 5.0 mg of *tetrazepam impurity C CRS* in *acetonitrile R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 40 volumes of *acetonitrile R* and 60 volumes of a 3.4 g/L solution of *potassium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	100	0
35 - 40	100 → 55	0 → 45
40 - 50	55	45

Flow rate 1.5 mL/min.

Detection A spectrophotometer at 229 nm.

Injection 20 µL.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to tetrazepam and to impurity C.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

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— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dissolve 0.750 g in 10 mL of *methylene chloride R* and add 15 mL of *water R*. Shake and separate the 2 layers. Dilute 10 mL of the aqueous layer to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

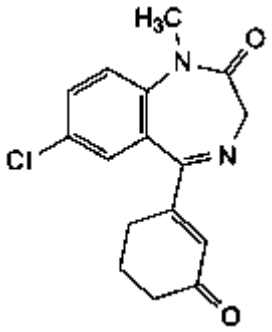
Dissolve 0.230 g in 50.0 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 28.88 mg of $C_{16}H_{17}ClN_2O$.

STORAGE

Protected from light.

IMPURITIES



A. 7-chloro-1-methyl-5-(3-oxocyclohex-1-enyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,

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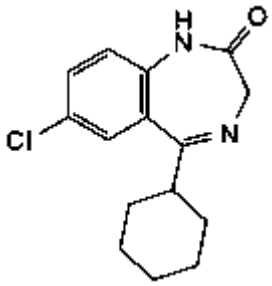
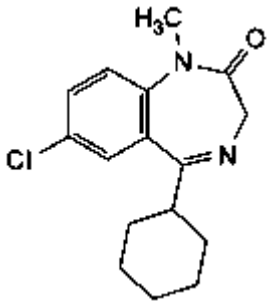
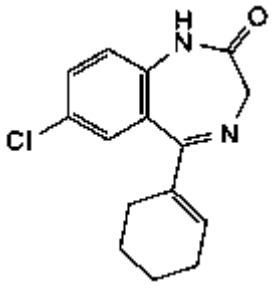


B. 7-chloro-5-cyclohexyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,



C. 7-chloro-5-cyclohexyl-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,

D. 7-chloro-5-(1-chlorocyclohexyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,



E. 7-chloro-5-(cyclohex-1-enyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Ph Eur

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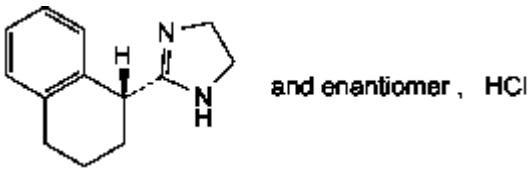
Tetryzoline Hydrochloride

General Notices

(Ph. Eur. monograph 2101)



$C_{13}H_{17}ClN_2$ 236.7 *522-48-5*

Action and use

Adrenoceptor agonist; decongestant.

Ph Eur

DEFINITION

2-[(1*RS*)-1,2,3,4-Tetrahydronaphthalen-1-yl]-4,5-dihydro-1*H*-imidazole hydrochloride.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, in anhydrous ethanol and in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tetryzoline hydrochloride CRS*.

B. Dissolve 50 mg in 10 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

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TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 1.0 g in water R and dilute to 10 mL with the same solvent.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 1.0 g of the substance to be examined in a mixture of 25 volumes of 1 M sodium hydroxide and 75 volumes of methanol R and dilute to 10 mL with the same mixture of solvents.

Reference solution Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of 25 volumes of 1 M sodium hydroxide and 75 volumes of methanol R. Dilute 1.0 mL of this solution to 10.0 mL with a mixture of 25 volumes of 1 M sodium hydroxide and 75 volumes of methanol R.

Column:

— *material*: fused silica,

— *size*: *l* = 25 m, Ø = 0.32 mm,

— *stationary phase*: methylpolysiloxane R (1 µm).

Carrier gas helium for chromatography R.

Split ratio 1:40.

Flow rate 2.5 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 8	160
	8 - 11	160 → 220
	11 - 15	220
Injection port		220
Detector		220

Detection Flame ionisation.

Injection 1 µL.

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Relative retention With reference to tetryzoline (retention time = about 12 min): impurity A = about 0.5.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 50 for the principal peak.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

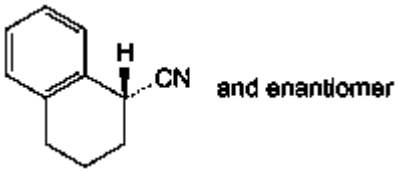
ASSAY

Dissolve 0.200 g in 100 mL of a mixture of 3 volumes of *anhydrous acetic acid R* and 7 volumes of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 23.67 mg of $C_{13}H_{17}ClN_2$.

IMPURITIES

Specified impurities *A.*



A. (1*RS*)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (α-cyanotetraline).

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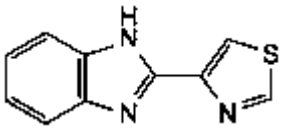
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Tiabendazole

General Notices

(Ph. Eur. monograph 0866)



$C_{10}H_7N_3S$ 201.2 *148-79-8*

Action and use

Benzimidazole antihelminthic.

Ph Eur

DEFINITION

Tiabendazole contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 2-(thiazol-4-yl)-1*H*-benzimidazole, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute mineral acids. It melts at about 300 °C.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Dissolve 25 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 2.0 mL of the solution to 100.0 mL with *0.1 M hydrochloric acid*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows two absorption maxima, at 243 nm and 302 nm. The ratio of the absorbance measured at the maximum at 302 nm to that measured at the maximum at 243 nm is 1.8 to 2.1.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *tiabendazole CRS*. Examine the substances prepared as discs.

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C. Examine the chromatograms obtained in the test for related substances in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 5 mg in *0.1 M hydrochloric acid* and dilute to 5 mL with the same acid. Add 3 mg of *p-phenylenediamine dihydrochloride R* and shake until dissolved. Add 0.1 g of *zinc powder R*, mix, allow to stand for 2 min and add 5 mL of *ferric ammonium sulfate solution R2*. A bluish-violet colour develops.

TESTS

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel HF_{254} R* as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 2 mL of test solution (a) to 20 mL with *methanol R*.

Reference solution (a) Dissolve 20 mg of *tiabendazole CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (b) Dilute 1 mL of test solution (b) to 10 mL with *methanol R*.

Reference solution (c) Dilute 1 mL of test solution (b) to 25 mL with *methanol R*.

Apply separately to the plate 20 µL of each solution. Develop over a path of 15 cm using a mixture of 2.5 volumes of *water R*, 10 volumes of *acetone R*, 25 volumes of *glacial acetic acid R* and 62.5 volumes of *toluene R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (1.0 per cent) and at most one such spot is more intense than the spot in the chromatogram obtained with reference solution (c) (0.4 per cent).

o-Phenylenediamine

To 5.0 g in a flask fitted with a ground-glass stopper, add 25 mL of a mixture of 1 volume of *methanol R* and 2 volumes of *water R*. Shake for 3 min. Filter through a sintered-glass filter (16) (*2.1.2*) under reduced pressure. To 10 mL of the filtrate add 0.5 mL of *hydrochloric acid R* and 0.5 mL of *acetylacetone R* and shake until the solution is clear. The solution is not more intensely coloured than reference solution R_7 (*2.2.2, Method I*) (10 ppm).

Water (*2.5.12*)

Not more than 0.5 per cent, determined on 1.00 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.2 per cent, determined on 1.0 g.

ASSAY

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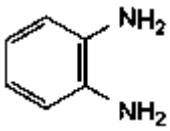
Dissolve 0.150 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 20.12 mg of $C_{10}H_7N_3S$.

STORAGE

Store protected from light.

IMPURITIES



A. benzene-1,2-diamine.

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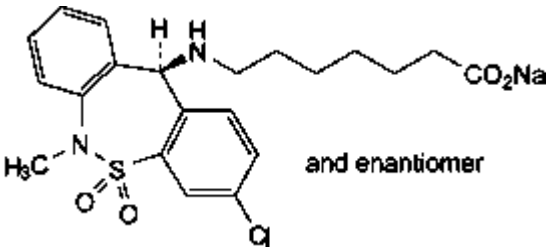
Tianeptine Sodium

General Notices

(Ph. Eur. monograph 2022)



$C_{21}H_{24}ClN_2NaO_4S$ 458.9 *30123-17-2*

Action and use

Antidepressant.

Ph Eur

DEFINITION

Sodium 7-[[(11*RS*)-3-chloro-6-methyl-6,11-dihydrodibenzo[*c*,*f*][1,2]thiazepin-11-yl]amino]heptanoate *S*,*S*-dioxide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish powder, very hygroscopic.

Solubility

Freely soluble in water, in methanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of tianeptine sodium*.

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B. It gives reaction (a) of sodium (2.3.1).

TESTS

Impurity A

Gas chromatography (2.2.28).

Internal standard solution Dilute 1 mL of *ethyl 5-bromovalerate R* in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 250.0 mL with *anhydrous ethanol R*.

Test solution Dissolve 0.1000 g of the substance to be examined in the internal standard solution and dilute to 2.0 mL with the same solution.

Reference solution Dissolve 10.0 mg of *tianeptine impurity A CRS* in the internal standard solution and dilute to 200.0 mL with the same solution.

Column:

— *material*: fused silica,

— *size*: *l* = 25 m, Ø = 0.25 mm,

— *stationary phase*: *cyanopropylpolysiloxane R* (film thickness 0.2 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 26 cm/s.

Split ratio 1:100.

Temperature:

— *column*: 150 °C,

— *injection port and detector*: 210 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time Twice the retention time of ethyl 5-bromovalerate.

System suitability Reference solution:

— *elution order*: ethanol, ethyl 5-bromovalerate, impurity A,

— *resolution*: minimum 10 between the peaks due to ethyl 5-bromovalerate and impurity A,

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— *signal-to-noise ratio*: minimum 20 for the peak due to impurity A.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mix 50 volumes of *methanol R* and 50 volumes of *water R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 20 mg of *sodium tianeptine for system suitability CRS* in the solvent mixture and dilute to 200 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm) with a pore size of 0.01 µm,

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 21 volumes of *methanol R1*, 31.5 volumes of *acetonitrile R1* and 47.5 volumes of a 2 g/L solution of *sodium laurilsulfate R*, adjusted to pH 2.5 with *phosphoric acid R*,

— *mobile phase B*: mix 20 volumes of *methanol R1*, 20 volumes of a 2 g/L solution of *sodium laurilsulfate R*, adjusted to pH 2.5 with *phosphoric acid R* and 60 volumes of *acetonitrile R1*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	100	0
35 - 45	100 → 40	0 → 60
45 - 60	40	60
60 - 70	40 → 100	60 → 0

Flow rate 1 mL/min.

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Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Relative retention with reference to tianeptine (retention time = about 30 min): impurity C = about 0.4; impurity D1 = about 0.6; impurity D2 = about 0.8; impurity E = about 1.1; impurity B = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to tianeptine and impurity E.

Limits:

— *any impurity*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent),

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 5.0 per cent, determined on 0.100 g.

ASSAY

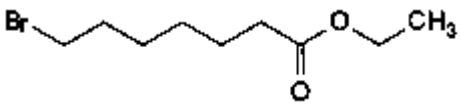
Dissolve 0.165 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 22.95 mg of $C_{21}H_{24}ClN_2NaO_4S$.

STORAGE

In an airtight container.

IMPURITIES



A. ethyl 7-bromoheptanoate,

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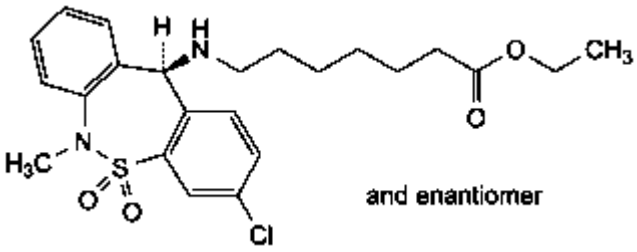
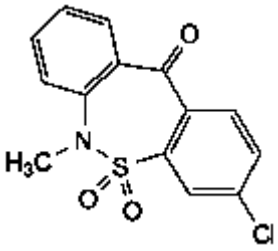
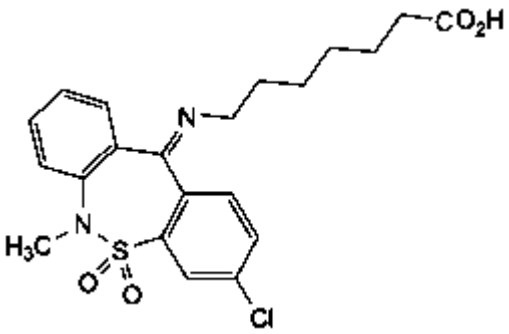


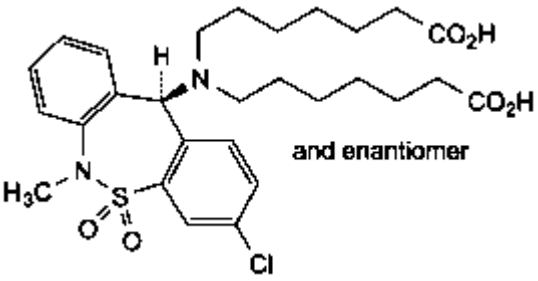
B. ethyl 7-[[(11*RS*)-3-chloro-6-methyl-6,11-dihydrodibenzo[*c*,*f*][1,2]thiazepin-11-yl]amino]heptanoate *S*,*S*-dioxide,



C. 3-chloro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-one *S*,*S*-dioxide,



D. 7-[[(11*RS*)-3-chloro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-ylidene]amino]heptanoic acid *S*,*S*-dioxide,



E. 7,7′-[[(11*RS*)-3-chloro-6-methyl-6,11-dihydrodibenzo[*c*,*f*][1,2]thiazepin-11-yl]imino]diheptanoic acid *S*,*S*-dioxide.

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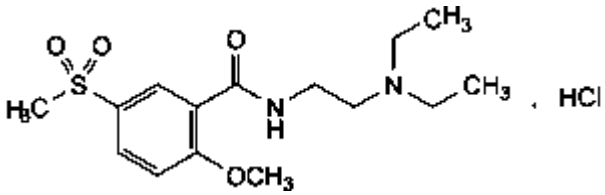
Tiapride Hydrochloride

General Notices

(Ph. Eur. monograph 1575)



$C_{15}H_{25}ClN_2O_4S$ 364.9 *51012-33-0*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

N-[2-(Diethylamino)ethyl]-2-methoxy-5-(methylsulfonyl)benzamide hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, soluble in methanol, slightly soluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tiapride hydrochloride CRS*.

B. Solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

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TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 450 nm is not greater than 0.030.

pH (*2.2.3*)

4.0 to 6.0 for solution S.

Impurity C

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.400 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20.0 mg of *metoclopramide impurity E CRS* (impurity C) in *methanol R* and dilute to 50 mL with the same solvent. Dilute 2.0 mL of the solution to 20 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *dioxan R*, *methanol R*, *methylene chloride R* (2:10:14:90 *V/V/V/V*).

Application 10 µL.

Development Over 4/5 of the plate.

Drying In air.

Detection Spray with a 2 g/L solution of *ninhydrin R* in *butanol R* and heat at 100 °C for 15 min.

Retardation factors Impurity C = about 0.1; tiapride = about 0.6.

Limit:

— *impurity C*: any spot due to impurity C is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

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Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *tiapride hydrochloride CRS* and 5.0 mg of *tiapride N-oxide CRS* (impurity D) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Dissolve 5.44 g of *potassium dihydrogen phosphate R* and 0.08 g of *sodium octanesulfonate R* in 780 mL of *water R*, adjust to pH 2.7 with *phosphoric acid R* and dilute to 800 mL with *water R*; add 150 mL of *methanol R* and 50 mL of *acetonitrile R* and mix.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time 3 times the retention time of tiapride.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to tiapride (retention time = about 7 min): impurity D = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to tiapride and impurity D.

Calculation of percentage contents:

— for each impurity, use the concentration of tiapride hydrochloride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

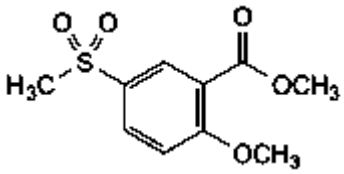
Dissolve 0.300 g in 20 mL of *anhydrous acetic acid R*. Add 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 36.49 mg of $C_{15}H_{25}ClN_2O_4S$.

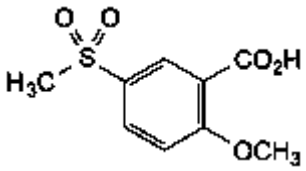
IMPURITIES

Specified impurities C.

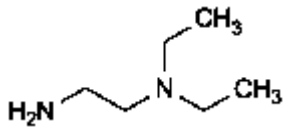
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D.



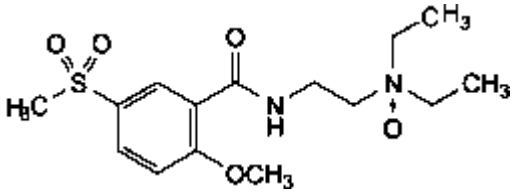
A. methyl 2-methoxy-5-(methylsulfonyl)benzoate,



B. 2-methoxy-5-(methylsulfonyl)benzoic acid,



C. *N*,*N*-diethylethane-1,2-diamine,



D. *N*-[2-(diethyloxidoaminol)ethyl]-2-methoxy-5-(methylsulfonyl)benzamide (tiapride *N*-oxide).

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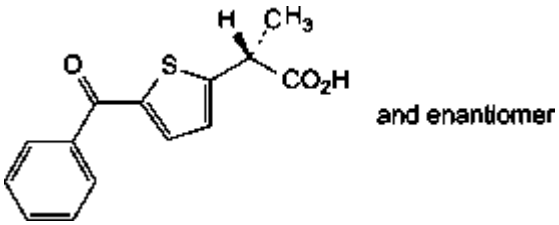
Tiaprofenic Acid

General Notices

(Ph. Eur. monograph 1157)



$C_{14}H_{12}O_3S$ 260.3 *33005-95-7*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

(2*RS*)-2-(5-Benzoylthiophen-2-yl)propanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

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A. Melting point (2.2.14): 95 °C to 99 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25.0 mg in *ethanolic hydrochloric acid R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 50.0 mL with *ethanolic hydrochloric acid R*.

Spectral range 220-350 nm.

Absorption maximum 305 nm.

Shoulder 262 nm.

Specific absorbance at the absorption maximum 550 to 590.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *tiaprofenic acid CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *tiaprofenic acid CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *ketoprofen CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 2 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetic acid R*, *methylene chloride R*, *acetone R* (1:20:80 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Tiaprofenic acid = about 0.3; ketoprofen = about 0.4.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

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Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 2.0 g in ethanol (96 per cent) R and dilute to 20 mL with the same solvent.

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 0.50 g in ethyl acetate R and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 10.0 mg of tiaprofenic acid impurity C CRS in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (d) Dilute 1 mL of reference solution (a) to 2 mL with reference solution (c).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: silica gel for chromatography R (5 µm).

Mobile phase water for chromatography R, glacial acetic acid R, hexane R, methylene chloride R (0.25:20:500:500 *V/V/V/V*); add the water to the acetic acid, then hexane and methylene chloride; sonicate the mixture for 2 min. Do not degas with helium during analysis.

Flow rate 1 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 20 µL.

Run time Twice the retention time of tiaprofenic acid.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to tiaprofenic acid (retention time = about 14 min): impurity C = about 0.86.

System suitability Reference solution (d):

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— *resolution*: minimum 3.0 between the peaks due to impurity C and tiaprofenic acid.

Limits:

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *sum of impurities other than C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 25 mL of *ethanol (96 per cent) R*. Add 25 mL of *water R* and 0.5 mL of *phenolphthalein solution R*. Titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 26.03 mg of $C_{14}H_{12}O_3S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D, E, F.

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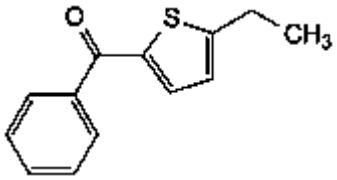
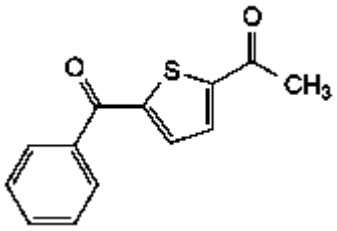
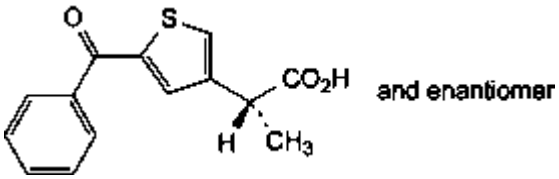


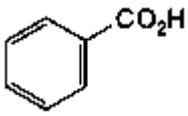
A. (5-ethylthiophen-2-yl)phenylmethanone,



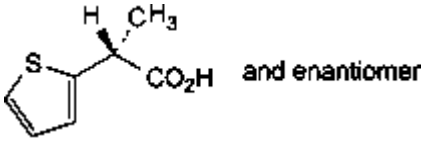
B. 1-(5-benzoylthiophen-2-yl)ethanone,



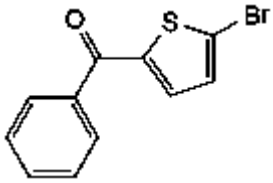
C. (2*RS*)-2-(5-benzoylthiophen-3-yl)propanoic acid,



D. benzoic acid,



E. (2*RS*)-2-(thiophen-2-yl)propanoic acid,



F. (5-bromothiophen-2-yl)phenylmethanone.

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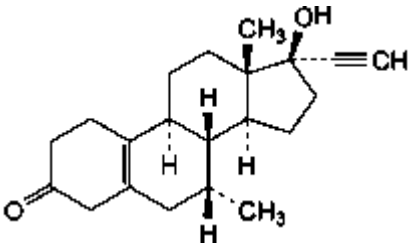
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Tibolone

General Notices

(Ph. Eur. monograph 1739)



$C_{21}H_{28}O_2$ 312.5

Action and use

Steroid with estrogenic and progestogenic properties.

Preparation

Tibolone Tablets

Ph Eur

DEFINITION

17-Hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

Practically insoluble in water, soluble in acetone and in methanol.

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It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison tibolone CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined in the minimum volume of anhydrous ethanol R, evaporate to dryness on a water-bath and record a new spectrum using the residue.

TESTS

Specific optical rotation (2.2.7)

+ 100 to + 106 (dried substance).

Dissolve 0.250 g in anhydrous ethanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Select a brand of acetonitrile such that the formation of possible artefact peaks, eluting after impurity C at relative retentions 0.6 to 0.8, is avoided.

Solvent mixture water R, acetonitrile R1 (25:75 *V/V*).

Test solution Dissolve 40 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 4 mg of tibolone for system suitability CRS (containing impurities A, B, C, D and E) in 1 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped extra-dense bonded octylsilyl silica gel for chromatography R (5 µm).

Mobile phase methanol R2, acetonitrile R1, water for chromatography R (8:40:52 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 5 µL.

Run time 3 times the retention time of tibolone.

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Identification of impurities Use the chromatogram supplied with *tibolone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to tibolone (retention time = about 14 min): impurity A = about 0.22; impurity B = about 0.24; impurity C = about 0.6; impurity D = about 1.1; impurity E = about 2.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to tibolone.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.7; impurity B = 1.5; impurity C = 2.1;

— for each impurity, use the concentration of tibolone in reference solution (b).

Limits:

— *impurity C*: maximum 0.5 per cent;

— *impurity B*: maximum 0.4 per cent;

— *impurity D*: maximum 0.2 per cent;

— *impurities A, E*: for each impurity, maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *tibolone for system suitability CRS* (containing impurity D) in 10 mL of *methanol R*.

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Reference solution (b) Dissolve 50.0 mg of *tibolone CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *water for chromatography R*, *methanol R2* (20:80 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL.

Run time 2.5 times the retention time of tibolone.

Identification of impurities Use the chromatogram supplied with *tibolone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to tibolone (retention time = about 6 min): impurity D = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peak due to tibolone and the peak due to impurity D.

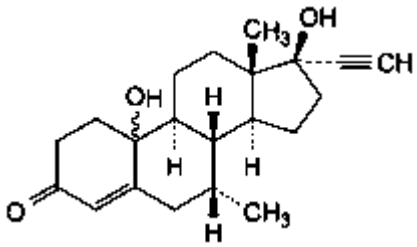
Calculate the percentage content of $C_{21}H_{28}O_2$ taking into account the assigned content of *tibolone CRS*.

STORAGE

At a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A, B, C, D, E*.



A. 10,17-dihydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one,

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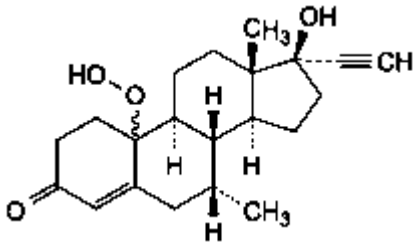
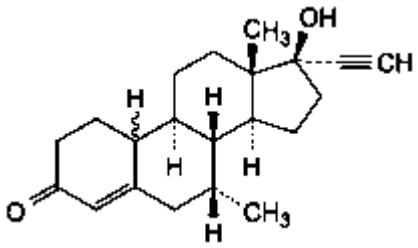
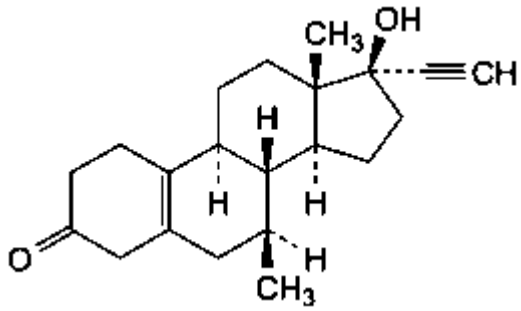


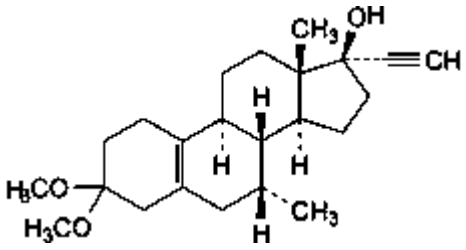
B. 10-hydroperoxy-17-hydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one,



C. 17-hydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one,



D. 17-hydroxy-7β-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one,



E. 3,3-dimethoxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-17-ol.

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Tibolone Tablets

General Notices

DEFINITION

Tibolone Tablets contain Tibolone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tibolone, $C_{21}H_{28}O_2$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 5 mg of Tibolone with 5 mL of *acetonitrile*, centrifuge and use the supernatant liquid.

(2) 0.1% w/v of *tibolone BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 4 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air, spray with *ethanolic sulfuric acid (2%)* and heat at 100° to 105° for 3 minutes. Allow to cool and examine under *ultraviolet light (366 nm)* and in daylight.

MOBILE PHASE

5 volumes of *acetone* and 95 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the peak due to tibolone in the chromatogram obtained with solution (2).

TESTS

Dissolution

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Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of a 0.25% w/v solution of *sodium lauryl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with a 0.25% w/v solution of *sodium lauryl sulfate* to produce a solution expected to contain about 0.0005% w/v of Tibolone.

(2) 0.0005% w/v of *tibolone BPCRS* in a mixture of 1 volume of *methanol* and 99 volumes of a 0.25% w/v solution of *sodium lauryl sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

23 volumes of *water* and 77 volumes of *methanol R2*.

DETERMINATION OF CONTENT

Calculate the total content of tibolone, $C_{21}H_{28}O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{28}O_2$ in *tibolone BPCRS*.

LIMITS

The amount of tibolone released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *absolute ethanol*.

(1) To a quantity of the powdered tablets containing 25 mg of Tibolone add 40 mL of *absolute ethanol*, mix with the aid of ultrasound, add sufficient *absolute ethanol* to produce 50 mL, centrifuge and use the supernatant.

(2) 0.05% w/v of *tibolone impurity standard BPCRS* (containing impurity B, impurity C and 1% w/w of impurity A).

(3) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Waters Nova-Pak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

28 volumes of *tetrahydrofuran* and 72 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (2) closely resembles the chromatogram supplied with *tibolone impurity standard BPCRS*;

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0;

in the chromatogram obtained with solution (3), the *signal-to-noise* ratio of the peak due to impurity A is at least 10.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity C using the chromatogram obtained with solution (2) and multiply the area of this peak by the following correction factor: 0.79.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity B is not greater than the area of the peak due to impurity A in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity C is not greater than 5 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (5%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* is not greater than 6.5 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (6.5%).

Disregard any peak with an area less than the area of the peak due to impurity A in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

For tablets containing 2 mg or less or 2% w/w or less of tibolone

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *absolute ethanol*.

(1) Finely crush one tablet, moisten the powdered tablet with sufficient *absolute ethanol* to produce a solution containing 0.05% w/v of Tibolone, disperse with the aid of ultrasound for 10 minutes and centrifuge.

(2) 0.05% w/v of *tibolone BPCRS*.

(3) 0.05% w/v of *tibolone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used with a detection wavelength of 210 nm.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *tibolone impurity standard BPCRS*;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{28}O_2$ in each tablet using the declared content of $C_{21}H_{28}O_2$ in *tibolone BPCRS*.

ASSAY

For tablets containing 2 mg or less or 2% w/w or less of tibolone

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing more than 2 mg and more than 2% w/w of tibolone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *absolute ethanol*.

(1) To a quantity of the powdered tablets containing 25 mg of Tibolone add 40 mL of *absolute ethanol*, mix with the aid of ultrasound, add sufficient *absolute ethanol* to produce 50 mL and centrifuge.

(2) 0.05% w/v of *tibolone BPCRS*.

(3) 0.05% w/v of *tibolone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used with a detection wavelength of 210 nm.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *tibolone impurity standard BPCRS*;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{21}H_{28}O_2$ in the tablets using the declared content of $C_{21}H_{28}O_2$ in *tibolone BPCRS*.

IMPURITIES

A. 10,17-dihydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one (European Pharmacopoeia impurity A),

B. 10-hydroperoxy-17-hydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one (European Pharmacopoeia impurity B),

C. 17-hydroxy-7α-methyl-19-nor-10ξ,17α-pregn-4-en-20-yn-3-one (European Pharmacopoeia impurity C).

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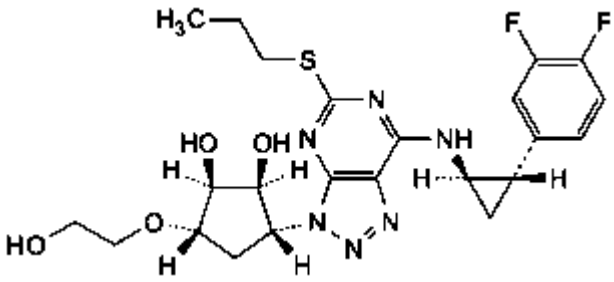
Ticagrelor

General Notices

(Ph. Eur. monograph 3087)



$C_{23}H_{28}F_2N_6O_4S$ 522.6 *274693-27-5*

Action and use

Platelet aggregation inhibitor.

Ph Eur

DEFINITION

(1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is produced by highly stereoselective methods of manufacture; consideration must be given to the formation of potential stereoisomeric impurities during the manufacturing process, and procedures must be implemented for the appropriate control of these impurities.

CHARACTERS

Appearance

White or almost white to pale pink powder.

Solubility

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Practically insoluble in water, freely soluble in methanol, soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison ticagrelor CRS.

TESTS

Impurity E

Liquid chromatography (2.2.29).

Buffer solution 156 g/L solution of sodium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R.

Test solution Dissolve 30.0 mg of the substance to be examined in 2 mL of a mixture of equal volumes of acetonitrile R and water R and dilute to 10.0 mL with water R. Centrifuge for 15 min at about 1200 *g* or until a clear solution is obtained. Use the clear supernatant.

Reference solution Dissolve 4.5 mg of ticagrelor impurity E CRS ((*R*)-mandelate salt) in acetonitrile R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with acetonitrile R. Dilute 1.0 mL of this solution to 10.0 mL with water R (solution equivalent to a 24 ng/mL solution of impurity E).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (1.8 µm);

— *temperature*: 55 °C.

Mobile phase:

— *mobile phase A*: mix 1 volume of the buffer solution and 89 volumes of water for chromatography R and add 10 volumes of acetonitrile for chromatography R;

— *mobile phase B*: mix 1 volume of the buffer solution and 29 volumes of water for chromatography R and add 70 volumes of acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	94	6
8 - 9	94 → 0	6 → 100
9 - 20	0	100

Flow rate 1.0 mL/min.

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Detection Spectrophotometer at 222 nm.

Injection: 100 µL.

Relative retention With reference to ticagrelor (retention time = about 11.5 min): impurity E = about 0.6.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 10.0 per cent determined on 6 injections.

Limit:

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (8 ppm).

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture acetonitrile R, water R (35:65 *V/V*).

Buffer solution 156 g/L solution of sodium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of ticagrelor CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of ticagrelor for system suitability CRS (containing impurities A, B, C and D) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: base-deactivated end-capped phenylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 1 volume of the buffer solution and 89 volumes of water for chromatography R and add 10 volumes of acetonitrile for chromatography R;

— *mobile phase B*: mix 1 volume of the buffer solution and 29 volumes of water for chromatography R and add 70 volumes of acetonitrile for chromatography R;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 42	80 → 25	20 → 75
42 - 47	25	75

Flow rate 0.65 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *ticagrelor for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify impurities A, B, C and D.

Relative retention With reference to ticagrelor (retention time = about 23 min): impurity A = about 0.15; impurity B = about 1.06; impurity C = about 1.23; impurity D = about 1.5.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to ticagrelor and impurity B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.5;

— for each impurity, use the concentration of ticagrelor in reference solution (b).

Limits:

— *impurity D*: maximum 0.3 percent;

— *impurities A, B*: for each impurity, maximum 0.2 per cent;

— *impurity C*: maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent determined on 0.500 g using the evaporation technique at 130 °C.

Sulfated ash (*2.4.14*)

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Maximum 0.6 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solutions (a) and (c).

Mobile phase Mix 1 volume of the buffer solution and 56 volumes of *water for chromatography R* and add 43 volumes of *acetonitrile for chromatography R*.

Run time 4.5 times the retention time of ticagrelor.

Relative retention With reference to ticagrelor (retention time = about 6 min): impurity B = about 1.15.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to ticagrelor and impurity B.

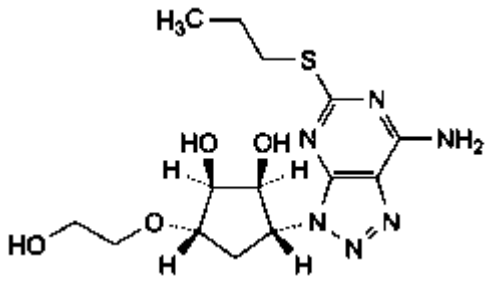
Calculate the percentage content of $C_{23}H_{28}F_2N_6O_4S$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *ticagrelor CRS*.

STORAGE

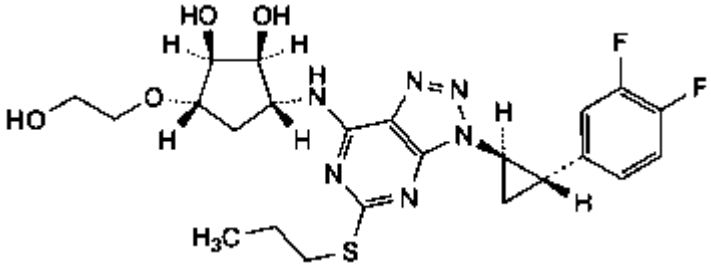
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*



A. (1*S*,2*S*,3*R*,5*S*)-3-[7-amino-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol,



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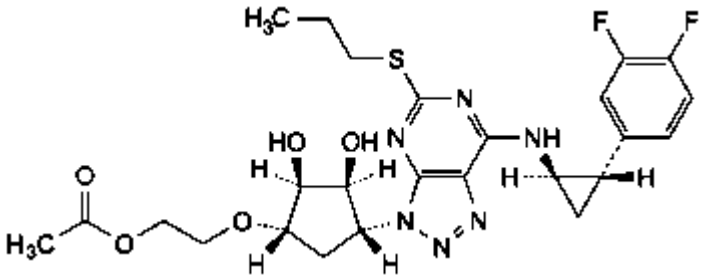
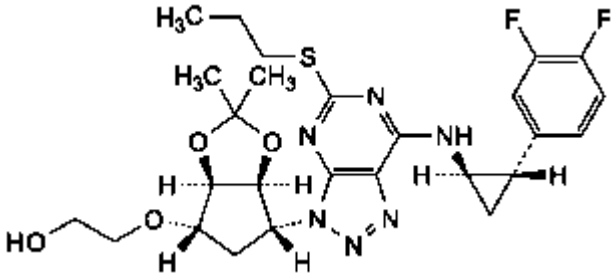
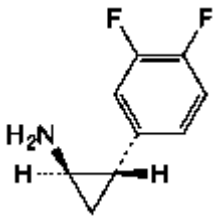
B. (1*S*,2*S*,3*R*,5*S*)-3-[[3-[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl]amino]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol,



C. 2-[[(1*S*,2*S*,3*S*,4*R*)-4-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]ethyl acetate,



D. 2-[[(3a*R*,4*S*,6*R*,6a*S*)-6-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,2-dimethyltetrahydro-2*H*,3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]oxy]ethan-1-ol,



E. (1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropan-1-amine.

Ph Eur

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Ticagrelor Tablets

General Notices

(Ph. Eur. monograph 3097)

Action and use

Platelet aggregation inhibitor.

Ph Eur

DEFINITION

Tablets containing *Ticagrelor (3087)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of ticagrelor ($C_{23}H_{28}F_2N_6O_4S$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture *acetonitrile R*, *water R* (35:65 *V/V*).

Buffer solution 156 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*.

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Test solution To an appropriate number of tablets add about half of a suitable volume of the solvent mixture. Shake using a mechanical shaker until the tablets have disintegrated completely and dilute to volume with the solvent mixture to obtain a concentration of ticagrelor of 0.45 mg/mL. If necessary, more than 1 dilution with the solvent mixture may be performed to obtain this concentration.

Reference solution (a) Dissolve 45.0 mg of *ticagrelor CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 4.5 mg of *ticagrelor for system suitability CRS* (containing impurities A, B and D) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (1.8 µm);

— *temperature*: 55 °C.

Mobile phase:

— *mobile phase A*: mix 1 volume of the buffer solution and 89 volumes of *water for chromatography R* and add 10 volumes of *acetonitrile for chromatography R*;

— *mobile phase B*: mix 1 volume of the buffer solution and 29 volumes of *water for chromatography R* and add 70 volumes of *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 9	90 → 35	10 → 65
9 - 17	35	65
17 - 18	35 → 0	65 → 100
18 - 25	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *ticagrelor for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and D.

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Relative retention With reference to ticagrelor (retention time = about 15 min): impurity A = about 0.5; impurity B = about 1.1; impurity D = about 1.5.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to ticagrelor and impurity B.

Calculation of percentage contents:

— for each impurity, use the concentration of ticagrelor in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.1 per cent; disregard the peaks due to impurities A, B and D.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium 2 g/L solution of *polysorbate 80 R*. Use 900 mL of the medium.

Rotation speed 75 r/min.

Time 45 min.

Analysis Ultraviolet and visible absorption spectrophotometry (*2.2.25*), using a path length of 2 mm.

Test solutions The samples withdrawn from the dissolution vessel and filtered.

When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 5-fold dilution for 90 mg tablets).

Measure the absorbance of the solutions at the absorption maximum at 300 nm.

Calculate the amount of dissolved ticagrelor ($C_{23}H_{28}F_2N_6O_4S$), expressed as a percentage of the content stated on the label, taking the specific absorbance to be 311.

Acceptance criterion:

— *Q* = 70 per cent after 45 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mix 1 volume of the buffer solution and 47 volumes of *water for chromatography R* and add 52 volumes of *acetonitrile for chromatography R*.

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Flow rate 1.2 mL/min.

Injection Test solution and reference solution (a).

Run time Twice the retention time of ticagrelor.

Retention time Ticagrelor = about 4 min.

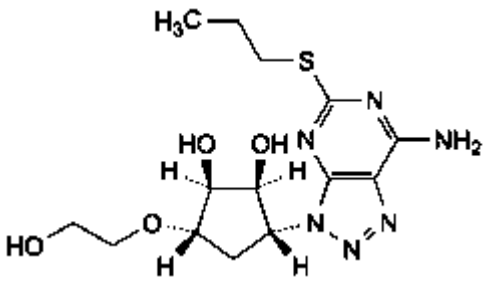
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

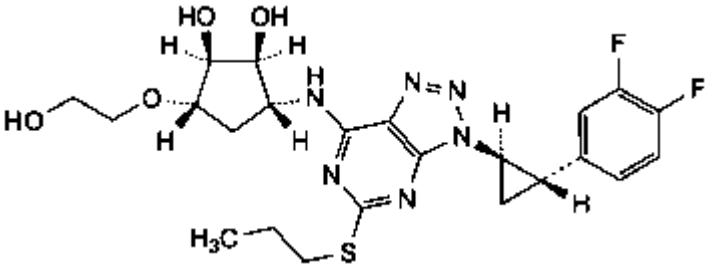
Calculate the percentage content of ticagrelor ($C_{23}H_{28}F_2N_6O_4S$) taking into account the assigned content of *ticagrelor CRS*.

IMPURITIES

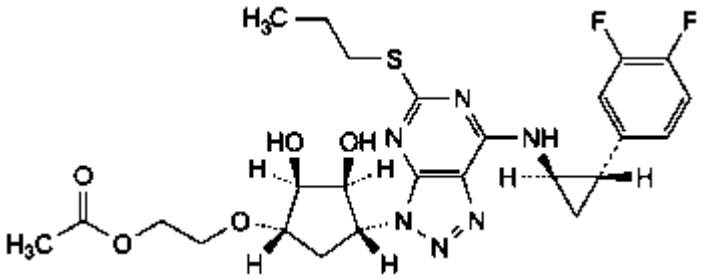
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, B, C, D.*



A. (1*S*,2*S*,3*R*,5*S*)-3-[7-amino-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol,



B. (1*S*,2*S*,3*R*,5*S*)-3-[[3-[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl]amino]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol,



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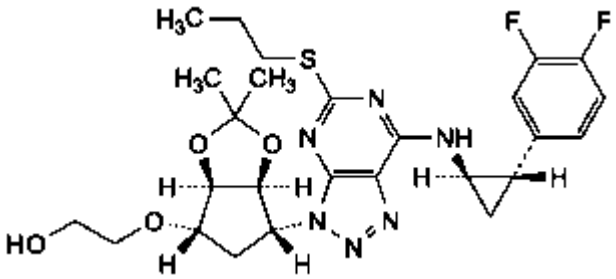
C. 2-[[(1*S*,2*S*,3*S*,4*R*)-4-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]ethyl acetate,



D. 2-[[(3a*R*,4*S*,6*R*,6a*S*)-6-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-2,2-dimethyltetrahydro-2*H*,3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]oxy]ethan-1-ol.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

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Ticarcillin and Clavulanic Acid Infusion

General Notices

Ticarcillin and Clavulanic Acid Intravenous Infusion

Ticarcillin Sodium and Potassium Clavulanate Intravenous Infusion

Ticarcillin and Clavulanic Acid for Intravenous Infusion

Action and use

Penicillin antibacterial + beta-lactamase inhibitor.

DEFINITION

Ticarcillin and Clavulanic Acid Infusion is a sterile solution containing Ticarcillin Sodium and Potassium Clavulanate. It is prepared by dissolving Ticarcillin and Clavulanic Acid for Infusion with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations.

STORAGE

Ticarcillin and Clavulanic Acid Infusion should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

TICARCILLIN AND CLAVULANIC ACID FOR INFUSION

DEFINITION

Ticarcillin and Clavulanic Acid for Infusion is a sterile material consisting of Ticarcillin Sodium and Potassium Clavulanate with or without excipients. It is supplied in a sealed container.

PRODUCTION

The methods of production, extraction and purification of Potassium Clavulanate used in the formulation of Ticarcillin and Clavulanic Acid Infusion are such that potassium clavam-2-carboxylate is eliminated or present at a level not exceeding 0.01%.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of ticarcillin, $C_{15}H_{16}N_2O_6S_2$

90.0 to 105.0% of the stated amount.

Content of clavulanic acid, $C_8H_9NO_5$

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content of clavulanic acid, $C_8H_9NO_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the contents of a sealed container containing the equivalent of 1.5 g of ticarcillin in 5 mL of *water*, add 0.5 mL of *hydrochloric acid R1*, swirl and allow to stand in a bath of iced water for 10 minutes. Filter the precipitate (Whatman GF/C is suitable), wash with 5 mL of *water* and dissolve in a mixture of 1 volume of *water* and 9 volumes of *acetone*. Evaporate the solvent almost to dryness under a stream of nitrogen and then dry in an oven at 60° for 1 hour. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of ticarcillin (*RS 458*).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of 4 volumes of *methanol* and 6 volumes of *0.1M mixed phosphate buffer pH 7.0*.

(1) Dissolve a quantity of the contents of a sealed container to produce a solution containing the equivalent of 0.4% w/v of clavulanic acid.

(2) 0.4% w/v of *lithium clavulanate EPCRS*.

(3) 0.4% w/v of *ticarcillin monosodium BPCRS*.

(4) Mix equal volumes of solutions (2) and (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel F_{254} plate* (Merck silica gel 60 F_{254} plates are suitable). Impregnate the plate by spraying it with a 0.1% w/v solution of *disodium edetate* in *mixed phosphate buffer pH 4.0* and allow to dry overnight. Activate the plate by heating at 105° for 1 hour just prior to use.

(b) Use the mobile phase described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *butan-1-ol*, 2 volumes of a 0.1% w/v solution of *disodium edetate* in *mixed phosphate buffer pH 4.0*, 6 volumes of *glacial acetic acid* and 10 volumes of *butyl acetate*.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (4), the spot with the lower Rf value corresponds to the principal spot in the chromatogram obtained with solution (2) and the spot with the higher Rf value corresponds to the principal spot in the chromatogram obtained with solution (3) and the spots are clearly separated.

CONFIRMATION

In the chromatogram obtained with solution (1), the spots corresponding to clavulanic acid and ticarcillin correspond in position and colour to the principal spots in the chromatogram obtained with solution (4).

C. In the Assay, the retention times of the two principal peaks in the chromatogram obtained with solution (1) correspond to those of the two principal peaks in the chromatogram obtained with solution (2).

TESTS

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Acidity or alkalinity

pH of a solution containing the equivalent of 10% w/v of ticarcillin, 5.5 to 8.0, Appendix V L.

Clavulanate polymer and other fluorescent impurities

Carry out the method for *fluorescence spectrophotometry*, Appendix II E, using the following freshly prepared solutions.

(1) To a quantity of the contents of a sealed container containing the equivalent of 0.1 g of clavulanic acid add 50 mL of a 0.1M phosphate buffer solution pH 5.0, prepared as described below, shake vigorously for 1 minute and then shake with the aid of ultrasound for 5 minutes; add sufficient of the buffer solution to produce 100 mL and filter through a 0.45-µm filter. To prepare the buffer solution dissolve 15.6 g of *sodium dihydrogen orthophosphate* in 800 mL of *water*, adjust the pH to 5.0 using 1M *sodium hydroxide* and add sufficient *water* to produce 1000 mL.

(2) Prepare a solution containing 0.42 µg per mL of *quinine sulfate BPCRS* in 0.5M *sulfuric acid*. [*NOTE:* The fluorescence of quinine sulfate is 118 times more intense than that of an equivalent concentration of clavulanate polymer.]

PROCEDURE

Measure the *fluorescence* of the solutions using an excitation wavelength of 360 nm and an emission wavelength of 440 nm, using the phosphate buffer solution in the reference cell.

LIMITS

The fluorescence obtained with solution (1) is not more intense than that obtained with solution (2) (5% w/w, calculated with respect to the content of clavulanic acid).

Related substances (ticarcillin)

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a solution prepared by dissolving 10.35 g of *sodium dihydrogen orthophosphate monohydrate* in 1500 mL of *water* and adjusting the pH to 6.4 using 10M *sodium hydroxide* (solvent A). The solutions should be freshly prepared.

(1) Dissolve a quantity of the contents of a sealed container in sufficient solvent A to produce a solution containing the equivalent of 0.2% w/v of ticarcillin.

(2) 0.004% w/v of *ticarcillin monosodium BPCRS*.

(3) Dissolve 11 mg of *ticarcillin monosodium BPCRS* and 2.9 mg of *ticarcillin impurity A BPCRS* in 10 mL of 0.1M *sodium hydroxide* and allow to stand for 15 minutes (generation of ticarcillin impurity D). Transfer the solution into a 500 mL volumetric flask quantitatively, washing the beaker out with solvent A. Add 400 mL of solvent A, ensuring that all traces of the degraded solution are washed from the neck of the flask. Add 11 mg of *ticarcillin impurity A BPCRS*, 10 mg of *ticarcillin impurity B BPCRS*, 10 mg of *ticarcillin impurity C BPCRS* and 55 mg of *ticarcillin monosodium BPCRS* to the flask and dilute to 500 mL with solvent A.

(4) Dilute 1 volume of solution (2) to 40 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *methylsilyl silica gel for chromatography* (5 µm) with a pore size of 6 nm (ES Industries Chromegabond TMS C1 5u 60A is suitable).

(b) Use gradient elution and the mobile phase described below.

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(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 54 volumes of *acetonitrile* and 246 volumes of a buffer solution prepared as described below; adjust the pH of the mixture to 3.0 with 2M *orthophosphoric acid*. To prepare the buffer solution dissolve 10.35 g of *sodium dihydrogen orthophosphate monohydrate* and 4.83 g of *tetrabutylammonium bromide* in 3000 mL of *water* and mix.

Mobile phase B Equal volumes of *acetonitrile* and buffer solution; adjust the pH of the mixture to 3.0 with 2M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-40	100→0	0→100	linear gradient
40-48	0	100	isocratic
48-49	0→100	100→0	linear gradient
49-57	100	0	isocratic

When the chromatograms are recorded under the prescribed conditions, the retention time of ticarcillin is about 14 minutes. If necessary, adjust the content of *acetonitrile* in mobile phase A to achieve the stated retention time. Retention times relative to ticarcillin are: ticarcillin impurity B, about 0.37; ticarcillin impurity C, about 0.42; ticarcillin impurity D, about 0.5; ticarcillin impurity A, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity B and impurity C is at least 1.6 and the *resolution factor* between the peaks due to impurity C and impurity D is at least 1.6.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C and D using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity B by the following correction factor: 0.5; multiply the area of any peak corresponding to impurity C by the following correction factor: 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (4%);

the area of any peak corresponding to impurity D is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (6%);

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the area of any other *secondary peak* is not greater than 1.25 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%);

the sum of the areas of all the *secondary peaks* is not greater than six times the area of the principal peak in the chromatogram obtained with solution (2) (12%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Bacterial endotoxins

Carry out the test for *bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of ticarcillin per mL (solution A). The endotoxin limit concentration of solution A is 0.7 IU of endotoxin per mL.

Water

Not more than 4.5% w/w, Appendix IX C. Use 0.3 g.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a solution prepared by dissolving 7.8 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 6.4 using 5M *sodium hydroxide* (solvent B). The solutions should be stored at 2° to 8° and used within 4 hours.

(1) Dissolve a quantity of the mixed contents of the 10 containers in sufficient *water* to produce a solution containing the equivalent of 1.4% w/v of ticarcillin. Dilute 1 volume to 10 volumes with solvent B.
(2) 0.15% w/v of *ticarcillin monosodium BPCRS* and 0.01% w/v of *lithium clavulanate EPCRS* in solvent B.
(3) 0.1% w/v of each of *ampicillin trihydrate BPCRS* and *ticarcillin monosodium BPCRS* in solvent B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped phenylethyl silica gel for chromatography* (4 µm) (Phenomenex Synergi 4µ Polar-RP 80A is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 31.2 g of *sodium dihydrogen orthophosphate* in 4000 mL of *water* and adjust the pH to 3.9 using 1M *orthophosphoric acid*.

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Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	100	0	isocratic
1-1.5	100→92	0→8	linear gradient
1.5-6	92	8	isocratic
6-7	92→50	8→50	linear gradient
7-8	50→100	50→0	linear gradient
8-9	100	0	isocratic

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to ampicillin and ticarcillin is at least 4.0 and the *symmetry factor* of the peak corresponding to ticarcillin is less than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{16}N_2O_6S_2$ and $C_8H_9NO_5$ in a container of average content weight using the declared content of $C_{15}H_{15}N_2NaO_6S_2$ in *ticarcillin monosodium BPCRS* and the declared content of $C_8H_8LiNO_5$ in *lithium clavulanate EPCRS*. Each mg of $C_{15}H_{15}N_2NaO_6S_2$ is equivalent to 0.9459 mg of $C_{15}H_{16}N_2O_6S_2$. Each mg of $C_8H_8LiNO_5$ is equivalent to 0.9711 mg of $C_8H_9NO_5$

LABELLING

The label of the sealed container states the quantity of Ticarcillin Sodium contained in it, in terms of the equivalent amount of ticarcillin, and the quantity of Potassium Clavulanate, in terms of the equivalent amount of clavulanic acid.

The label of the sealed container states that the preparation contains penicillin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ticarcillin Sodium.

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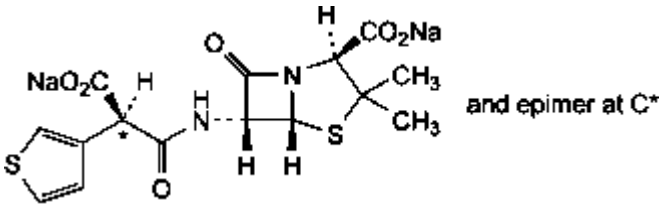
Ticarcillin Sodium

General Notices

(Ph. Eur. monograph 0956)



$C_{15}H_{14}N_2Na_2O_6S_2$ 428.4 *4697-14-7*

Action and use

Penicillin antibacterial.

Preparation

Ticarcillin and Clavulanic Acid Infusion

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DEFINITION

Disodium (2*S*,5*R*,6*R*)-6-[[(2*RS*)-2-carboxylato-2-(thiophen-3-yl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

89.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow, hygroscopic powder.

Solubility

Freely soluble in water, soluble in methanol.

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IDENTIFICATION

First identification: A, D, E.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 50 mg of the substance to be examined in 1 mL of water R, add 0.1 mL of hydrochloric acid R1, swirl and allow to stand in iced water for 10 min. Filter the precipitate and rinse with 2 mL of water R. Dissolve in a mixture of 1 volume of water R and 9 volumes of acetone R. Evaporate the solvent almost to dryness, then dry in an oven at 60 °C for 30 min.

Comparison Repeat the operations using ticarcillin monosodium CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in methanol R and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of ticarcillin monosodium CRS in methanol R and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 25 mg of carbenicillin sodium CRS and 25 mg of ticarcillin monosodium CRS in methanol R and dilute to 5 mL with the same solvent.

Plate TLC silanised silica gel plate R.

Mobile phase Mix 10 volumes of acetone R and 90 volumes of a 154 g/L solution of ammonium acetate R, adjusted to pH 5.0 with glacial acetic acid R.

Application 1 µL.

Development Over a path of 12 cm.

Drying In a current of hot air.

Detection Expose to iodine vapour.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 15 cm long and 15 mm in diameter. Moisten with 0.05 mL of water R and add 2 mL of sulfuric acid-formaldehyde reagent R. Mix the contents of the tube by swirling; the solution is brown. Place the test-tube in a water-bath for 1 min; a dark reddish-brown colour develops.

D. It gives reaction (a) of sodium (2.3.1).

E. Specific optical rotation (see Tests).

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TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

pH (*2.2.3*)

5.5 to 7.5 for solution S.

Specific optical rotation (*2.2.7*)

+ 172 to + 187 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 25.0 mL with mobile phase A.

Reference solution (a) Dissolve 20.0 mg of *ticarcillin impurity A CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase A.

Reference solution (b) Dilute 1 mL of the test solution to 50 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.3 g/L solution of *ammonium phosphate R* adjusted to pH 7.0 with *phosphoric acid R*;

— *mobile phase B*: *methanol R*, mobile phase A (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 30	0 → 70
30 - 40	30	70

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Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the 2 principal peaks (diastereoisomers).

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (4 per cent);

— *any other impurity*: for each impurity, not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent).

N,N-Dimethylaniline (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.5 per cent *m/m*.

Water (*2.5.12*)

Maximum 5.5 per cent, determined on 0.150 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.05 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution Dissolve 50.0 mg of *ticarcillin monosodium CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

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Mobile phase Mix 20 volumes of *methanol R* and 80 volumes of a 1.3 g/L solution of *ammonium phosphate R* adjusted to pH 7.0 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

System suitability Reference solution:

— *resolution*: minimum 2.5 between the 2 principal peaks;

— *repeatability*: maximum relative standard deviation of 1.0 per cent for the 2 peaks due to ticarcillin after 6 injections.

Calculate the percentage content of ticarcillin sodium as the sum of the areas of the 2 peaks, multiplying the content of ticarcillin monosodium by 1.054.

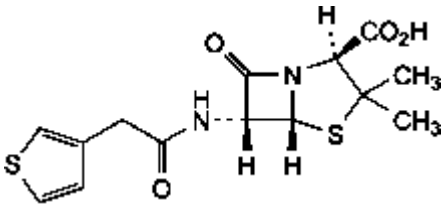
STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

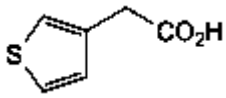
IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*



A. (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[[(thiophen-3-yl)acetyl]amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (decarboxyticarcillin),



B. (thiophen-3-yl)acetic acid,

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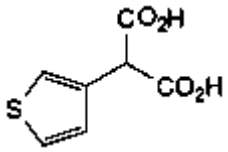
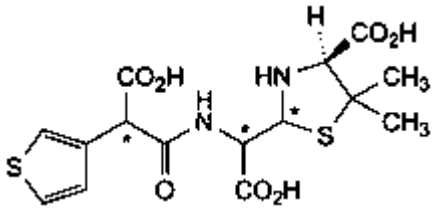
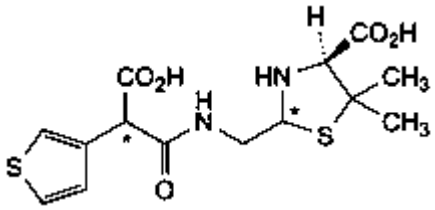


C. 2-(thiophen-3-yl)propanedioic acid (3-thienylmalonic acid),



D. (4*S*)-2-[carboxy[[2-carboxy-2-(thiophen-3-yl)acetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of ticarcillin),



E. (4*S*)-2-[[[2-carboxy-2-(thiophen-3-yl)acetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of ticarcillin).

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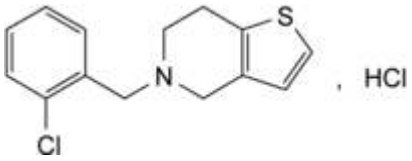
Ticlopidine Hydrochloride

General Notices

(Ph. Eur. monograph 1050)



$C_{14}H_{15}Cl_2NS$ 300.2 *53885-35-1*

Action and use

Inhibition of adenosine diphosphate (ADP)-mediated platelet aggregation; antiplatelet drug.

Ph Eur

DEFINITION

5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water and in anhydrous ethanol, very slightly soluble in ethyl acetate.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

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Test solution (a) Dissolve 40 mg in *water R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 5.0 mL of test solution (a) to 100.0 mL with *water R*.

Spectral range 250-350 nm for test solution (a); 200-350 nm for test solution (b).

Absorption maxima At 268 nm and 275 nm for test solution (a); at 214 nm and 232 nm for test solution (b).

Absorption ratio A_{268}/A_{275} = 1.1 to 1.2.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ticlopidine hydrochloride CRS*.

C. Mix about 6 mg of *citric acid monohydrate R* and 0.3 mL of *acetic anhydride R*. Add about 5 mg of the substance to be examined and heat in a water-bath at 80 °C. A red colour develops.

D. About 20 mg gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.5 g in a 1 per cent *V/V* solution of *hydrochloric acid R* and dilute to 20 mL with the same solution.

pH (*2.2.3*)

3.5 to 4.0.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase B, mobile phase A (20:80 *V/V*).

Test solution Dissolve 0.250 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution Dissolve 5.0 mg of *ticlopidine impurity F CRS* in the solvent mixture. Add 1.00 mL of the test solution and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

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— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 0.95 g/L solution of *sodium pentanesulfonate monohydrate R*, adjusted to pH 3.4 with a 50 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 45	80 → 20	20 → 80
45 - 50	20	80

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL; inject the solvent mixture as a blank.

Identification of impurities Use the chromatogram obtained with the reference solution to identify the peak due to impurity F.

Retention time Ticlopidine = about 15 min.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to ticlopidine and impurity F; if necessary, adjust the pH of mobile phase A;

— *signal-to-noise ratio*: minimum 50 for the peak due to ticlopidine.

Limits:

— *impurity F*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.05 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to ticlopidine in the chromatogram obtained with the reference solution (0.10 per cent);

— *total*: not more than the area of the peak due to ticlopidine in the chromatogram obtained with the reference solution (0.10 per cent);

— *disregard limit*: 0.5 times the area of the peak due to ticlopidine in the chromatogram obtained with the reference solution (0.05 per cent). Do not disregard the peak due to impurity F.

Formaldehyde

Maximum 20 ppm.

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Dissolve 0.200 g in 4.0 mL of *water R*. Add 0.4 mL of *dilute sodium hydroxide solution R*. Centrifuge, filter the supernatant through cotton previously impregnated with *water R* and dilute to 5.0 mL with *water R*. Transfer to a test-tube. Add 5.0 mL of *acetylacetone reagent R1*. Place the test-tube in a water-bath at 40 °C for 40 min. The test solution is not more intensely coloured than a standard prepared at the same time and in the same manner using 5.0 mL of a 0.8 ppm solution of formaldehyde (CH_2O), obtained by dilution of *formaldehyde standard solution (5 ppm CH_2O) R* with *water R*. Examine the tubes down their vertical axis.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

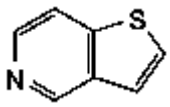
Dissolve 0.150 g in 15 mL of *anhydrous acetic acid R*. Add 35 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 30.02 mg of $C_{14}H_{15}Cl_2NS$.

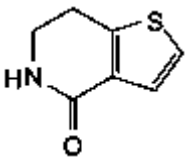
IMPURITIES

Specified impurities *F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, G, H, I, J, K, L.*



A. thieno[3,2-*c*]pyridine,



B. 6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one,

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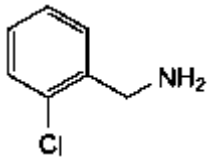
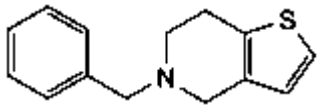
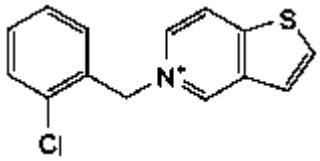


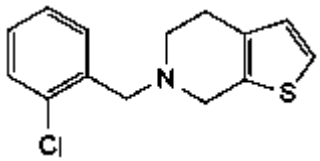
C. (2-chlorophenyl)methanamine,



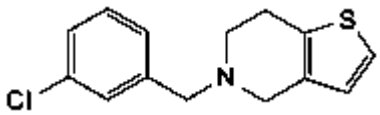
D. 5-benzyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine,



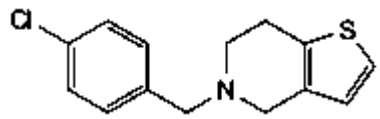
E. 5-(2-chlorobenzyl)thieno[3,2-*c*]pyridinium,



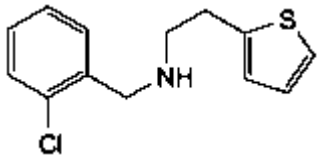
F. 6-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine,



G. 5-(3-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine,



H. 5-(4-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine,



I. *N*-(2-chlorobenzyl)-2-(thiophen-2-yl)ethanamine,

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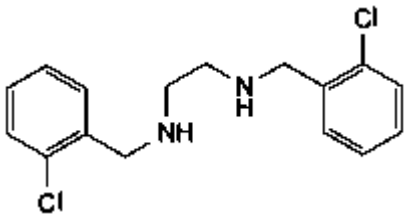
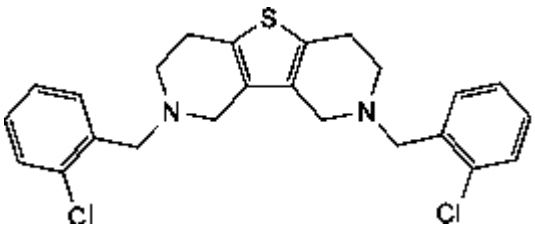
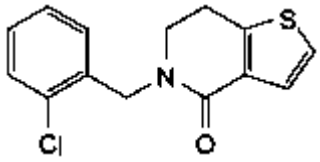


J. *N*,*N*′-bis(2-chlorobenzyl)ethane-1,2-diamine,



K. 2,8-bis(2-chlorobenzyl)-1,2,3,4,6,7,8,9-octahydrothieno[3,2-*c*:4,5-*c*′]dipyridine (bis-ticlopidine),



L. 5-(2-chlorobenzyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one.

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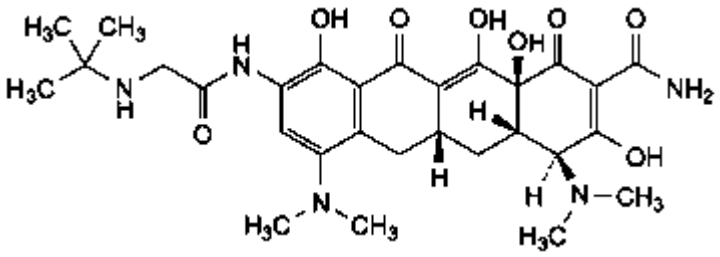
Tigecycline

General Notices

(Ph. Eur. monograph 2825)



$C_{29}H_{39}N_5O_8$ 585.7 *220620-09-7*

Action and use

Antibacterial.

Preparation

Tigecycline for Infusion

Ph Eur

DEFINITION

(4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.

Semi-synthetic product derived from a fermentation product.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Orange, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in anhydrous ethanol and in heptane.

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It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison tigecycline CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

TESTS

pH (2.2.3)

7.7 to 8.2.

Dissolve 0.500 g in carbon dioxide-free water R and dilute to 50.0 mL with the same solvent.

Impurity D

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solutions (b) and (e).

Identification of impurities Use the chromatogram obtained with reference solution (e) to identify the peak due to impurity D.

Relative retention With reference to tigecycline (retention time = about 20 min): impurity D = about 0.36.

Limit:

— *impurity D*: not more than 0.2 times the area of the peak due to tigecycline in the chromatogram obtained with reference solution (b) (0.02 per cent).

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light. Store the solutions at 2-8 °C and use them within 12 h.*

Solution A Solution containing 4.35 g/L of dipotassium hydrogen phosphate R and 0.5 g/L of sodium hydrogensulfite R adjusted to pH 8.0 with a 56.1 g/L solution of potassium hydroxide R.

Test solution (a) Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 100.0 mL with solution A.

Test solution (b) Dilute 10.0 mL of test solution (a) to 50.0 mL with solution A.

Reference solution (a) Dissolve 50.0 mg of tigecycline CRS in solution A and dilute to 100.0 mL with solution A. Dilute 10.0 mL of this solution to 50.0 mL with solution A.

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Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (c) Dissolve 2 mg of *tigecycline impurity B CRS* and 2 mg of *minocycline hydrochloride R* (impurity C) in solution A and dilute to 25 mL with solution A. Dilute 3 mL of the solution to 20 mL with solution A. Dissolve 2.5 mg of *tigecycline for system suitability CRS* (containing impurity A) in 1 mL of this solution and dilute to 5 mL with solution A.

Reference solution (d) Dissolve 2.5 mg of *tigecycline for system suitability CRS* (containing impurity A) in solution A and dilute to 5 mL with solution A.

Reference solution (e) To prepare impurity D *in situ* expose 10 mL of test solution (a) to air and light for 1 h.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 4.35 g of *dipotassium hydrogen phosphate R* and 0.93 g of *sodium edetate R* in 940 mL of *water for chromatography R*, and adjust to pH 6.4 with *phosphoric acid R*; make up to 950 mL with *water for chromatography R* and dilute to 1000 mL with *acetonitrile for chromatography R*;

— *mobile phase B*: dissolve 4.35 g of *dipotassium hydrogen phosphate R* and 0.93 g of *sodium edetate R* in 490 mL of *water for chromatography R*, and adjust to pH 6.4 with *phosphoric acid R*; make up to 500 mL with *water for chromatography R* and dilute to 1000 mL with *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 42	85 → 57	15 → 43
42 - 57	57 → 0	43 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 248 nm.

Injection 25 µL of test solution (a) and reference solutions (b) and (c).

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Identification of impurities Use the chromatogram supplied with *tigecycline for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

Relative retention With reference to tigecycline (retention time = about 20 min): impurity B = about 0.6; impurity A = about 0.7; impurity C = about 1.6.

System suitability Reference solution (c):

— *resolution*: minimum 1.6 between the peaks due to impurities B and A.

Calculation of percentage contents:

— for each impurity, use the concentration of tigecycline in reference solution (b).

Limits:

— *impurity A*: maximum 0.6 per cent;

— *impurity C*: maximum 0.2 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 2.5 per cent, determined on 60.0 mg using the evaporation technique at 90 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Column:

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 14 volumes of *acetonitrile for chromatography R* and 86 volumes of a solution containing 4.35 g/L of *dipotassium hydrogen phosphate R* and 0.93 g/L of *sodium edetate R* previously adjusted to pH 6.2 with *phosphoric acid R*.

Injection 20 µL of test solution (b) and reference solutions (a) and (d).

Run time 4.5 times the retention time of tigecycline.

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Relative retention With reference to tigecycline (retention time = about 12 min): impurity A = about 0.6.

System suitability Reference solution (d):

— *resolution*: minimum 3.0 between the peaks due to impurity A and tigecycline.

Calculate the percentage content of $C_{29}H_{39}N_5O_8$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *tigecycline CRS*.

STORAGE

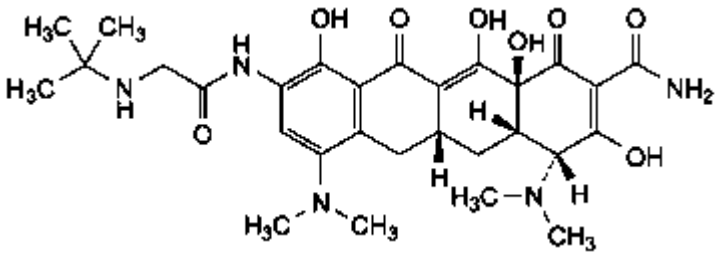
Under nitrogen, in an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

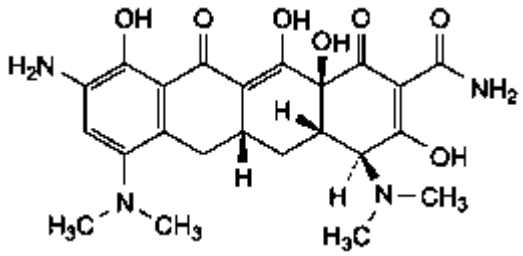
The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, B, C, D.*



A. (4*R*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide,



B. (4*S*,4a*S*,5a*R*,12a*S*)-9-amino-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (9-aminominocycline),

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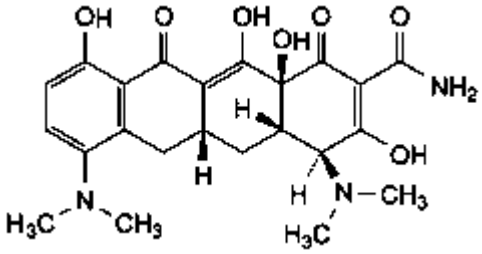
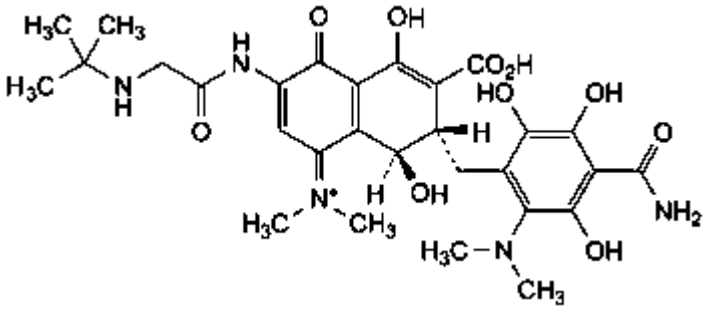


C. (4*S*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (minocycline),



D. (7*S*,8*R*)-3-[2-(*tert*-butylamino)acetamido]-7-[[4-carbamoyl-2-(dimethylamino)-3,5,6-trihydroxyphenyl]methyl]-6-carboxy-5,8-dihydroxy-*N*,*N*-dimethyl-4-oxo-7,8-dihydronaphthalen-1(4*H*)-iminium.

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Tigecycline for Infusion

General Notices

Action and use

Antibacterial.

DEFINITION

Tigecycline for Infusion is a sterile material consisting of Tigecycline with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of tigecycline, $C_{29}H_{39}N_5O_8$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the reference spectrum produced with *tigecycline EPCRS*. If the spectra shows differences, record a new spectrum after recrystallisation from *methanol*.

TESTS

Acidity

pH of a solution containing 1% w/v of Tigecycline, 4.2 to 5.4. Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a solution containing 0.44% w/v of *dipotassium hydrogen phosphate* and 0.05% w/v of *sodium hydrogensulfite* in *water*, adjusted to pH 8.0 with 1M *potassium hydroxide*. Store solutions at 10°, protected from light. Use solutions within 12 hours of preparation.

(1) Dissolve a quantity of the contents of the sealed container to produce a solution containing 0.05% w/v tigecycline.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.05% w/v of *tigecycline for system suitability EPCRS*, (impurity A) 0.00024% w/v of *tigecycline impurity B EPCRS* and 0.00024% w/v of *minocycline hydrochloride BPCRS* (impurity C).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Luna C18 is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use an autosampler temperature of 10°.

(f) Use a detection wavelength of 248 nm.

(g) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 50 volumes of *acetonitrile*, 950 volumes of a solution containing 0.46% w/v of *dipotassium hydrogen orthophosphate* and 0.10% w/v of *disodium edetate* in *water*, previously adjusted to pH 6.4 with *orthophosphoric acid*.

Mobile phase B 500 volumes of *acetonitrile*, 500 volumes of a solution containing 0.87% w/v of *dipotassium hydrogen orthophosphate* and 0.19% w/v of *disodium edetate* in *water*, previously adjusted to pH 6.4 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-42	85→57	15→43	linear gradient
42-57	57→0	43→100	linear gradient
57-60	0	100	isocratic
60-61	0→85	100→15	linear gradient
61-68	85	15	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to tigecycline (retention time about 20 minutes) are: impurity 1, about 0.55; impurity B, about 0.64; impurity A, about 0.7; impurity 2, about 1.3; impurity C, about 1.6; impurity 3, about 1.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity B and impurity A is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity B is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

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the area of any peak corresponding to impurity 2 is not greater than three times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any peak corresponding to impurity 1 or impurity 3 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Water

Not more than 3.5%, Appendix IX C, Method III. Use the contents of one vial.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a solution of 0.44% w/v of *dipotassium hydrogen orthophosphate* and 0.05% w/v of *sodium hydrogensulfite* in *water*, adjusted to pH 8.0 with 1M *potassium hydroxide*. Store solutions at 10° and protected from light.

(1) Dissolve a quantity of the mixed contents of 10 containers to produce a solution containing 0.01% w/v of tigecycline.
(2) 0.01% w/v of *tigecycline EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Prodigy ODS2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 30°.
(e) Use an autosampler temperature of 10°.
(f) Use a detection wavelength of 248 nm.
(g) Inject 20 µL of each solution.

MOBILE PHASE

140 volumes of *acetonitrile* and 860 volumes of a solution of 0.44% w/v of *dipotassium hydrogen orthophosphate* and 0.093% w/v of *disodium edetate* in *water*, previously adjusted to pH 6.2 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

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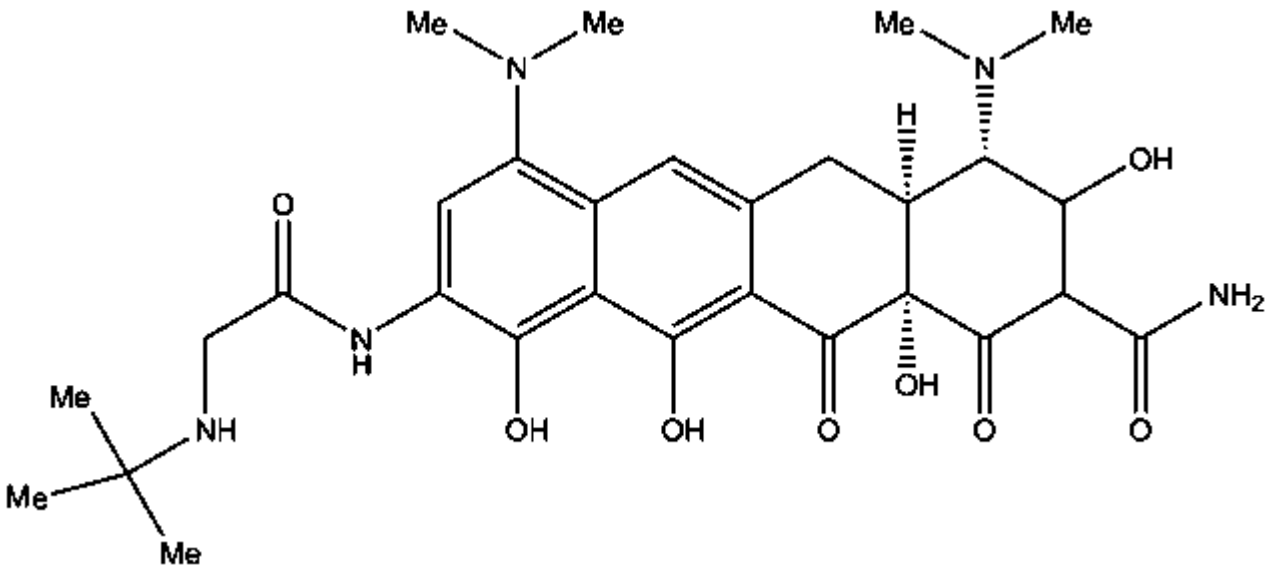
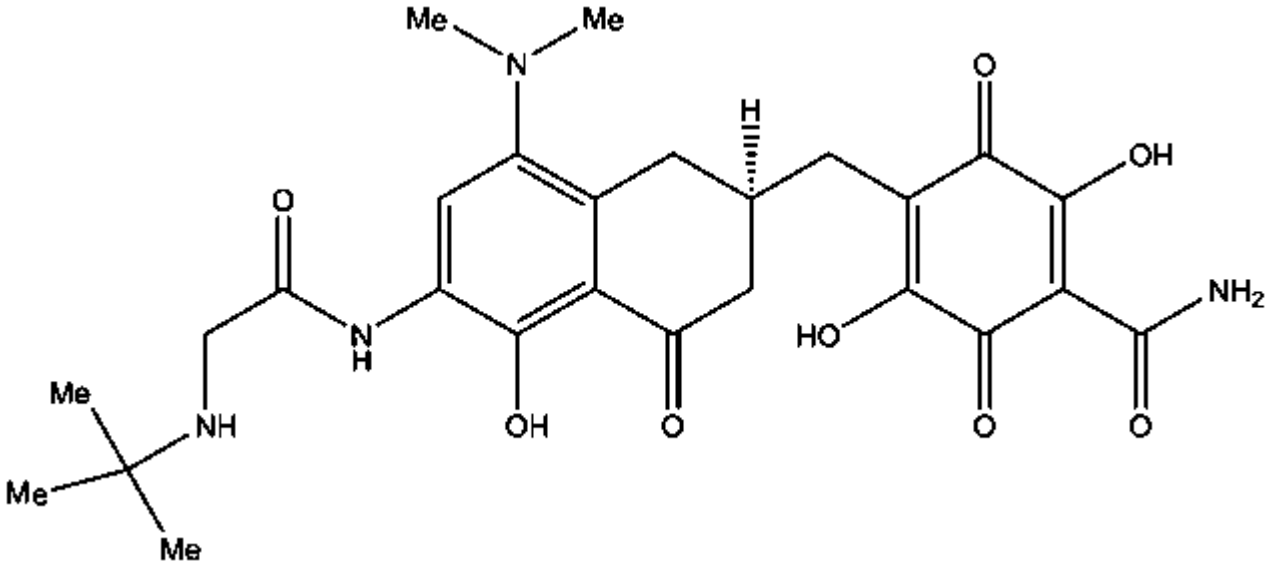
Calculate the content of $C_{29}H_{39}N_5O_8$ in a container of average content weight using the declared content of $C_{29}H_{39}N_5O_8$ in tigecycline EPCRS.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Tigecycline and the following:



1. (4*S*,4a*S*,12a*S*)-9-[(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide



2. 4-{[(2*R*)-6-[(*tert*-Butylamino)acetamido]-8-(dimethylamino)-5-hydroxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]methyl}-2,5-dihydroxy-3,6-dioxocyclohexa-1,4-diene-1-carboxamide

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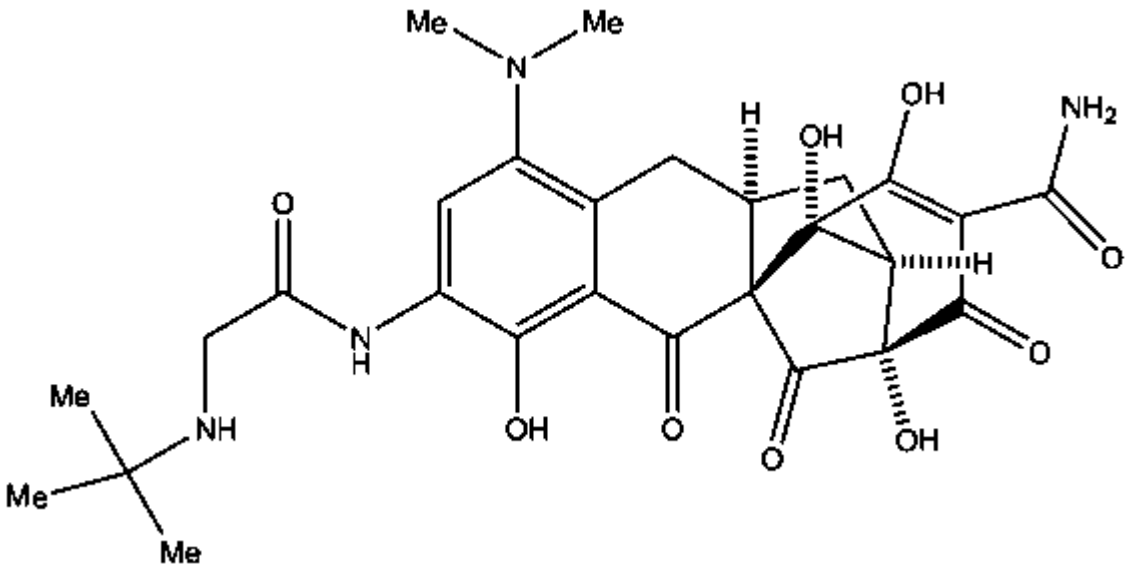

3. (1*S*,4a*R*,4b*R*,10a*R*,11a*S*)-7-[(*tert*-Butylamino)acetamido]-9-(dimethyamino)-1,4,4a,6-tetrahydroxy-2,5,12-trioxo-1,2,4a,5,10,10a,11,11a-octahydro-1,4b-methanobenzo[b]fluorene-3-carboxamide

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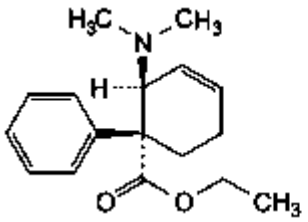
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Tilidine Hydrochloride Hemihydrate

General Notices

(Ph. Eur. monograph 1767)



and enantiomer , HCl , ½ H_2O

$C_{17}H_{24}ClNO_2,½H_2O$ 318.8 *255733-17-6*

Action and use

Opioid analgesic.

Ph Eur

DEFINITION

Ethyl (1*RS*,6*SR*)-6-(dimethylamino)-3,6-dihydro[1,1′-biphenyl]-1(2*H*)-carboxylate hydrochloride hemihydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

A suitable antioxidant may be added.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 per cent).

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tilidine hydrochloride hemihydrate CRS* or *Ph. Eur. reference spectrum of tilidine hydrochloride hemihydrate*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Acidity or alkalinity

To 20.0 mL of solution S add 0.2 mL of *0.01 M sodium hydroxide*. The pH is not less than 4.1. Add 0.4 mL of *0.01 M hydrochloric acid*. The pH is not more than 4.3.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *tilidine for system suitability CRS* (containing impurities D and E) in the mobile phase and dilute to 5 mL with the mobile phase.

Precolumn:

— *size*: *l* = 4 mm, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm).

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm).

Mobile phase Mix equal volumes of *acetonitrile for chromatography R* and a 0.98 g/L solution of *ammonium carbonate R*.

Flow rate 0.8 mL/min.

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Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time Twice the retention time of tilidine.

Identification of impurities Use the chromatogram supplied with *tilidine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities D and E; impurities D and E may be inverted in the elution order, therefore take into account the heights of the corresponding peaks in the chromatogram supplied with *tilidine for system suitabity CRS*.

Relative retention With reference to tilidine (retention time = about 15 min): impurity E = about 0.4; impurity D = about 0.5 (D and E may be inverted).

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities E and D.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity E by 0.5;

— for each impurity, use the concentration of tilidine hydrochloride hemihydrate in reference solution (a).

Limits:

— *impurity E*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

2.5 per cent to 3.1 per cent, determined on 0.300 g.

ASSAY

Dissolve 0.250 g in a mixture of 10 mL of *anhydrous acetic acid R* and 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 30.98 mg of $C_{17}H_{24}ClNO_2$.

STORAGE

Protected from light.

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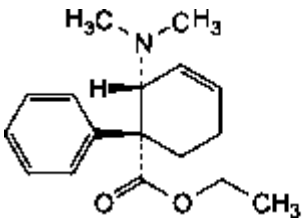
IMPURITIES

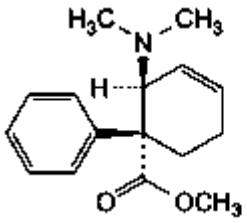
Specified impurities E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



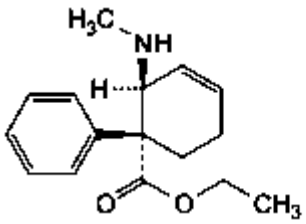
and enantiomer

A. ethyl (1*RS*,6*RS*)-6-(dimethylamino)-3,6-dihydro[1,1′-biphenyl]-1(2*H*)-carboxylate,



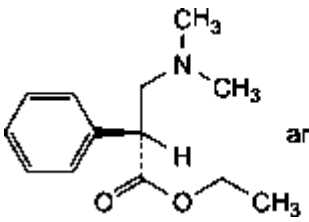
and enantiomer

B. methyl (1*RS*,6*SR*)-6-(dimethylamino)-3,6-dihydro[1,1′-biphenyl]-1(2*H*)-carboxylate,



and enantiomer

C. ethyl (1*RS*,6*SR*)-6-(methylamino)-3,6-dihydro[1,1′-biphenyl]-1(2*H*)-carboxylate,



and enantiomer

D. ethyl (2*RS*)-3-(dimethylamino)-2-phenylpropanoate,

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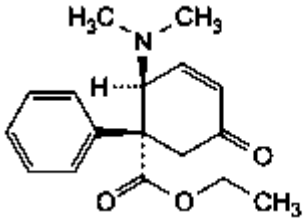

and enantiomer

E. ethyl (1*RS*,6*SR*)-6-(dimethylamino)-3-oxo-3,6-dihydro[1,1′-biphenyl]-1(2*H*)-carboxylate.

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Timolol Eye Drops

General Notices

Action and use

Beta-adrenoceptor antagonist; treatment of glaucoma.

DEFINITION

Timolol Eye Drops are a sterile solution of Timolol Maleate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of timolol, $C_{13}H_{24}N_4O_3S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Add a volume of the eye drops containing the equivalent of 50 mg of timolol to an equal volume of *carbonate buffer pH 9.7* and extract with two 40-mL quantities of *dichloromethane*. Reserve the aqueous layer for test B, dry the extracts with *anhydrous sodium sulfate*, evaporate to dryness using a rotary evaporator and dry at 60° under reduced pressure for 15 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of timolol (*RS 339*).

B. Evaporate the aqueous solution reserved in test A to about 1 mL. Add 1 mL of *bromine solution*, heat in a water bath for 10 minutes, boil, cool and add 0.1 mL of the solution to a solution of 10 mg of *resorcinol* in 3 mL of *sulfuric acid*. A bluish black colour is produced on heating in a water bath for 15 minutes.

TESTS

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the eye drops undiluted.

(2) Dilute 1 volume of the eye drops to 250 volumes with the mobile phase.

(3) Dilute 1 volume of the eye drops to 500 volumes with the mobile phase.

(4) 0.30% w/v of *maleic acid* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 295 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

42.5 volumes of 0.02M *sodium octanesulfonate* and 57.5 volumes of *methanol*, adjusted to pH 3.0 using *glacial acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak*, other than the peak corresponding to maleic acid, is not greater than the area of the peak obtained with solution (2) (0.4%);

not more than two such peaks have an area greater than that of the peak obtained with solution (3) (0.2%).

ASSAY

Dilute a volume containing the equivalent of 25 mg of timolol to 50 mL with *water*. To 5 mL add 15 mL of *carbonate buffer pH 9.7* and extract with three 20-mL quantities and one 10-mL quantity of *toluene*. Wash each extract successively with the same 10 mL volume of *carbonate buffer pH 9.7*, combine the toluene extracts and extract with four 20-mL quantities of 0.05M *sulfuric acid*. Combine the extracts, dilute to 100 mL, filter and measure the *absorbance* at the maximum at 295 nm, Appendix II B, using in the reference cell a solution prepared by treating 5 mL of *water* in the same manner, beginning at the words ‘add 15 mL...’. Calculate the content of $C_{13}H_{24}N_4O_3S$ taking 279 as the value of A(1%, 1 cm) at the maximum at 295 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of timolol.

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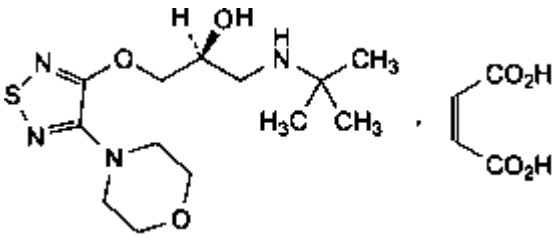
Timolol Maleate

General Notices

(Ph. Eur. monograph 0572)



$C_{17}H_{28}N_4O_7S$ 432.5 *26921-17-5*

Action and use

Beta-adrenoceptor antagonist.

For Timolol Eye Drops only: treatment of glaucoma.

Preparations

Dorzolamide and Timolol Eye Drops

Timolol Eye Drops

Timolol Tablets

Ph Eur

DEFINITION

(2*S*)-1-[(1,1-Dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (*Z*)-butenedioate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

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Soluble in water and in ethanol (96 per cent).

mp

About 199 °C, with decomposition.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (2.2.7): -6.2 to -5.7.

Dissolve 1.000 g in *1 M hydrochloric acid* and dilute to 10.0 mL with the same acid.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *timolol maleate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 5 mg of *timolol maleate CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (1:20:80 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour for 2 h.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Triturate 0.1 g with a mixture of 1 mL of *dilute sodium hydroxide solution R* and 3 mL of *water R*. Shake with 3 quantities, each of 5 mL, of *ether R*. To 0.1 mL of the aqueous layer add a solution containing 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min; no violet-red colour develops. Neutralise the remainder of the aqueous layer with *dilute sulfuric acid R* and add 1 mL of *bromine water R*. Heat on a water-bath for 15 min, then heat to boiling and cool. To 0.2 mL of this solution add a solution containing 10 mg of *resorcinol R* in 3 mL of *sulfuric acid R*. Heat on a water-bath for 15 min; a violet-red colour develops. Add 0.2 mL of a 100 g/L solution of *potassium bromide R* and heat for 5 min on a water-bath; the colour becomes violet-blue.

TESTS

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Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

pH (*2.2.3*)

3.8 to 4.3 for solution S.

Enantiomeric purity

Liquid chromatography (*2.2.29*). *Carry out the test protected from actinic light.*

Solvent mixture *methylene chloride R*, *2-propanol R* (10:30 *V/V*).

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 30 mg of *timolol maleate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 3 mg of *(R)-timolol CRS* (impurity A) in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dilute 1 mL of reference solution (a) to 100 mL with the solvent mixture. Mix 1 mL of this solution with 1 mL of reference solution (b).

Reference solution (d) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (5 µm).

Mobile phase *diethylamine R*, *2-propanol R*, *hexane R* (2:40:960 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 297 nm.

Injection 5 µL.

Elution order Impurity A is eluted first.

System suitability:

— *resolution*: minimum 4.0 between the peaks due to impurity A and the (*S*)-enantiomer in the chromatogram obtained with reference solution (c);

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— the retention times of the principal peaks due to the (*S*)-enantiomer in the chromatograms obtained with the test solution and reference solution (a) are identical.

Limit:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (1.0 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 20 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 3 mg of *timolol impurity F CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with mobile phase A (solution A). Dissolve the contents of a vial of *timolol for system suitability CRS* (containing impurities B, C and D) in 1.0 mL of solution A.

Reference solution (c) Dissolve 2 mg of the substance to be examined and 20 mg of *maleic acid R* in 10 mL of *acetonitrile R*. Evaporate 1 mL of the solution to dryness under a stream of *nitrogen R* in an amber glass vial. Heat the open vial at 105 °C for 1 h. Reconstitute the residue with 1.0 mL of mobile phase A (*in situ* preparation of impurity E).

Column:

— *size*: *l* = 0.150 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mixture of equal volumes of *methanol R* and a 4.32 g/L solution of *sodium octanesulfonate R* previously adjusted to pH 3.0 with *glacial acetic acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	97.5	2.5
10 - 11	97.5 → 70	2.5 → 30
11 - 20	70	30

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 295 nm.

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Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *timolol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D and F; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E.

Relative retention With reference to timolol (retention time = about 7.5 min): maleic acid = about 0.1; impurity D = about 0.3; impurity E = about 0.4; impurity B = about 0.7; impurity F = about 0.8; impurity C = about 2.1.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and F.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 0.6;

— *impurities B, C, D, E, F*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to maleic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 43.25 mg of $C_{17}H_{28}N_4O_7S$.

STORAGE

Protected from light.

IMPURITIES

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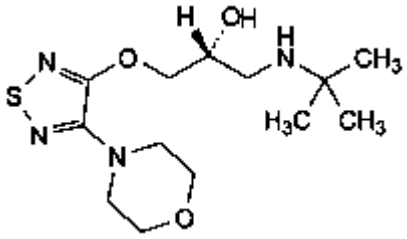
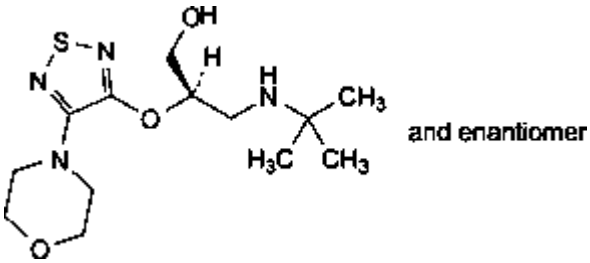
Specified impurities *A, B, C, D, E, F.*

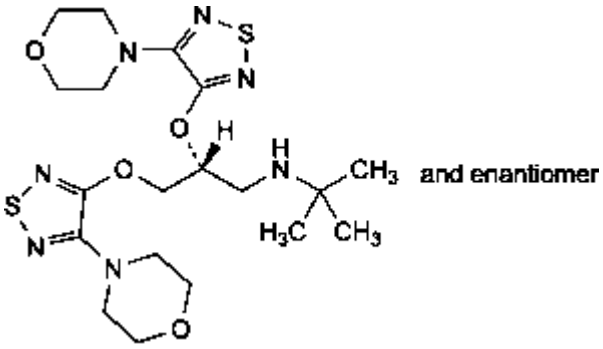
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G, H, I, J.*



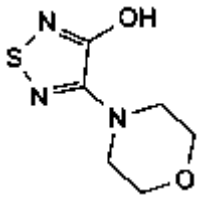
A. (2*R*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol ((*R*)-timolol),



B. (2*RS*)-3-[(1,1-dimethylethyl)amino]-2-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-1-ol,



C. (2*RS*)-*N*-(1,1-dimethylethyl)-2,3-bis[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-1-amine,



D. 4-(morpholin-4-yl)-1,2,5-thiadiazol-3-ol,

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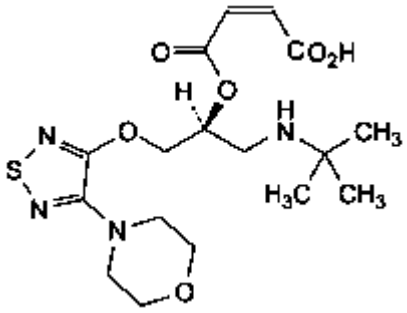
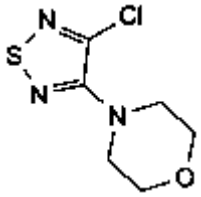
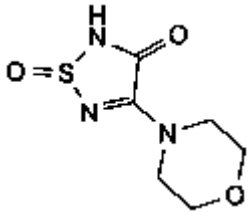


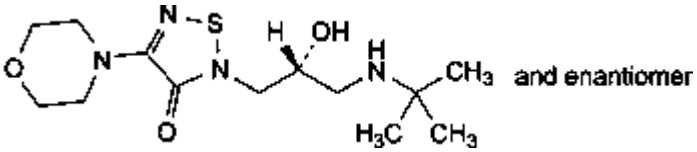
E. (2*Z*)-4-[(1*S*)-1-[[(1,1-dimethylethyl)amino]methyl]-2-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]ethoxy]-4-oxobut-2-enoic acid,



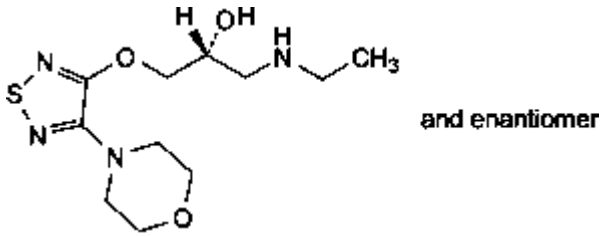
F. 4-(4-chloro-1,2,5-thiadiazol-3-yl)morpholine,



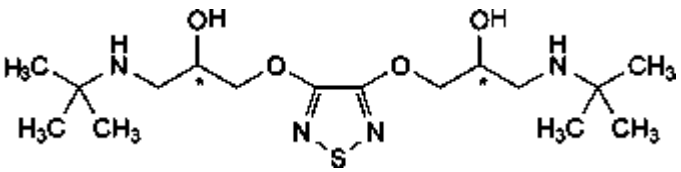
G. 4-(morpholin-4-yl)-1,2,5-thiadiazol-3(2*H*)-one 1-oxide,



H. 2-[(2*RS*)-3-[(1,1-dimethylethyl)amino]-2-hydroxypropyl]-4-(morpholin-4-yl)-1,2,5-thiadiazol-3(2*H*)-one,



I. (2*RS*)-1-(ethylamino)-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol,



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J. 1,1′-[1,2,5-thiadiazol-3,4-diylbis(oxy)]bis[3-[(1,1-dimethylethyl)amino]propan-2-ol].

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Timolol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Timolol Tablets contain Timolol Maleate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of timolol maleate, $C_{13}H_{24}N_4O_3S,C_4H_4O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 30 mg of Timolol Maleate with 2 mL of 0.1M *hydrochloric acid* until a smooth paste is formed, add 5 mL of *methanol* and continue shaking for about 20 minutes. Add sufficient *methanol* to produce 50 mL, centrifuge until a clear solution is produced and use the supernatant liquid.

(2) Dissolve, with shaking, 60 mg of *timolol maleate BPCRS* in 4 mL of 0.1M *hydrochloric acid* and add sufficient *methanol* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}* (Analtech Uniplates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia*, 19 volumes of *methanol* and 80 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

Disregard any spot remaining on the line of application (maleic acid).

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B. To a quantity of the powdered tablets containing 70 mg of Timolol Maleate add 20 mL of *carbonate buffer pH 9.7* and extract with two 40-mL quantities of *dichloromethane*. Filter the aqueous layer and evaporate to about 1 mL. Add 1 mL of *bromine solution*, heat in a water bath for 10 minutes, boil, cool and add 0.1 mL of the solution to a solution of 10 mg of *resorcinol* in 3 mL of *sulfuric acid*. A bluish black colour is produced on heating in a water bath for 15 minutes.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Timolol Maleate with 10 mL of the mobile phase for 10 minutes and filter.
(2) Dilute 1 volume of solution (1) to 250 volumes.
(3) Dilute 1 volume of solution (1) to 500 volumes.
(4) 0.30% w/v of *maleic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 295 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

42.5 volumes of 0.02M *sodium octanesulfonate* and 57.5 volumes of *methanol*, adjusted to pH 3.0 using *glacial acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak*, other than the peak corresponding to maleic acid, is not greater than the area of the peak obtained with solution (2) (0.4%);

not more than two such peaks have an area greater than that of the peak obtained with solution (3) (0.2%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 15 mg of Timolol Maleate add 25 mL of 0.05M *sulfuric acid*, shake for 20 minutes and centrifuge until clear. Add 5 mL of the resulting supernatant liquid to 15 mL of *carbonate buffer pH 9.7* and extract with three 20-mL quantities and one 10-mL quantity of *toluene*. Wash each extract successively with the same 10-mL volume of *carbonate buffer pH 9.7*, combine the toluene extracts and extract with four 20-mL quantities of 0.05M *sulfuric acid*. Combine the acid extracts, dilute to 100 mL, filter and measure the *absorbance* at the maximum at 295 nm, Appendix II B, using in the reference cell a solution prepared by treating a

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mixture of 5 mL of *water* and 15 mL of *carbonate buffer pH 9.7* in the same manner. Calculate the content of $C_{13}H_{24}N_4O_3S,C_4H_4O_4$ taking 204 as the value of A(1%, 1 cm) at the maximum at 295 nm.

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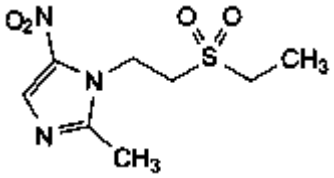
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Tinidazole

General Notices

(Ph. Eur. monograph 1051)



$C_8H_{13}N_3O_4S$ 247.3 *19387-91-8*

Action and use

Antiprotozoal; antibacterial.

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DEFINITION

1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Almost white or pale yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone and in methylene chloride, sparingly soluble in methanol.

IDENTIFICATION

First identification: A, B.

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Second identification: A, C.

A. Melting point (2.2.14): 125 °C to 128 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *tinidazole CRS*.

C. To about 10 mg add about 10 mg of *zinc powder R*, 0.3 mL of *hydrochloric acid R* and 1 mL of *water R*. Heat in a water-bath for 5 min and cool. The solution gives the reaction of primary aromatic amines (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Dissolve 1.0 g in *acetone R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Protect solutions from light*.

Test solution Dissolve 10.0 mg of the substance to be examined in 10.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *tinidazole impurity A CRS* and 5.0 mg of *tinidazole impurity B CRS* in 10.0 mL of *methanol R* and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Regular column conditioning by subsequent flushing with 50 mL of *water for chromatography R*, 100 mL of *methanol R*, 25 mL of *water for chromatography R* and 100 mL of the mobile phase is recommended.

Mobile phase *acetonitrile R*, *methanol R*, *water for chromatography R* (10:20:70 *V/V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 320 nm.

Injection 20 µL.

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Run time 1.5 times the retention time of tinidazole.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to tinidazole (retention time = about 6 min): impurity A = about 0.6; impurity B = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 24.73 mg of $C_8H_{13}N_3O_4S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B*.

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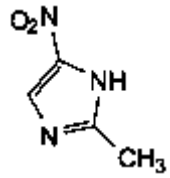
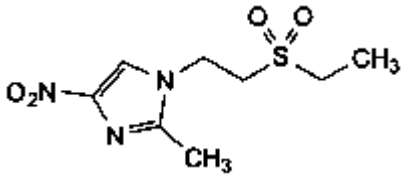


A. 2-methyl-5-nitro-1*H*-imidazole,



B. 1-[2-(ethylsulfonyl)ethyl]-2-methyl-4-nitro-1*H*-imidazole.

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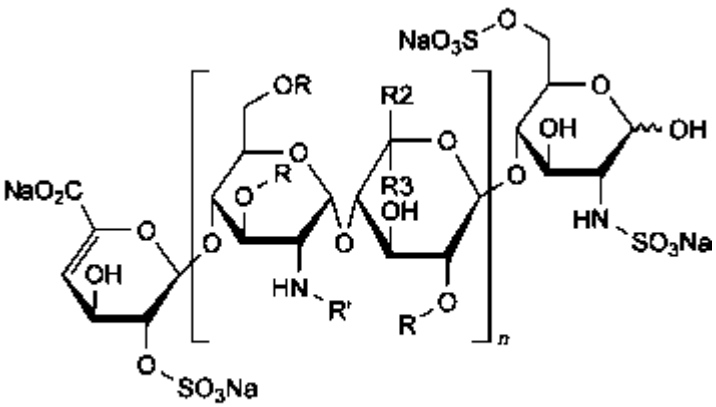
Tinzaparin Sodium

General Notices

(Ph. Eur. monograph 1271)



n = 1 to 25 , R = H or SO_3Na , R' = H or SO_3Na or CO-CH_3
R2 = H and R3 = CO_2Na or R2 = CO_2Na and R3 = H

Action and use

Low molecular weight heparin.

Preparation

Tinzaparin Sodium Injection

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DEFINITION

Tinzaparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by controlled enzymatic depolymerisation of heparin from porcine intestinal mucosa using heparinase from *Flavobacterium heparinum*. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain.

Tinzaparin sodium complies with the monograph on Low-molecular-mass heparins (0828) with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 5500 and 7500 with a characteristic value of about 6500.

The degree of sulfatation is 1.8 to 2.5 per disaccharide unit.

The potency is not less than 70 IU and not more than 120 IU of anti-factor Xa activity per milligram calculated with reference to the dried substance. The ratio of the anti-factor Xa activity to anti-factor IIa activity is between 1.5 and 2.5.

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IDENTIFICATION

Carry out identification test A as described in the monograph *Low-molecular-mass heparins (0828)* using *tinzaparin sodium CRS*.

Carry out identification test C as described in the monograph *Low-molecular-mass heparins (0828)*. The following requirements apply.

The mass-average relative molecular mass ranges between 5500 and 7500. The mass percentage of chains lower than 2000 is not more than 10.0 per cent. The mass percentage of chains between 2000 and 8000 ranges between 60.0 and 72.0 per cent. The mass percentage of chains above 8000 ranges between 22.0 and 36.0 per cent.

TESTS

Appearance of solution

Dissolve 1.0 g in 10 mL of *water R*. The solution is clear (*2.2.1*) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*)

Absorbance (*2.2.25*)

Dissolve 50.0 mg in 100 mL of *0.01 M hydrochloric acid*. The specific absorbance, measured at 231 nm and calculated with reference to the dried substance, is 8.0 to 12.5.

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Tinzaparin Sodium Injection

General Notices

Action and use

Low molecular weight heparin.

DEFINITION

Tinzaparin Sodium Injection is a sterile solution of Tinzaparin Sodium in Water for Injections.

PRODUCTION

The final product is produced by methods of manufacturing designed to ensure that substances lowering blood pressure are not introduced and to ensure freedom from contamination by over-sulfated glycosaminoglycans. The production method is validated to demonstrate that the product if tested, would comply with the test for Related substances given below.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Activity

The estimated activity for anti-factor Xa is not less than 90% and not more than 110% of the stated activity.

The ratio of anti-factor Xa to anti-factor IIa is not less than 1.5 and not more than 2.5.

IDENTIFICATION

A. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions in the mobile phase.

(1) Dilute the injection to contain 950 units of anti-factor Xa per mL.

(2) 1% w/v of *heparin low-molecular-mass for calibration EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (30 cm × 7.8 mm) packed with appropriate porous silica beads (5 µm) with a fractionation range for proteins of approximately 15 000 to 100 000 Da (Tosoh Bioscience TSK-GEL G2000SWXL or TSK-GEL G3000SWXL are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) For detection use a differential refractometer (RI).

(f) Inject 25 µL of each solution.

To calibrate, inject 25 µL of solution (2) and record the chromatogram for a suitable period of time, ensuring complete elution of sample, salt and solvent peaks. Calculate the total area under the RI curve (ΣRI) by numerical integration over the range of interest (i.e. excluding salt

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and solvent peaks at the end of the chromatogram as well as the artefact peak (*), that if present elutes at the same retention time as the peak that would be obtained after injection of sodium sulfate) as shown in Figure 1.

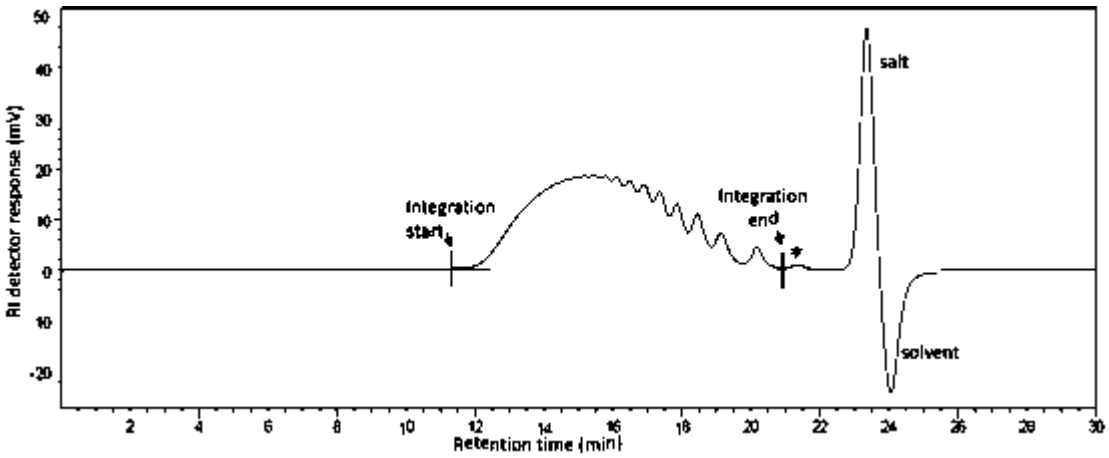

Figure 1 - Example chromatogram of a low-molecular-mass heparin sample analysed using the method described in identification test A indicating peak integration

Calculate the area under the curve up to each point as a percentage of the total area.

Using the leaflet supplied with *heparin low-molecular-mass for calibration EPCRS*, identify those points in the chromatogram for which the percentage of the total area under the curve is closest to the percentage mass fractions listed in the Broad Standard Table, and assign the molecular mass in the table to the corresponding retention time in the chromatogram. A calibration curve for the chromatographic system is derived by fitting a suitable mathematical relationship to the set of retention times and logarithms of the molecular masses. A polynomial of the 3rd degree is recommended.

Inject 25 µL of the test solution and record the chromatogram for a sufficient period of time to ensure complete elution of sample, salt and solvent peaks.

The mass-average relative molecular mass is defined by the following expression:

$$\frac{\sum \left(\mathrm{RI}_i M_i \right)}{\sum \mathrm{RI}_i}$$

where:

RI_i	=	Refractive Index of substance eluting in the fraction *i* (proportional to the mass of the substance);
M_i	=	relative molecular mass corresponding to fraction *i*.

MOBILE PHASE

0.77% w/v of *ammonium acetate*.

CONFIRMATION

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The mass-average relative molecular mass ranges between 5500 and 7500. The mass percentage of chains lower than 2000 is not more than 10.0%. The mass percentage of chains between 2000 and 8000 ranges between 60.0% and 72.0%. The mass percentage of chains above 8000 ranges between 22.0% and 36.0%.

B. The ratio of anti-factor Xa activity to anti-factor IIa activity, determined as described under Assay, is not less than 1.5 and not more than 2.5.

C. Yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Clarity and colour of solution

The solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* Y_5 or BY_5, Appendix IV B, Method II.

Acidity or alkalinity

pH, 5.5 to 8.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions. Solutions (3) to (6) are stable at room temperature for 24 hours.

(1) Dilute the injection with *water for chromatography* to give 5000 IU per mL. Mix using a vortex mixer until dissolution is complete.

(2) Mix 500 µL of solution (1) and 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.

(3) Dissolve 0.25 g of *heparin for physico-chemical analysis EPCRS* in *water for chromatography* and dilute to 2.0 mL with the same solvent. Mix using a vortex mixer until dissolution is complete.

(4) Add 1200 µL of solution (3) to 300 µL of *dermatan sulfate and over-sulfated chondroitin sulfate EPCRS*. Mix using a vortex mixer to homogenise.

(5) Add 400 µL of solution (3) to 100 µL of *water for chromatography* and mix using a vortex mixer. Add 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.

(6) To 500 µL of solution (4), add 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 2 mm) packed with *anion-exchange resin* (9 µm) (Dionex Ionpac AS11-HC is suitable) and a stainless steel pre-column (5 cm × 2 mm) packed with *anion-exchange resin R* (13 µm) (Dionex Ionpac AG11-HC is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.22 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 202 nm.

(f) Inject 20 µL of solutions (2), (5) and (6).

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MOBILE PHASE

Mobile phase A 0.040% w/v of *sodium dihydrogen orthophosphate* in *water for chromatography* adjusted to pH 3.0 with *dilute orthophosphoric acid*.

Mobile phase B 0.040% w/v of *sodium dihydrogen orthophosphate* and 14% w/v of *sodium perchlorate* in *water for chromatography*, adjusted to pH 3.0 with *dilute orthophosphoric acid*, filtered and degassed.

Equilibrate the column with the mobile phase in the initial gradient ratio for at least 15 minutes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	75	25	isocratic
10-35	75→0	25→100	linear gradient
35-40	0	100	isocratic
40-45	0→75	100→25	linear gradient
45-60	75	25	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to heparin (retention time about 26 minutes) are: dermatan sulfate and chondroitin sulfate, about 0.9; over-sulfated chondroitin sulfate, 1.3.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (5), no peak is present at the retention time of heparin;

in the chromatogram obtained with solution (6), the *resolution* between the peaks due to dermatan sulfate/chondroitin sulfate and over-sulfated chondroitin sulfate is at least 3.0.

LIMITS

In the chromatogram obtained with solution (2):

the area of any peak due to dermatan sulfate/chondroitin sulfate is not greater than 0.4 times the area of the corresponding peak in the chromatogram obtained with solution (6) (2.0%);

no peaks other than the peak due to dermatan sulfate and chondroitin sulfate are detected.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 0.01 IU per International Unit of anti-Xa activity.

ASSAY

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The anticoagulant activity of low-molecular-mass heparins is determined *in vitro* by two assays which determine its ability to accelerate the inhibition of factor Xa (anti-Xa assay) and thrombin, factor IIa (anti-IIa assay), by antithrombin III.

The International Units for anti-Xa and anti-IIa activity are the activities contained in a stated amount of the International Standard for low-molecular-mass heparin.

Heparin low-molecular-mass for assay EPBRP, calibrated in International Units by comparison with the International Standard using the two assays given below, is used as the reference preparation.

Provided the equivalence with the below methods is demonstrated, the volumes below can be adjusted in order to use automated methods.

For anti-factor Xa activity

Test solutions (1) to *(4)* Prepare a series of 4 dilutions of the injection being examined in *tris-chloride buffer pH 7.4;* the concentration range of the solutions should be within 0.025 IU to 0.2 IU of anti-factor Xa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Reference solutions (1) to *(4)* Prepare a series of 4 dilutions of the reference preparation of low-molecular-mass heparin in *tris-chloride buffer pH 7.4;* the concentration range of the solutions should be within 0.025 IU to 0.2 IU of anti-factor Xa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Label 16 tubes in duplicate: T1, T2, T3, T4 for the dilutions of the injection being examined and R1, R2, R3, R4 for the dilutions of the reference preparation. To each tube add 50 µL of *antithrombin III solution R1* and 50 µL of the appropriate dilution of the injection being examined, or the reference preparation. After each addition, mix but do not allow bubbles to form. Treating the tubes in the order R1, R2, R3, R4, T1, T2, T3, T4, T1, T2, T3, T4, R1, R2, R3, R4, allow to equilibrate at 37° (in a water-bath or heating block) for 1 minute and add to each tube 100 µL of *bovine factor Xa solution*. Incubate for exactly 1 minute and add 250 µL of *chromophore substrate R1*. Stop the reaction after exactly 4 minutes by adding 375 µL of *acetic acid*. Transfer the mixtures to semi-micro cuvettes and measure the *absorbance* at 405 nm, Appendix II B, using a suitable reading device. Determine the blank amidolytic activity at the beginning and at the end of the procedure in a similar manner, using *tris-chloride buffer pH 7.4* instead of the reference and test solutions; the 2 blank values do not differ significantly. Calculate the regression of the absorbance on log concentrations of the solutions of the injection being examined and of the reference preparation of low-molecular-mass heparins and calculate the potency of the substance being examined in International Units of anti-factor Xa activity per mL using the usual statistical methods for parallel-line assays.

For anti-factor IIa activity

Test solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the injection being examined in *tris-chloride buffer pH 7.4*; the concentration range should be within 0.015 IU to 0.075 IU of anti-factor IIa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Reference solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the reference preparation of low-molecular-mass heparin in *tris-chloride buffer pH 7.4*; the concentration range should be within 0.015 IU to 0.075 IU of anti-factor IIa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Label 16 tubes in duplicate: T1, T2, T3, T4 for the dilutions of the injection being examined and R1, R2, R3, R4 for the dilutions of the reference preparation. To each tube add 50 µL of *antithrombin III solution R2* and 50 µL of the appropriate dilution of the injection being

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examined or the reference preparation. After each addition, mix but do not allow bubbles to form. Treating the tubes in the order R1, R2, R3, R4, T1, T2, T3, T4, T1, T2, T3, T4, R1, R2, R3, R4, allow to equilibrate at 37° (in a water-bath or heating block) for 1 minute and add to each tube 100 µL of *human thrombin solution*. Incubate for exactly 1 minute and add 250 µL of *chromophore substrate R2*. Stop the reaction after exactly 4 minutes by adding 375 µL of *acetic acid*. Transfer the mixtures to semi-micro cuvettes and measure the *absorbance* at 405 nm, Appendix II B, using a suitable reading device. Determine the blank amidolytic activity at the beginning and at the end of the procedure in a similar manner, using *tris-chloride buffer pH 7.4* instead of the reference and test solutions; the 2 blank values do not differ significantly. Calculate the regression of the absorbance on log concentrations of the solutions of the substance to be examined and of the reference preparation of low-molecular-mass heparins, and calculate the potency of the substance being examined in International Units of anti-factor IIa activity per mL using the usual statistical methods for parallel-line assays.

LABELLING

The label states the number of IU (Units) of anti-factor Xa and anti-factor IIa per unit volume.

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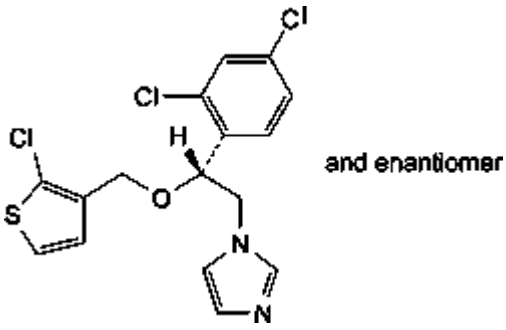
Tioconazole

General Notices

(Ph. Eur. monograph 2074)



$C_{16}H_{13}Cl_3N_2OS$ 387.7 *65899-73-2*

Action and use

Antifungal.

Preparation

Tioconazole Nail Solution

Ph Eur

DEFINITION

1-[(2*RS*)-2-[(2-Chlorothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Very slightly soluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of tioconazole*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *tioconazole for system suitability CRS* in the mobile phase and dilute to 2.5 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 170 m^2/g, a pore size of 12 nm and a carbon loading of 10 per cent.

Mobile phase Mix 1 volume of a 1.7 g/L solution of *tetrabutylammonium dihydrogen phosphate R* previously adjusted to pH 7.4 with *dilute ammonia R2* and 3 volumes of *methanol R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 218 nm.

Injection 20 µL.

Run time 2.5 times the retention time of tioconazole.

System suitability Reference solution (b):

— *resolution*: minimum 1.0 between the peaks due to impurity B and impurity C (locate impurities A, B and C by comparison with the chromatogram provided with *tioconazole for system suitability CRS*).

Limits:

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— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.7; impurity C = 1.7.

— *impurities A, B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 38.77 mg of $C_{16}H_{13}Cl_3N_2OS$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B, C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D.

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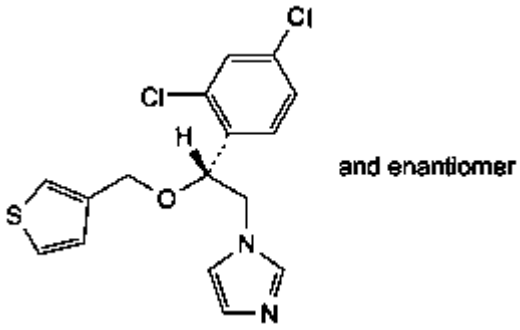
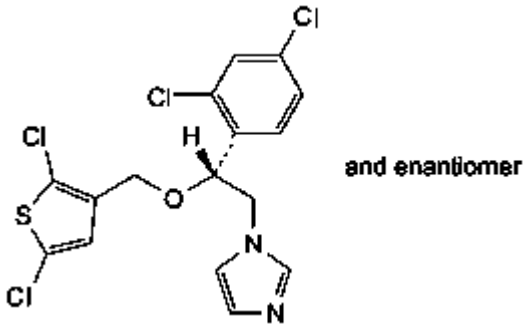
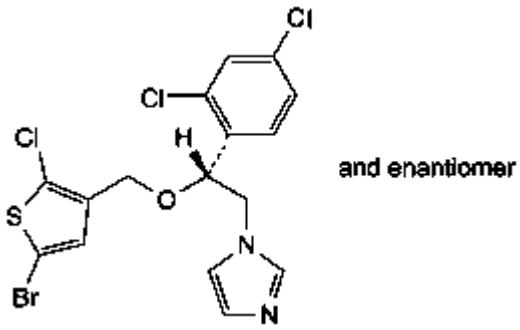


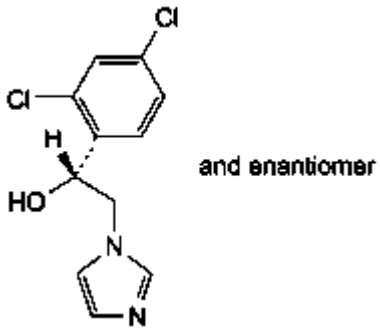
A. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[(thiophen-3-yl)methoxy]ethyl]-1*H*-imidazole,



B. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[(2,5-dichlorothiophen-3-yl)methoxy]ethyl]-1*H*-imidazole,



C. 1-[(2*RS*)-2-[(5-bromo-2-chlorothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole,



D. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol.

Ph Eur

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Tioconazole Nail Solution

General Notices

Tioconazole Cutaneous Solution

Action and use

Antifungal.

DEFINITION

Tioconazole Nail Solution is a *cutaneous solution*. It contains Tioconazole in a suitable vehicle.

The nail solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of tioconazole, $C_{16}H_{13}Cl_3N_2OS$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the nail solution containing 28 mg of Tioconazole to 10 mL with *methanol*.

(2) 0.28% w/v solution of *tioconazole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel 60 F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

The upper layer obtained from a mixture of 40 volumes of *glacial acetic acid*, 40 volumes of *water* and 80 volumes *4-methylpentan-2-one*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the test for Related substances, the chromatogram obtained with solution (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (5).

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TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the nail solution containing 20 mg of Tioconazole to 10 mL.

(2) Dilute 1 volume of solution (1) to 10 volumes.

(3) Dilute 1 volume of solution (2) to 20 volumes.

(4) 0.20% w/v of *tioconazole impurity standard BPCRS*.

(5) 0.02% w/v of *tioconazole BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 218 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of 0.005M *tetrabutylammonium dihydrogen orthophosphate* adjusted to pH 7.4 with 2M *ammonia* and 4 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *tioconazole impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the areas of any peaks corresponding to tioconazole impurities A, B and C are not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5% of each).

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using a quantity of the nail solution containing 0.28 g of Tioconazole. Each mL of *0.1M perchloric acid VS* is equivalent to 38.77 mg of $C_{16}H_{13}Cl_3N_2OS$. Determine the *weight per mL* of the nail solution, Appendix V G, and calculate the content of $C_{16}H_{13}Cl_3N_2OS$, weight in volume.

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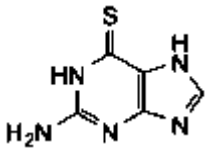
Tioguanine

General Notices



$C_5H_5N_5S$ 167.2 *154-42-7*

Action and use

Purine analogue; cytostatic.

Preparation

Tioguanine Tablets

DEFINITION

Tioguanine is 2-aminopurine-6(1*H*)-thione. It contains not less than 96.0% and not more than 102.0% of $C_5H_5N_5S$, calculated with reference to the dried substance.

CHARACTERISTICS

A pale yellow, crystalline powder.

Practically insoluble in *water* and in *ethanol (96%)*. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

Heat a suitable quantity at 105° at a pressure not exceeding 0.7 kPa for 5 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of tioguanine *(RS 340)*.

TESTS

Phosphate

To 0.5 g add 2 mL of 5M *sulfuric acid* and heat on a water bath for 5 minutes. Add, dropwise, 5 mL of *nitric acid* and continue heating until a clear solution is obtained. Cool and add 10 mL of *water* and 0.75 mL of a solution prepared by dissolving 8.3 g of *ammonium molybdate* in 40 mL of *water* and adding 33 mL of 5M *sulfuric acid* and sufficient *water* to produce 100 mL. Add 1.0 mL of *strong*

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aminohydroxynaphthalenesulfonic acid solution, mix and dilute to 25 mL with *water*. Measure the *absorbance* of the resulting solution at 820 nm, Appendix II B, using in the reference cell a solution prepared in the same manner but omitting the substance being examined. The absorbance is not more than that obtained by treating 1.5 mL of *phosphate standard solution (100 ppm PO_4)* in the same manner, beginning at the words 'add 10 mL of *water* ...'.

Free sulfur

Dissolve 50 mg in 5 mL of 1M *sodium hydroxide*. The solution is *clear*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve 40 mg of the substance being examined in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 2 volumes with the mobile phase.
(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 1 volume of 0.01M *sodium hydroxide* and 9 volumes of the mobile phase. Further dilute 1 volume of the resulting solution to 5 volumes with the same solvent mixture.
(3) Dissolve 12 mg of *guanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.
(4) Dissolve 40 mg each of *tioguanine BPCRS* and *guanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Atlantis dC18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 248 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

0.05M *anhydrous sodium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to tioguanine and guanine is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to guanine is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

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the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Loss on drying

When dried at 105° at a pressure not exceeding 0.7 kPa for 5 hours, loses not more than 1.0% of its weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve 40 mg of the substance being examined in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(2) Dissolve 40 mg of *tioguanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of this solution to 10 volumes with the mobile phase.
(3) Dissolve 40 mg each of *tioguanine BPCRS* and *guanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to tioguanine and guanine is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_5H_5N_5S$ in the substance being examined from the chromatograms obtained and using the declared content of $C_5H_5N_5S$ in *tioguanine BPCRS*.

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Tioguanine Tablets

General Notices

Action and use

Purine analogue; cytostatic.

DEFINITION

Tioguanine Tablets contain Tioguanine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tioguanine, $C_5H_5N_5S$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Tioguanine with 10 mL of 1M *sodium hydroxide* and filter. Acidify the filtrate with *hydrochloric acid*, filter, dissolve the precipitate in 13.5M *ammonia*, evaporate to dryness and dry the residue at 105° at a pressure not exceeding 0.7 kPa for 5 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of tioguanine (*RS 340*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of *water* at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw 10 mL of the medium and filter. To 2 mL of the filtrate add 2 mL of 1M *hydrochloric acid* and dilute to 20 mL with *water*. Measure the *absorbance* of the solution at the maximum at 348 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *tioguanine BPCRS* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of tioguanine, $C_5H_5N_5S$, in the medium from the absorbances obtained and using the declared content of $C_5H_5N_5S$ in *tioguanine BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 40 mg of Tioguanine in 100 mL of 0.01M *sodium hydroxide* with the aid of ultrasound for 5 minutes. Mix and filter. Dilute 1 volume of the filtrate to 2 volumes with mobile phase.
(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 1 volume of 0.01M *sodium hydroxide* and 9 volumes of mobile phase. Further dilute 1 volume of this solution to 5 volumes with the same solvent mixture.
(3) Dissolve 16 mg of *guanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.
(4) Dissolve 40 mg each of *tioguanine BPCRS* and *guanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of this solution to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Atlantis dC18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 248 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

0.05M *anhydrous sodium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid (85%)*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to tioguanine and guanine is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to guanine is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

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Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 40 mg of Tioguanine add 70 mL of 0.01M *sodium hydroxide*, shake for 15 minutes and dilute to 100 mL with the same solvent. Filter and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(2) Dissolve 40 mg of *tioguanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(3) Dissolve 40 mg each of *tioguanine BPCRS* and *guanine BPCRS* in 100 mL of 0.01M *sodium hydroxide* and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to tioguanine and guanine is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_5H_5N_5S$ in the tablets from the chromatograms obtained and using the declared content of $C_5H_5N_5S$ in *tioguanine BPCRS*.

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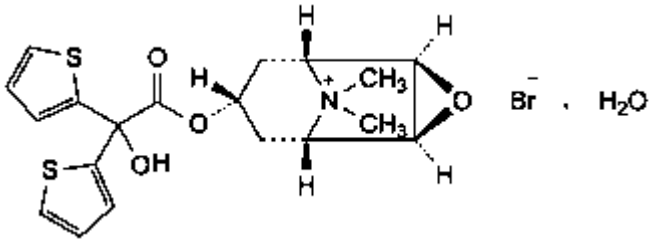
Tiotropium Bromide Monohydrate

General Notices

(Ph. Eur. monograph 2420)



$C_{19}H_{22}BrNO_4S_2,H_2O$ 490.4 *411207-31-3*

Action and use

Anticholinergic (antimuscarinic) bronchodilator.

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DEFINITION

(1*R*,2*R*,4*S*,5*S*,7*s*)-7-[[Hydroxy[di(thiophen-2-yl)]acetyl]oxy]-9,9-dimethyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]nonan-9-ium bromide monohydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white powder or crystals.

Solubility

Sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *tiotropium bromide monohydrate CRS*.

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B. It gives reaction (a) of bromides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 0.2 g in water R and dilute to 20 mL with the same solvent.

Impurities G and H

Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use.*

Solvent mixture Dilute 1 volume of a 103 g/L solution of hydrochloric acid R to 100 volumes with methanol R.

Test solution Dissolve 0.40 g of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of tiotropium impurity mixture CRS (containing impurities G and H) in 1.0 mL of the solvent mixture.

Reference solution (b) Mix 0.1 mL of the test solution with 0.1 mL of reference solution (a).

Plate TLC silica gel F_{254} plate R (2-10 µm).

Mobile phase water R, *anhydrous formic acid R*, acetonitrile R, methylene chloride R (10:15:35:50 *V/V/V/V*).

Application 10 µL of the test solution and reference solution (a), and 20 µL of reference solution (b).

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots are clearly visible (about 15 min); remove the plate and examine immediately.

Retardation factors Impurity G = about 0.33; impurity H = about 0.38; tiotropium = about 0.64.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Limits:

— *impurity G*: any spot due to impurity G is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity H*: any spot due to impurity H is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.1 per cent).

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Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase B and dilute to 25.0 mL with mobile phase B.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase B.

Reference solution (b) Dissolve 4 mg of *tiotropium for system suitability 1 CRS* (containing impurity C) in 2.0 mL of mobile phase B.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *propylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *sodium methanesulfonate R* and 5.0 g of *potassium dihydrogen phosphate R* in about 980 mL of *water R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R*, mobile phase A (10:40:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	90	10
3 - 17	90 → 80	10 → 20
17 - 28	80 → 25	20 → 75
28 - 30	25	75

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *tiotropium for system suitability 1 CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to tiotropium (retention time = about 15 min): impurity C = about 1.2.

System suitability Reference solution (b):

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— *resolution*: minimum 2.4 between the peaks due to tiotropium and impurity C.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

2.5 per cent to 4.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

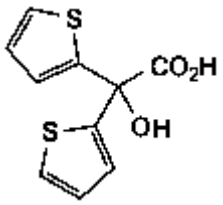
Dissolve 0.35 g in 100 mL of *water R*. Add 10 mL of *dilute nitric acid R2*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 47.24 mg of $C_{19}H_{22}BrNO_4S_2$.

IMPURITIES

Specified impurities G, H.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, E, F.



A. hydroxy[di(thiophen-2-yl)]acetic acid,

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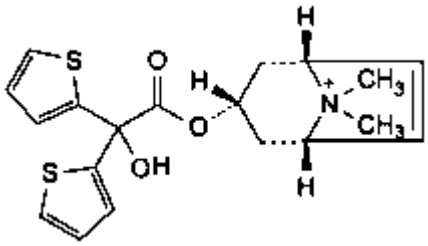
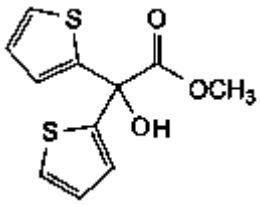
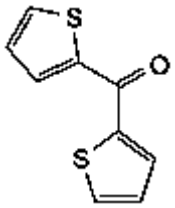


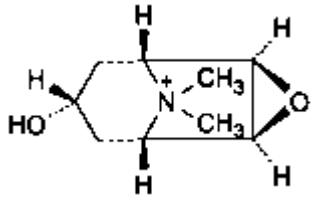
C. (1*R*,3*s*,5*S*)-3-[[hydroxy[di(thiophen-2-yl)]acetyl]oxy]-8,8-dimethyl-8-azabicyclo[3.2.1]oct-6-en-8-ium,



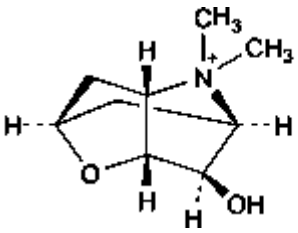
E. methyl hydroxy[di(thiophen-2-yl)]acetate,



F. di(thiophen-2-yl)methanone,



G. (1*R*,2*R*,4*S*,5*S*,7*s*)-7-hydroxy-9,9-dimethyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]nonan-9-ium,



H. (1*s*,3*RS*,4*RS*,5*RS*,7*SR*)-4-hydroxy-6,6-dimethyl-2-oxa-6-azatricyclo[3.3.1.$0^{3,7}$]nonan-6-ium.

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This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Titanium Dioxide

General Notices

(Ph. Eur. monograph 0150)

TiO_2 79.9 *13463-67-7*

Action and use

Protective; excipient.

Preparation

Titanium Ointment

Ph Eur

DEFINITION

Content

98.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water. It does not dissolve in dilute mineral acids but dissolves slowly in hot concentrated sulfuric acid.

IDENTIFICATION

A. When strongly heated, it becomes pale yellow; the colour disappears on cooling.

B. To 5 mL of solution S (see Tests) add 0.1 mL of *strong hydrogen peroxide solution R*. An orange-red colour appears.

C. To 5 mL of solution S add 0.5 g of *zinc R* in granules. After 45 min, the mixture has a violet-blue colour.

TESTS

Solution S

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Mix 0.500 g (*m* g) and 5 g of *anhydrous sodium sulfate R* in a 300 mL long-necked combustion flask. Add 10 mL of *water R* and mix. Add 10 mL of *sulfuric acid R* and boil vigorously, with the usual precautions, until a clear solution is obtained. Cool, add slowly a cooled mixture of 30 mL of *water R* and 10 mL of *sulfuric acid R*, cool again and dilute to 100.0 mL with *water R*.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Acidity or alkalinity

Shake 5.0 g with 50 mL of *carbon dioxide-free water R* for 5 min. Centrifuge or filter until a clear solution is obtained. To 10 mL of the solution add 0.1 mL of *bromothymol blue solution R1*. Not more than 1.0 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Water-soluble substances

Maximum 0.5 per cent.

To 10.0 g add a solution of 0.5 g of *ammonium sulfate R* in 150 mL of *water R* and boil for 5 min. Cool, dilute to 200 mL with *water R* and filter until a clear solution is obtained. Evaporate 100 mL of the solution to dryness in a tared evaporating dish and ignite. The residue weighs a maximum of 25 mg.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20. Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Antimony	20
Arsenic	1
Barium	20
Lead	5

Iron

Maximum 200 ppm.

To 8 mL of solution S add 4 mL of *water R*. Mix and add 0.05 mL of *bromine water R*. Allow to stand for 5 min and remove the excess of bromine with a current of air. Add 3 mL of *potassium thiocyanate solution R*. Any colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 4 mL of *iron standard solution (2 ppm Fe) R* and 8 mL of a 200 g/L solution of *sulfuric acid R*.

ASSAY

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To 300 g of *zinc R* in granules (710) (*2.1.4*) add 300 mL of a 20 g/L solution of *mercuric nitrate R* and 2 mL of *nitric acid R*, shake for 10 min and wash with *water R*. Pack the amalgamated zinc into a glass tube about 400 mm long and about 20 mm in diameter fitted with a tap and a filter plate. Pass through the column 100 mL of *dilute sulfuric acid R* followed by 100 mL of *water R*, making sure that the amalgam is always covered with liquid. Pass slowly at a rate of about 3 mL/min through the column a mixture of 100 mL of *dilute sulfuric acid R* and 100 mL of *water R* followed by 100 mL of *water R*. Collect the eluate in a 500 mL conical flask containing 50.0 mL of a 150 g/L solution of *ferric ammonium sulfate R* in a mixture of 1 volume of *sulfuric acid R* and 3 volumes of *water R*. Add 0.1 mL of *ferroin R* and titrate immediately with *0.1 M ammonium and cerium nitrate* until a greenish colour is obtained (n_1 mL). Pass slowly at a rate of about 3 mL/min through the column a mixture of 50 mL of *dilute sulfuric acid R* and 50 mL of *water R*, followed by 20.0 mL of solution S, a mixture of 50 mL of *dilute sulfuric acid R* and 50 mL of *water R* and finally 100 mL of *water R*. Collect the eluate in a 500 mL conical flask containing 50.0 mL of a 150 g/L solution of *ferric ammonium sulfate R* in a mixture of 1 volume of *sulfuric acid R* and 3 volumes of *water R*. Rinse the lower end of the column with *water R*, add 0.1 mL of *ferroin R* and titrate immediately with *0.1 M ammonium and cerium nitrate* until a greenish colour is obtained (n_2 mL).

Calculate the percentage content of TiO_2 using the following expression:

$$\frac{3.99 \times \left(n_2 - n_1\right)}{m}$$

m = mass of the substance to be examined used for the preparation of solution S, in grams.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for titanium dioxide used as opacifier in solid oral dosage forms and in preparations for cutaneous application.

Particle-size distribution (*2.9.31*)

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Titanium Ointment

General Notices

DEFINITION

Titanium Ointment contains a large proportion of Titanium Dioxide with smaller quantities of titanium peroxide and titanium salicylate in a suitable basis containing 5.0% w/w of Dimeticone 350.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of total titanium, as titanium dioxide TiO_2

22.5 to 27.5% w/w.

Content of titanium salicylate

2.70 to 3.30% w/w.

CHARACTERISTICS

A yellow, greasy ointment.

IDENTIFICATION

A. Disperse 5 g in 20 mL of warm *dichloromethane* on a water bath and filter the resulting suspension (Whatman No 1 paper is suitable). Wash the residue with 50 mL of warm *dichloromethane* and transfer the residue to a 50 mL beaker with the aid of a few mL of *water*. Add carefully 10 mL of *sulfuric acid* and 5 g of *ammonium sulfate* and heat until a clear solution is obtained. Allow to cool, add sufficient *water* to produce about 30 mL and add 1 mL of *hydrogen peroxide solution* (*20 vol*). A bright orange colour is produced immediately.

B. Disperse 5 g in 20 mL of warm *dichloromethane* on a water bath and filter the resulting suspension (Whatman No 1 paper is suitable). Wash the residue with 50 mL of warm *dichloromethane* and transfer the residue to a 50 mL beaker with the aid of a few mL of *water*. Mix well, filter again and add 0.05 mL of a 5% w/v solution of *iron(III) chloride hexahydrate* to the filtrate. A purple colour is produced immediately.

ASSAY

For TiO_2

Weigh 0.5 g into a tared silica crucible, heat gently over a small flame until the basis is completely volatilised or charred, increasing the rate of heating until almost all of the carbon has been removed. Heat at about 800° for about 30 minutes, allow to cool in a desiccator and weigh. Repeat the heating at 800° to constant weight. Calculate the content of total titanium as a percentage weight in weight using the formula:

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$$\left(\frac{W_r}{W_s}\times 100\right)-1.55$$

where

W_r	=	weight of the residue,
W_s	=	weight of the sample
1.55	=	percentage correction for contribution from Dimeticone 350.

For titanium salicylate

To 1.5 g in an iodine flask add 50 mL of 2M *ammonia* and heat gently until the solution boils. Add 25 mL of *0.0167M potassium bromate VS* and 10 mL of a 10% w/v solution of *potassium bromide*, add 20 mL of 7M *hydrochloric acid*, close the flask immediately and shake while cooling under running water. Allow the flask to stand for 30 minutes, protected from light. Add 10 mL of a 10% w/v solution of *potassium iodide*, shake and titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch solution*, added towards the end of the titration, as indicator. Each mL of *0.0167M potassium bromate VS* is equivalent to 2.818 mg of titanium salicylate.

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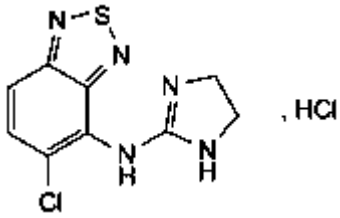
Tizanidine Hydrochloride

General Notices

(Ph. Eur. monograph 2578)



$C_9H_9Cl_2N_5S$ 290.2 *64461-82-1*

Action and use

Alpha$_2$-adrenoceptor agonist; skeletal muscle relaxant.

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DEFINITION

5-Chloro-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *tizanidine hydrochloride CRS*.

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B. Solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

pH (2.2.3)

3.7 to 5.0 for solution S.

Impurity H

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.200 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 8.0 mg of *ethylenediamine R* (impurity H) in *methanol R* and dilute to 100.0 mL with the same solvent.

Plate *TLC cellulose plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R* (1:25:75 *V/V/V*).

Application 5 µL.

Development Over 1/2 of the plate.

Drying In a current of cold air.

Detection Spray with a mixture of 15 volumes of a 20 g/L solution of *ninhydrin R* in *glacial acetic acid R* and 85 volumes of *butanol R*, then heat at 100 °C for 5 min.

Relative retention with reference to tizanidine (R_F = about 0.8): impurity H = about 0.3.

Limit:

— *impurity H*: any spot due to impurity H is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in mobile phase A, using sonication if necessary, and dilute to 25.0 mL with mobile phase A. Dilute 5.0 mL of the solution to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 3 mg of *tizanidine impurity B CRS* in mobile phase A and dilute to 25.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

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Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 30.0 mg of *tizanidine hydrochloride CRS* in mobile phase A, using sonication if necessary, and dilute to 25.0 mL with mobile phase A. Dilute 5.0 mL of the solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 18 volumes of *acetonitrile R1* and 82 volumes of a 3.86 g/L solution of *sodium pentanesulfonate monohydrate R* previously adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: mix 20 volumes of a 3.86 g/L solution of *sodium pentanesulfonate monohydrate R* previously adjusted to pH 3.0 with *phosphoric acid R* and 80 volumes of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 25	100 → 0	0 → 100
25 - 27	0	100

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to tizanidine (retention time = about 6 min): impurity B = about 1.3.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to tizanidine and impurity B.

Calculation of percentage contents:

— for each impurity, use the concentration of tizanidine hydrochloride in reference solution (b).

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Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

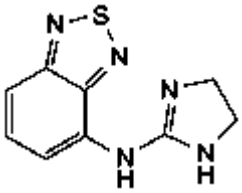
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_9H_9Cl_2N_5S$ taking into account the assigned content of *tizanidine hydrochloride CRS*.

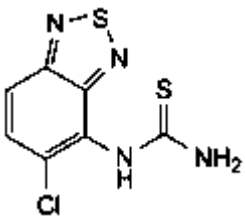
IMPURITIES

Specified impurities *H*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, I*.



A. *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine,



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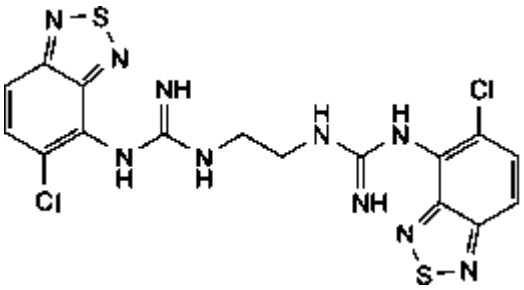
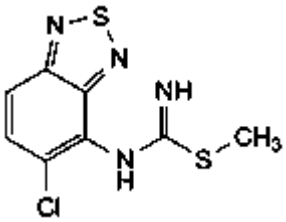
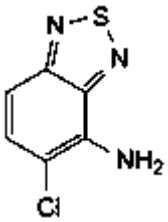
B. *N*-(5-chloro-2,1,3-benzothiadiazol-4-yl)thiourea,



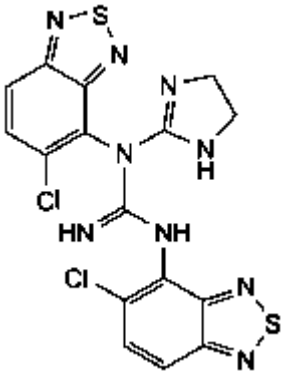
C. 1,1′-ethane-1,2-diylbis[3-(5-chloro-2,1,3-benzothiadiazol-4-yl)guanidine],



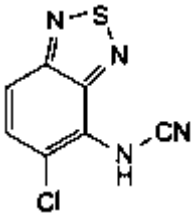
D. methyl *N*-(5-chloro-2,1,3-benzothiadiazol-4-yl)carbamimidothioate,



E. 5-chloro-2,1,3-benzothiadiazol-4-amine,



F. 1,3-bis(5-chloro-2,1,3-benzothiadiazol-4-yl)-1-(4,5-dihydro-1*H*-imidazol-2-yl)guanidine,



G. (5-chloro-2,1,3-benzothiadiazol-4-yl)cyanamide,

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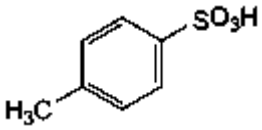
H. ethane-1,2-diamine (ethylenediamine),



I. 4-methylbenzenesulfonic acid (*p*-toluenesulfonic acid).

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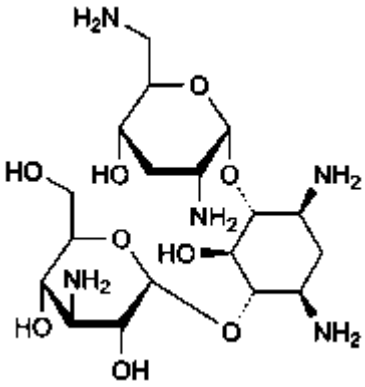
Tobramycin

General Notices

(Ph. Eur. monograph 0645)



$C_{18}H_{37}N_5O_9$ 467.5 *32986-56-4*

Action and use

Aminoglycoside antibacterial.

Preparations

Tobramycin and Dexamethasone Eye Drops, Suspension

Tobramycin Eye Drops

Tobramycin Inhalation Powder, Hard Capsule

Tobramycin Injection

Tobramycin Nebuliser Solution

Ph Eur

DEFINITION

4-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-6-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)-L-streptamine.

Substance produced by *Streptomyces tenebrarius* or obtained by any other means.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

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PRODUCTION

It is produced by methods of manufacture designed to eliminate or minimise substances lowering blood pressure.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Nuclear magnetic resonance spectrometry (*2.2.33*).

Preparation 100 g/L solution in *deuterium oxide R*.

Comparison 100 g/L solution of *tobramycin for identification CRS* in *deuterium oxide R*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 20 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *tobramycin for identification CRS* in *water R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 4 mg of *neomycin sulfate CRS* and 4 mg of *kanamycin monosulfate CRS* in 1 mL of reference solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *methylene chloride R*, *concentrated ammonia R*, *methanol R* (17:33:50 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Spray with a mixture of equal volumes of a 2 g/L solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and a 460 g/L solution of *sulfuric acid R*; heat at 105 °C for 5-10 min.

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System suitability The chromatogram obtained with reference solution (b) shows 3 major spots which are clearly separated.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 5 mg in 5 mL of *water R*. Add 5 mL of a 1 g/L solution of *ninhydrin R* in *ethanol (96 per cent) R* and heat in a water-bath for 3 min. A violet-blue colour develops.

TESTS

pH (*2.2.3*)

9.0 to 11.0.

Dissolve 1.0 g in 10 mL of *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

+ 138 to + 148 (anhydrous substance).

Dissolve 1.00 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *tobramycin CRS* in the mobile phase to obtain a concentration of 0.25 mg/mL.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Reference solution (d) Dissolve 10 mg of *kanamycin B sulfate CRS* in 20 mL of the mobile phase. To 1 mL of this solution, add 2 mL of reference solution (a) and dilute to 10 mL with the mobile phase.

Reference solution (e) Dilute 10.0 mL of reference solution (a) to 25.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm) with a pore size of 100 nm;

— *temperature*: 55 °C.

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Mobile phase Mixture prepared with *carbon dioxide-free water R* containing 52 g/L of *anhydrous sodium sulfate R*, 1.5 g/L of *sodium octanesulfonate R*, 3 mL/L of *tetrahydrofuran R* stabilised with *butylhydroxytoluene R*, and 50 mL/L of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*. Degas.

Flow rate 1.0 mL/min.

Post-column solution *carbonate-free sodium hydroxide solution R* diluted 25-fold with *carbon dioxide-free water R*, which is added pulselessly to the column effluent using a 375 µL polymeric mixing coil.

Flow rate 0.3 mL/min.

Detection Pulsed amperometric detector or equivalent with an electrochemical cell comprising a gold working electrode, a silver-silver chloride reference electrode and a stainless steel auxiliary electrode, held at respectively + 0.05 V detection, + 0.75 V oxidation and -0.15 V reduction potentials, with pulse durations according to the instrument used. The temperature of the detector is set at 35 °C.

NOTE: to prevent problems due to salt precipitation, the electrochemical cell can be flushed with water R overnight.

Injection 20 µL using a refrigerated injector (4-8 °C); inject test solution (a) and reference solutions (b), (c) and (d).

Run time 1.5 times the retention time of tobramycin.

Relative retention With reference to tobramycin (retention time = about 18 min): impurity C = about 0.35; impurity B = about 0.40, impurity A = about 0.70.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to impurity A and tobramycin in the chromatogram obtained with reference solution (d); if necessary, adjust the concentration of sodium octanesulfonate in the mobile phase;

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *any impurity*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent) and not more than 1 such peak has an area greater than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent).

2-Methyl-1-propanol (*2.4.24, System B*)

Maximum 1.0 per cent *m/m*.

Water (*2.5.12*)

Maximum 8.0 per cent, determined on 0.30 g.

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Sulfated ash (*2.4.14*)

Maximum 0.3 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 2.0 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

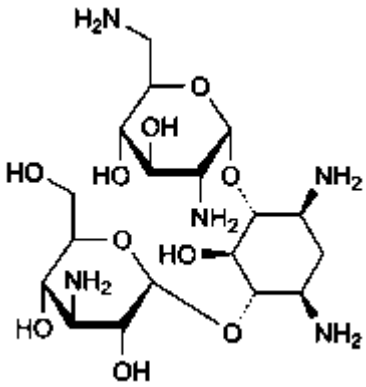
Injection Test solution (b) and reference solution (e).

Calculate the percentage content of tobramycin.

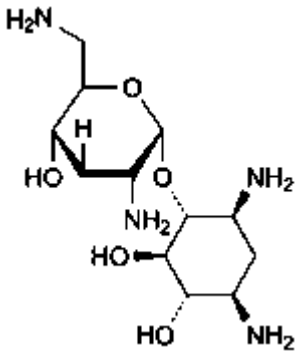
STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES



A. 4-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-6-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-L-streptamine (kanamycin B),



B. 2-deoxy-4-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)-D-streptamine (nebramine),

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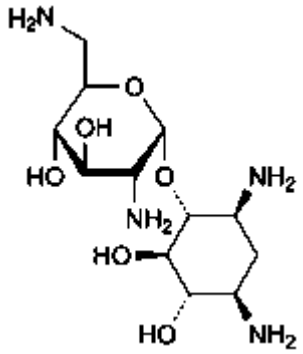

C. 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine (neamine).

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Tobramycin and Dexamethasone Eye Drops, Suspension

General Notices

Action and use

Aminoglycoside antibacterial + corticosteroid.

DEFINITION

Tobramycin and Dexamethasone Eye Drops, Suspension are a sterile suspension containing Tobramycin and Dexamethasone in a suitable vehicle.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of tobramycin, $C_{18}H_{37}N_5O_9$

95.0 to 110.0% of the stated amount.

Content of dexamethasone, $C_{22}H_{29}FO_5$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a suitable volume of the suspension with *water* to produce a concentration of 0.4% w/v of tobramycin and filter. Use the filtrate.

(2) 0.4% w/v of *tobramycin BPCRS* in *water*.

(3) 0.4% w/v each of *kanamycin monosulfate BPCRS*, *neomycin sulfate EPCRS* and *tobramycin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol* (*96%*) and a 46% w/v solution of *sulfuric acid* and heat at 105° for 5 to 10 minutes.

MOBILE PHASE

17 volumes of *dichloromethane*, 33 volumes of 13.5M *ammonia* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated principal spots.

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CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the test for Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to Tobramycin in the chromatogram obtained with solution (2).

C. Mix a quantity of the Eye drops containing 20 mg of dexamethasone with 5 mL of 0.1M *sodium hydroxide*, add 50 mL of *dichloromethane* and mix with the aid of ultrasound for 20 minutes, filter the dichloromethane layer and evaporate to dryness using a rotary evaporator. Dry the residue at 105° for 2 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the reference spectrum of dexamethasone (*RS 089*).

TESTS

Particle size

The eye drops are a suspension and comply with the following test:

Examine using an automated light obscuration instrument such as that described in Appendix XIII A. Not more than 20 particles greater than 25 µm, not more than 2 particles greater than 50 µm and no particles greater than 90 µm.

Acidity

pH 5.0 to 6.0, Appendix V L.

Related substances

For tobramycin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise the solutions prior to analysis.

Solution A 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)*

Solution B Dilute 20 volumes of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* to 100 volumes with *dimethyl sulfoxide*.

(1) Disperse a quantity of the eye drops containing 20 mg of Tobramycin in 70 mL of *water*, mix with the aid of ultrasound, dilute with sufficient *water* to produce 100 mL and filter. Wash with 3 x 20 mL of *dichloromethane*.
(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.
(3) Dilute 1 volume of solution (2) to 10 volumes with *water*.
(4) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.
(5) Heat a 50-mL portion of solution (4) at 100° for 8 to 9 hours, allow to cool and dilute to 50 mL with *water* (generation of impurity B).
(6) *water* (blank solution).

Derivatise the solutions using the following method. Transfer 3.75 mL of each of the 6 solutions separately into 15-mL glass tubes. To each solution add 2.5 mL *solution A* and 2.5 mL of *solution B*. Heat in a water bath at 60° for 50 minutes. Remove the tubes, allow to cool to

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room temperature, add 3.75 mL of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenyl silica gel for chromatography* (5 µm) (Waters XBridge Phenyl is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 365 nm.

(f) Inject 45 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08 volumes of *orthophosphoric acid*, 5 volumes of *acetonitrile* and 95 volumes of *water*.

Mobile phase B 0.08 volumes of *orthophosphoric acid*, 25 volumes of *water* and 75 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	79	21	isocratic
2-16	79→66	21→34	linear gradient
16-27	66→30	34→70	linear gradient
27-37	30	70	isocratic
37-42	30→20	70→80	linear gradient
42-52	20→5	80→95	linear gradient
52-62	5	95	isocratic
62-67	5→79	95→21	linear gradient
67-72	79	21	re-equillibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to tobramycin (retention time about 49 minutes) are: impurity 1, about 0.59; impurity 2, about 0.62; impurity C, about 0.9; impurity B, about 0.96 and impurity A, about 0.96.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity A and impurity B is at least 1.0.

LIMITS

Use the chromatograms obtained with solutions (4) and (5) to identify the peaks due to impurities A and B. The peak due to impurity B is observed to increase in solution (5).

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Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity 1 and multiply the area of this peak by a correction factor of 2.1.

Identify the peaks in the chromatogram obtained with solution (1) corresponding to any named impurity and subtract from the area the response from any corresponding peak in the chromatogram obtained with solution (6).

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any unknown *secondary peaks* corresponding to any peaks in the chromatograms obtained with solution (4) or solution (6), and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

For dexamethasone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Disperse a quantity of the eye drops containing 20 mg of dexamethasone in 70 mL of mobile phase, mix with the aid of ultrasound for 10 minutes, dilute with sufficient mobile phase to 100 mL and filter.
(2) Dilute 3 volumes of solution (1) to 100 volumes.
(3) 0.02% w/v of *dexamethasone impurity standard BPCRS.*
(4) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, dilute 1 volume of this solution to 10 volumes with mobile phase

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 50 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for six times the retention time of dexamethasone.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.3% w/v solution of *orthophosphoric acid* that has been previously adjusted to pH 3.0 with *dilute sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 3 and dexamethasone is at least 1.5.

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The test is not valid unless, the chromatogram obtained with solution (3), closely resembles the chromatogram supplied with *dexamethasone impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any secondary peaks is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

For tobramycin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)*

Solution B Dilute 20 volumes of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* to 100 mL with *dimethyl sulfoxide*.

(1) Disperse a weighed quantity of the eye drops containing 20 mg of Tobramycin in 70 mL of *water*, mix with the aid of ultrasound, dilute with sufficient *water* to produce 100 mL and filter. Was the filtrate with three 20-mL quantities of *dichloromethane*.
(2) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.
Derivatise solutions (1) and (2) using the following method. The solutions should be heated at the same temperature and for the same time as indicated below.

Transfer 4 mL of each solution separately into 50-mL volumetric flasks. To each solution add 10 mL of *solution A* and 10 mL of *solution B* and mix. Heat in a water bath at 60° for 50 minutes. Remove the flasks, allow to stand for 10 minutes and add *acetonitrile* to about 2 mL below the meniscus. Allow to cool to room temperature and add sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 365 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of *tris(hydroxymethyl)methylamine* in 800 mL of *water*, add 20 mL of 0.5M *sulfuric acid* and sufficient *acetonitrile* to produce 2000 mL; mix, allow to cool and filter through a 0.45-µm filter.

DETERMINATION OF CONTENT

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Determine the weight per mL of the Eye Drops. Calculate the content of $C_{18}H_{37}N_5O_9$ in the eye drops using the declared content of $C_{18}H_{37}N_5O_9$ in *tobramycin BPCRS*.

For dexamethasone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a weighed quantity of the eye drops containing 20 mg of dexamethasone in 70 mL of *mobile phase*, mix with the aid of ultrasound for 10 minutes, dilute with sufficient *mobile phase* to produce 100 mL and filter.

(2) 0.02% w/v of *dexamethasone BPCRS*.

(3) 0.01% w/v of *dexamethasone impurity standard BPCRS.*

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances *for dexamethasone* may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 3 and dexamethasone is at least 1.5.

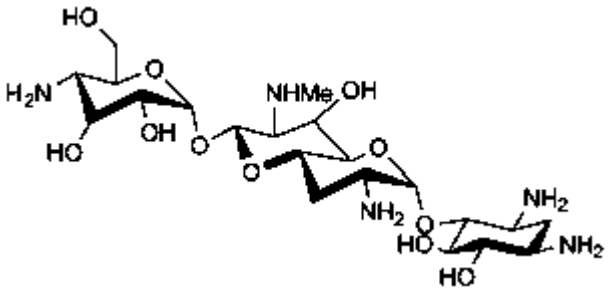
The test is not valid unless, the chromatogram obtained with solution (3), closely resembles the chromatogram supplied with dexamethasone impurity standard BPCRS.

DETERMINATION OF CONTENT

Determine the weight per mL of the Eye Drops. Calculate the content of $C_{22}H_{29}FO_5$ in the eye drops using the declared content of $C_{22}H_{29}FO_5$ in *dexamethasone BPCRS*.

IMPURITIES

The impurities related to Tobramycin limited by the requirements of this monograph include those listed under *Tobramycin* and the following:



1. Apramycin

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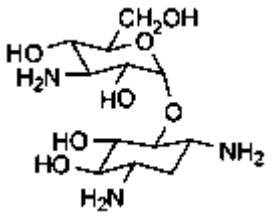
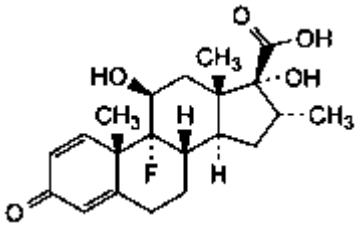
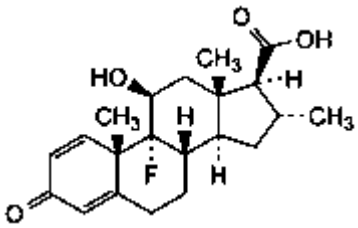


2. Deoxystreptamine kanosamide

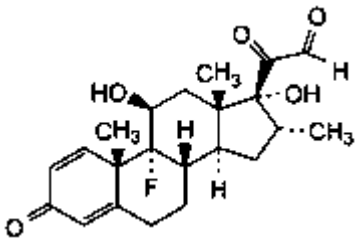
The impurities related to Dexamethasone limited by the requirements of this monograph include those listed under *Dexamethasone* and the following:



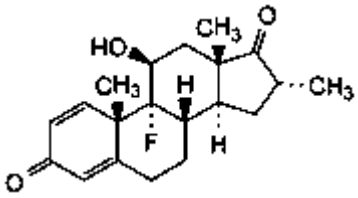
1. Dexamethasone-17β-carboxylic acid



2. Dexamethasone-17α-dehydroxy-17β-carboxylic acid



3. Dexamethasone-21-aldehyde



4. Dexamethasone-17-ketone

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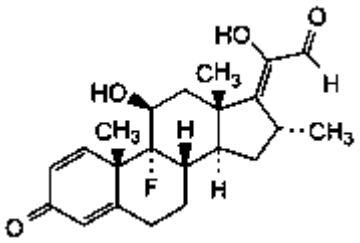

5. Dexamethasone-17(20)-enol-21-aldehyde

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Tobramycin Eye Drops

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Tobramycin Eye Drops are a sterile solution of Tobramycin in a suitable vehicle

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of tobramycin, $C_{18}H_{37}N_5O_9$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a suitable volume of the eye drops with *water* to produce a solution containing 0.3% w/v of Tobramycin.

(2) 0.3% w/v of *tobramycin BPCRS* in *water*.

(3) 0.4% w/v each of *kanamycin monosulfate BPCRS*, *neomycin sulfate EPCRS* and *tobramycin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol* (*96%*) and a 46% w/v solution of *sulfuric acid* and heat at 105° for 5 to 10 minutes.

MOBILE PHASE

17 volumes of *dichloromethane*, 33 volumes of 13.5M *ammonia* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

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B. In the test for Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to tobramycin in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise the solutions prior to analysis.

Solution A 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)*

Solution B Dilute 1 volume of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* to 5 volumes with *dimethyl sulfoxide*.

(1) Dilute a volume of the eye drops with sufficient *water*, if necessary, to produce a solution containing 0.02% w/v of Tobramycin.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(3) Dilute 1 volume of solution (2) to 10 volumes with *water*.

(4) Dissolve 50 mg of *tobramycin BPCRS* in 1 mL of 0.5M *sulfuric acid* and 30 mL of *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(5) Heat a 50-mL portion of solution (4) at 100° for 8 to 9 hours, allow to cool and dilute to 50 mL with *water* (generation of impurity B).

(6) *water* (blank solution).

Derivatise the solutions using the following method. Transfer 3.75 mL of each of the 6 solutions separately into 15-mL glass tubes. To each solution add 2.5 mL solution A and 2.5 mL of solution B. Heat in a water bath at 60° for 50 minutes. Remove the tubes, allow to cool to room temperature, add 3.75 mL of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenyl silica gel for chromatography* (5 µm) (Waters XBridge Phenyl is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 365 nm.

(f) Inject 45 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08 volumes of *orthophosphoric acid*, 5 volumes of *acetonitrile* and 95 volumes of *water*.

Mobile phase B 0.08 volumes of *orthophosphoric acid*, 25 volumes of *water* and 75 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	79	21	isocratic

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
2-16	79→66	21→34	linear gradient
16-27	66→30	34→70	linear gradient
27-37	30	70	isocratic
37-42	30→20	70→80	linear gradient
42-52	20→5	80→95	linear gradient
52-62	5	95	isocratic
62-67	5→79	95→21	linear gradient
67-72	79	21	re-equillibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to tobramycin (retention time about 49 minutes) are: impurity 1, about 0.59; impurity 2, about 0.62; impurity C, about 0.9; impurity B, about 0.96 and impurity A, about 0.96.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity A and impurity B is at least 1.0.

LIMITS

Use the chromatograms obtained with solutions (4) and (5) to identify the peaks due to impurities A and B. The peak due to impurity B is observed to increase in solution (5).

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurities A, B and 1 and subtract from the area the response from any corresponding peak in the chromatogram obtained with solution (6).

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity 1 and multiply the area of this peak by a correction factor of 2.1.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any unknown *secondary peaks* corresponding to any peaks in the chromatograms obtained with solution (4) or solution (6), and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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Solution A 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)*

Solution B Dilute 20 volumes of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* to 100 volumes with *dimethyl sulfoxide*.

(1) Dilute a volume of the eye drops, if necessary, with sufficient *water* to produce a solution containing 0.02% w/v of tobramycin.

(2) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Dilute 1 volume of a 0.024% w/v solution of *1-naphtholbenzein* in *acetonitrile* to 5 volumes with derivatised solution (2).

Derivatise solutions (1) and (2) using the following method.

Transfer 4 mL of each solution separately into 50-mL volumetric flasks. To each solution add 10 mL of solution A and 10 mL of solution B and mix. Heat in a water bath at 60° for 50 minutes. Remove the flasks, allow to stand for 10 minutes and add *acetonitrile* to about 2 mL below the meniscus. Allow to cool to room temperature and add sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 365 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of *tris(hydroxymethyl)methylamine* in 800 mL of *water*, add 20 mL of 0.5M *sulfuric acid* and sufficient *acetonitrile* to produce 2000 mL; mix, allow to cool and filter through a 0.45-µm filter.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to 1-naphtholbenzein and tobramycin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{37}N_5O_9$ in the eye drops using the declared content of $C_{18}H_{37}N_5O_9$ in *tobramycin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Tobramycin and the following:

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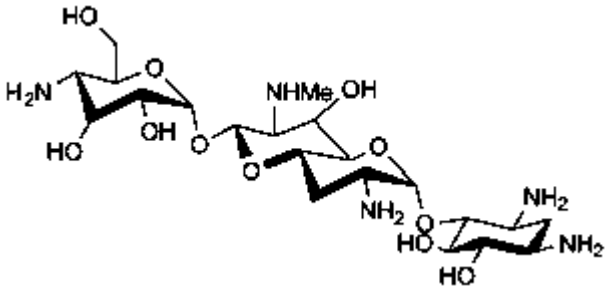
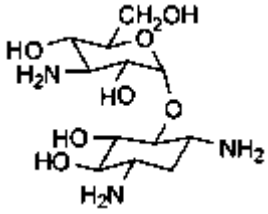


1. Apramycin,



2. Deoxystreptamine kanosamide.

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Tobramycin Injection

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Tobramycin Injection is a sterile solution of Tobramycin in Water for Injections containing Sulfuric Acid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of tobramycin, $C_{18}H_{37}N_5O_9$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a suitable volume of the injection with *water* to produce a solution containing 0.4% w/v of Tobramycin.

(2) 0.4% w/v of *tobramycin BPCRS* in *water*.

(3) 0.4% w/v each of *kanamycin monosulfate BPCRS*, *neomycin sulfate EPCRS* and *tobramycin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol* (*96%*) and a 46% w/v solution of *sulfuric acid* and heat at 105° for 5 to 10 minutes.

MOBILE PHASE

17 volumes of *dichloromethane*, 33 volumes of 13.5M *ammonia* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

ThLoading [MathJax]/jax/output/HTML-CSS/fonts/TeX/fontdata.js with solution (3) shows three clearly separated principal spots.

CONFIRMATION

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CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. Yields the reactions characteristic of *sulfates*, Appendix VI.

C. In the test for Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to Tobramycin in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise the solutions prior to analysis.

(1) Dilute a volume of the injection with sufficient *water* to produce a solution containing 0.02% w/v of Tobramycin.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(3) Dilute 1 volume of solution (2) to 10 volumes with *water*.

(4) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(5) Heat a 50-mL portion of solution (4) at 100° for 8 to 9 hours, allow to cool and dilute to 50 mL with *water* (generation of impurity B).

(6) *water* (blank solution).

Derivatise each of the solutions using the following method. The solutions should be heated at the same temperature and for the same time as indicated below.

Transfer 3.75 mL of each of the 6 solutions separately into 15-mL glass tubes. To each solution add 2.5 mL of a 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)* and 2.5 mL of a solution prepared by diluting 40 mL of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* in *water* to 200 mL with *dimethyl sulfoxide* and mixing. Heat in a water bath at 60° for 50 minutes. Remove the tubes, allow to cool to room temperature, add 3.75 mL of *acetonitrile* and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenyl silica gel for chromatography* (5 µm) (Waters XBridge Phenyl is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 25°

(e) Use a detection wavelength of 365 nm.

(f) Inject 45 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08 volumes of *orthophosphoric acid*, 5 volumes of *acetonitrile* and 95 volumes of *water*.

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Mobile phase B 0.08 volumes of *orthophosphoric acid*, 25 volumes of *water* and 75 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	79	21	isocratic
2-16	79→66	21→34	linear gradient
16-27	66→30	34→70	linear gradient
27-37	30	70	isocratic
37-42	30→20	70→80	linear gradient
42-52	20→5	80→95	linear gradient
52-62	5	95	isocratic
62-67	5→79	95→21	linear gradient
67-72	79	21	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to tobramycin (retention time about 49 minutes) are: impurity 1, about 0.59; impurity 2, about 0.62; impurity C, about 0.9; impurity B, about 0.96 and impurity A, about 0.96.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity A and impurity B is at least 1.0.

LIMITS

Use the chromatograms obtained with solutions (4) and (5) to identify the peaks due to impurities A and B. The peak due to impurity B is observed to increase in solution (5).

Identify the peak in the chromatogram obtained with solution (1) corresponding to impurity 1 and multiply the area of this peak by a correction factor of 2.1.

Identify the peaks in the chromatogram obtained with solution (1) corresponding to any named impurity and subtract from the area the response from any corresponding peak in the chromatogram obtained with solution (6).

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

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Disregard any unknown *secondary peaks* corresponding to any peaks in the chromatograms obtained with solution (4) or solution (6), and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing 10 mg of Tobramycin per mL (solution A). The endotoxin limit concentration of solution A is 20 IU per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection, if necessary, with sufficient *water* to produce a solution containing 0.02% w/v of Tobramycin.

(2) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Dilute 1 volume of a 0.024% w/v solution of *1-naphtholbenzein* in *acetonitrile* to 5 volumes with derivatised solution (2).

Derivatise solutions (1) and (2) using the following method. The solutions should be heated at the same temperature and for the same time as indicated below.

Transfer 4 mL of each solution separately into 50-mL volumetric flasks. To each solution add 10 mL of a 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)* and 10 mL of a solution prepared by diluting 40 mL of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* in *water* to 200 mL with *dimethyl sulfoxide* and mixing. Heat in a water bath at 60° for 50 minutes. Remove the flasks, allow to stand for 10 minutes and add *acetonitrile* to about 2 mL below the meniscus. Allow to cool to room temperature and add sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 365 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of *tris(hydroxymethyl)methylamine* in 800 mL of *water*, add 20 mL of 0.5M *sulfuric acid* and sufficient *acetonitrile* to produce 2000 mL; mix, allow to cool and filter through a 0.45-µm filter.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to 1-naphtholbenzein and tobramycin is at least 4.0.

DETERMINATION OF CONTENT

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C… …ng the declared content of $C_{18}H_{37}N_5O_9$ in *tobramycin BPCRS*.

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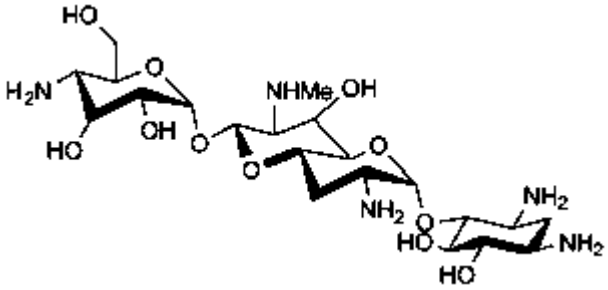
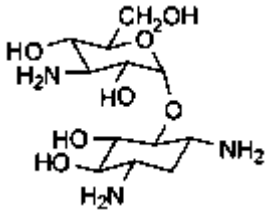
IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Tobramycin and the following:



1. Apramycin,



2. Deoxystreptamine kanosamide.

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Tobramycin Inhalation Powder, Hard Capsule

General Notices

Action and use

Antibacterial

DEFINITION

Tobramycin Inhalation Powder, Hard Capsule consists of Tobramycin, in microfine powder or aerodynamically equivalent, either alone or combined with a suitable carrier. The capsule is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, hard capsule complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. *Preparations for inhalation: Aerodynamic Assessment of Fine Particles*. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of tobramycin, $C_{18}H_{37}N_5O_9$

93.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

(1) Disperse a quantity of the capsule contents in sufficient *water* to produce a solution containing 0.4% w/v of Tobramycin.

(2) 0.4% w/v of *tobramycin BPCRS* in *water*.

(3) 0.4% w/v each of *kanamycin monosulfate BPCRS*, *neomycin sulfate EPCRS* and *tobramycin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol (96%)* and a 46% w/v solution of *sulfuric acid* and heat at 105°.

MOBILE PHASE

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MOBILE PHASE

17 volumes of *dichloromethane*, 33 volumes of 13.5M *ammonia* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solution A 1% w/v of *1-fluoro-2,4-dinitrobenzene* in *ethanol*.

Solution B Dilute 20 volumes of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* to 100 volumes with *dimethyl sulfoxide*.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve each collected dose in sufficient *water* to produce a solution expected to contain 0.014% w/v of tobramycin.
(2) 0.014% w/v of *tobramycin BPCRS* in *water*.
(3) Dilute 1 volume of a 0.024% w/v solution of *1-naphtholbenzein* in *acetonitrile* to 5 volumes with derivatised solution (2).
Derivatise the solutions using the following method. Transfer 3.75 mL of each of the solutions separately into 15-mL glass tubes. To each solution add 2.5 mL of solution A and 2.5 mL of solution B. Heat in a water bath at 60° for 50 minutes. Remove the tubes, allow to cool to room temperature, add 3.75 mL of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 365 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of *tris(hydroxymethyl)methylamine* in 800 mL of *water*, add 20 mL of 0.5M *sulfuric acid* and sufficient *acetonitrile* to produce 2000 mL; mix, allow to cool and filter through a 0.45-µm filter.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to 1-naphtholbenzein and tobramycin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of tobramycin, $C_{18}H_{37}N_5O_9$, per delivered dose from the chromatograms obtained and using the declared content of $C_{18}H_{37}N_5O_9$, in *tobramycin BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise each solution prior to analysis.

Solution A 1% w/v of *1-fluoro-2,4-dinitrobenzene* in *ethanol*.

Solution B Dilute 20 volumes of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* to 100 volumes with *dimethyl sulfoxide*.

(1) Disperse a quantity of the capsule contents with sufficient *water* to produce a solution containing 0.02% w/v of Tobramycin.
(2) Dilute 1 volume of solution (1) to 200 volumes with *water*.
(3) Dilute 1 volume of solution (2) to 5 volumes with *water*.
(4) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.
(5) Heat a 50-mL portion of solution (4) at 100° for 8 to 9 hours, allow to cool and dilute to 50 mL with *water* (generation of impurity B).
(6) *water* (blank solution).

Derivatise the solutions using the following method. Transfer 3.75 mL of each of the 6 solutions separately into 15-mL glass tubes. To each solution add 2.5 mL solution A and 2.5 mL of solution B. Heat in a water bath at 60° for 50 minutes. Remove the tubes, allow to cool to room temperature, add 3.75 mL of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenyl silica gel for chromatography* (5 µm) (Waters XBridge Phenyl is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 365 nm.
(f) Inject 45 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08 volumes of *orthophosphoric acid*, 5 volumes of *acetonitrile* and 95 volumes of *water*.

Mobile phase B 0.08 volumes of *orthophosphoric acid*, 25 volumes of *water* and 75 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	79	21	isocratic

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
2-16	79→66	21→34	linear gradient
16-27	66→30	34→70	linear gradient
27-37	30	70	isocratic
37-42	30→20	70→80	linear gradient
42-52	20→5	80→95	linear gradient
52-62	5	95	isocratic
62-67	5→79	95→21	linear gradient
67-72	79	21	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to tobramycin (retention time about 49 minutes) are: impurity 1, about 0.59; impurity 2, about 0.62; impurity C, about 0.9; impurity B, about 0.96 and impurity A, about 0.96.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity A and impurity B is at least 1.0.

LIMITS

Use the chromatograms obtained with solutions (4) and (5) to identify the peaks due to impurities A and B. The peak due to impurity B is observed to increase in solution (5).

Identify the peaks in the chromatogram obtained with solution (1) corresponding to any impurity A, B and 1 and subtract from the area the response from any corresponding peak in the chromatogram obtained with solution (6).

Identify the peak in the chromatogram obtained with solution (1) corresponding to impurity 1 and multiply the area of this peak by a correction factor of 2.1.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all the *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any unknown *secondary peaks* corresponding to any peaks in the chromatograms obtained with solution (4) or solution (6), and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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Solution A 1% w/v of *1-fluoro-2,4-dinitrobenzene* in *ethanol*.

Solution B Dilute 20 volumes of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* to 100 volumes with *dimethyl sulfoxide*.

(1) Disperse a quantity of the capsule contents, if necessary, with sufficient *water* to produce a solution containing 0.02% w/v of Tobramycin.

(2) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Dilute 1 volume of a 0.024% w/v solution of *1-naphtholbenzein* in *acetonitrile* to 5 volumes with derivatised solution (2).

Derivatise solutions (1) and (2) using the following method. Transfer 4 mL of each solution separately into 50-mL volumetric flasks. To each solution add 10 mL of solution A and 10 mL of solution B and mix. Heat in a water bath at 60° for 50 minutes. Remove the flasks, allow to stand for 10 minutes and add *acetonitrile* to about 2 mL below the meniscus. Allow to cool to room temperature and add sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Uniformity of delivered dose may be used

SYSTEM SUITABILITY

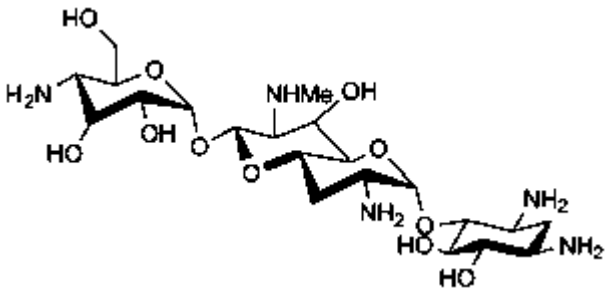
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to 1-naphtholbenzein and tobramycin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{37}N_5O_9$ in the inhalation powder using the declared content of $C_{18}H_{37}N_5O_9$ in *tobramycin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Tobramycin and the following:



1. Apramycin,

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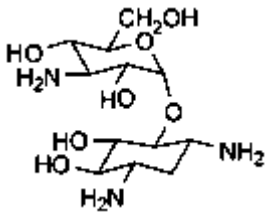

2. Deoxystreptamine kanosamide.

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Tobramycin Nebuliser Solution

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Tobramycin Nebuliser Solution is a solution of Tobramycin in a suitable vehicle, intended to be converted into an aerosol by a nebuliser.

The nebuliser solution complies with the requirements stated under Preparations for Inhalation and with the following requirements.

Content of tobramycin, $C_{18}H_{37}N_5O_9$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the nebuliser solution with *water* to produce a solution containing 0.4% w/v of Tobramycin.

(2) 0.4% w/v of *tobramycin BPCRS* in *water*.

(3) 0.4% w/v of each of *kanamycin monosulfate BPCRS*, *neomycin sulfate EPCRS* and *tobramycin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol* (*96%*) and a 46% w/v solution of *sulfuric acid* and heat at 105° for 5 to 10 minutes.

MOBILE PHASE

17 volumes of *dichloromethane*, 33 volumes of 13.5M *ammonia* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 5.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise the solutions prior to analysis.

(1) Dilute a volume of the nebuliser solution, if necessary, with sufficient *water* to produce a solution containing 0.02% w/v of Tobramycin.
(2) Dilute 1 volume of solution (1) to 200 volumes with *water*.
(3) Dilute 1 volume of solution (2) to 5 volumes with *water*.
(4) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.
(5) Heat a 50-mL portion of solution (4) at 100° for 8 to 9 hours, allow to cool and dilute to 50 mL with *water* (generation of impurity B).
(6) *water* (blank solution).

Derivatise each of the solutions using the following method. The solutions should be heated at the same temperature and for the same time as indicated below.

Transfer 3.75 mL of each of the 6 solutions separately into 15-mL glass tubes. To each solution add 2.5 mL of a 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)* and 2.5 mL of a solution prepared by diluting 40 mL of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* in *water* to 200 mL with *dimethyl sulfoxide* and mixing. Heat in a water bath at 60° for 50 minutes. Remove the tubes, allow to cool to room temperature, add 3.75 mL of *acetonitrile* and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenyl silica gel for chromatography* (5 µm) (Waters XBridge Phenyl is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 365 nm.
(f) Inject 45 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08 volumes of *orthophosphoric acid*, 5 volumes of *acetonitrile* and 95 volumes of *water*.

Mobile phase B 0.08 volumes of *orthophosphoric acid*, 25 volumes of *water* and 75 volumes of *acetonitrile*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	79	21	isocratic
2-16	79→66	21→34	linear gradient
16-27	66→30	34→70	linear gradient
27-37	30	70	isocratic
37-42	30→20	70→80	linear gradient
42-52	20→5	80→95	linear gradient
52-62	5	95	isocratic
62-67	5→79	95→21	linear gradient
67-72	79	21	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to tobramycin (retention time about 49 minutes) are: apramycin, about 0.59; deoxystreptamine kanosamide, about 0.62; impurity C, about 0.9; impurity B, about 0.96 and impurity A, about 0.96.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity A and impurity B is at least 1.0.

LIMITS

Use the chromatograms obtained with solutions (4) and (5) to identify the peaks due to impurities A and B. The peak due to impurity B is observed to increase in solution (5).

Identify the peak in the chromatogram obtained with solution (1) corresponding to apramycin and multiply the area of this peak by a correction factor of 2.1.

Identify the peaks in the chromatogram obtained with solution (1) corresponding to any named impurity and subtract from the area the response from any corresponding peak in the chromatogram obtained with solution (6).

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %);

not more than one such peak has an area greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

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Disregard any unknown *secondary peaks* corresponding to any peaks in the chromatograms obtained with solution (4) or solution (6), any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the nebuliser solution, if necessary, with sufficient *water* to produce a solution containing 0.02% w/v of Tobramycin.

(2) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Dilute 1 volume of a 0.024% w/v solution of *1-naphtholbenzein* in *acetonitrile* to 5 volumes with derivatised solution (2).

Derivatise solutions (1) and (2) using the following method. The solutions should be heated at the same temperature and for the same time as indicated below.

Transfer 4 mL of each solution separately into 50-mL volumetric flasks. To each solution add 10 mL of a 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)* and 10 mL of a solution prepared by diluting 40 mL of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* in *water* to 200 mL with *dimethyl sulfoxide* and mixing. Heat in a water bath at 60° for 50 minutes. Remove the flasks, allow to stand for 10 minutes and add *acetonitrile* to about 2 mL below the meniscus. Allow to cool to room temperature and add sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 365 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of *tris(hydroxymethyl)methylamine* in 800 mL of *water*, add 20 mL of 0.5M *sulfuric acid* and sufficient *acetonitrile* to produce 2000 mL; mix, allow to cool and filter through a 0.45-µm filter.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to 1-naphtholbenzein and tobramycin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{37}N_5O_9$ in the nebuliser solution using the declared content of $C_{18}H_{37}N_5O_9$ in *tobramycin BPCRS*.

STORAGE

Tobramycin Nebuliser Solution should be protected from light and stored at a temperature of 2° to 8°.

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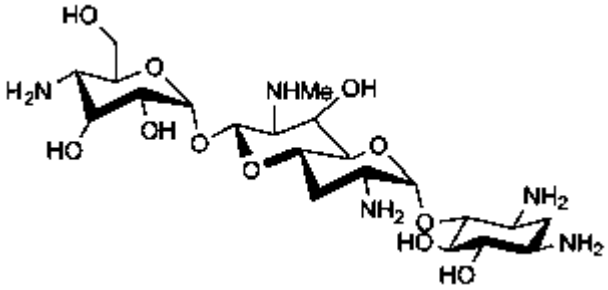
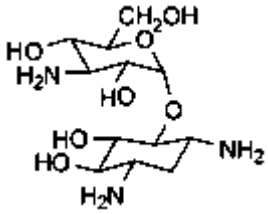
IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Tobramycin and the following.



1. Apramycin,



2. Deoxystreptamine kanosamide.

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Tobramycin Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Aminoglycoside antibacterial.

DEFINITION

Tobramycin Oral Solution is a solution of Tobramycin Sulfate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of tobramycin, $C_{18}H_{37}N_5O_9$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A pale yellow solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a suitable volume of the oral solution with *water* to produce a solution containing the equivalent of 0.4% w/v of tobramycin.

(2) 0.4% w/v of *tobramycin BPCRS* in *water*.

(3) 0.4% w/v of each of *kanamycin monosulfate BPCRS*, *neomycin sulfate EPCRS* and *tobramycin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol* (*96%*) and a 46% w/v solution of *sulfuric acid* and heat at 105° for 5 to 10 minutes.

MOBILE PHASE

17 volumes of *dichloromethane*, 33 volumes of 13.5M *ammonia* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

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SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

C. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

pH, 4.7 to 5.7, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise solutions (1), (2) and (4) prior to analysis.

(1) Dilute a quantity of the oral solution, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.01% w/v of tobramycin.

(2) Add 1 mL of 0.5M *sulfuric acid* to 25 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Dilute 1 volume of a 0.24% w/v solution of *1- naphtholbenzein* in *acetonitrile* to 5 volumes with derivatised solution (2).

(4) *water* (blank solution).

Derivatise solutions (1), (2) and (4) using the following method. The solutions should be heated at the same temperature and for the same time as indicated below.

Transfer 4 mL of each solution separately into 50-mL volumetric flasks. To each solution add 10 mL of a 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)* and 10 mL of a solution prepared by diluting 40 mL of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* in *water* to 200 mL with *dimethyl sulfoxide* and mixing. Heat in a water bath at 60° for 50 minutes. Remove the flasks, allow to stand for 10 minutes and add *acetonitrile* to about 2 mL below the meniscus. Allow to cool to room temperature and add sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 365 nm.

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(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of *tris(hydroxymethyl)methylamine* in 800 mL of *water*, add 20 mL of 0.5M *sulfuric acid* and sufficient *acetonitrile* to produce 2000 mL; mix, allow to cool and filter through a 0.45-µm filter.

When the chromatograms are recorded under the prescribed conditions the retention of 1-naptholbenzein relative to tobramycin (retention time, about 20 minutes) is about 0.6.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to 1-naphtholbenzein and tobramycin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{37}N_5O_9$ in the oral solution using the declared content of $C_{18}H_{37}N_5O_9$ in *tobramycin BPCRS*.

STORAGE

Tobramycin Oral Solution should be stored at a temperature of 2° to 8°.

LABELLING

The label states the quantity of active ingredient in terms of the equivalent amount of tobramycin.

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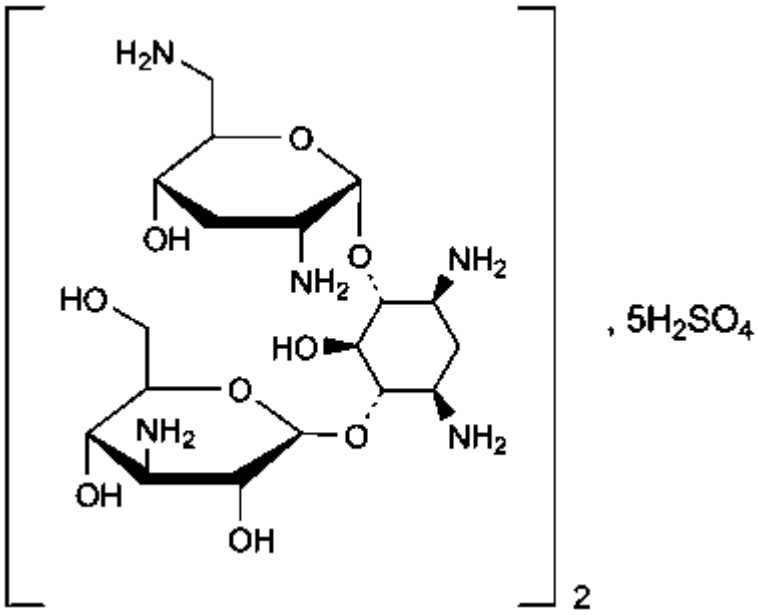
Tobramycin Sulfate

General Notices



$(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$ 1425.42 *79645-27-5*

Action and use

Aminoglycoside antibacterial.

Preparation

Tobramycin Oral Solution

DEFINITION

4-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-6-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)-L-streptamine sulfate.

Substance produced by *Streptomyces tenebrarius* or obtained by any other means.

It contains not less than 97.0% and not more than 102.0% of $(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white to off-white powder.

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Soluble in *water*.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve 90 mg of the substance being examined in sufficient *water* to produce 10 mL.

(2) 0.6% w/v of *tobramycin BPCRS* *in* *water*.

(3) 0.4% w/v of each of *kanamycin monosulfate BPCRS*, *neomycin sulfate EPCRS* and *tobramycin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air, spray with a mixture of equal volumes of a 0.2% w/v solution of *naphthalene-1,3-diol* in *ethanol (96%)* and a 46% w/v solution of *sulfuric acid* and heat at 105° for 5 to 10 minutes.

MOBILE PHASE

17 volumes of *dichloromethane*, 33 volumes of 13.5M *ammonia* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

C. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a 0.4% w/v solution, 6.0 to 8.0, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve 50 mg of the substance being examined in 7 mL of *water*, adjust the pH to 5.5 with 0.5M *sulfuric acid* and add sufficient water to produce 10 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use as the coating *silica gel for chromatography*.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 110° for 10 minutes and spray with a 20% v/v solution of *sodium hypochlorite solution* in *water*. Dry the plate in air and then spray with a solution prepared in the following manner. Dissolve 1.1 g of *potassium iodide* in 60 mL of *water*, boil for 15 minutes and slowly add a suspension containing 1.5 g of *soluble starch* in 10 mL of *water*. Add 25 mL of *water*, boil for 10 minutes, allow to cool and dilute to 100 mL with *water*.

MOBILE PHASE

20 volumes of *water*, 30 volumes of *ethanol* and 50 volumes of a 29.2% w/v solution of *sodium chloride* in *water*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the principal spot in the chromatogram obtained with solution (2) (1%).

Sulfated ash

Not more than 1% w/w, Appendix IX A, when determined by the following method. Moisten the charred residue with 2 mL of *nitric acid* and 5 drops of *sulfuric acid*.

Water

Not more than 2.0% w/w, Appendix IX C.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise solutions (1), (2) and (4) prior to analysis.

(1) Dissolve 30 mg of the substance being examined in sufficient *water* to produce 100 mL.

(2) Add 1 mL of 0.5M *sulfuric acid* to 50 mg of *tobramycin BPCRS*, dissolve in *water*, add sufficient *water* to produce 50 mL and mix. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Dilute 1 volume of a 0.024% w/v solution of *1-naphtholbenzein* in *acetonitrile* to 5 volumes with derivatised solution (2).

(4) *water* (blank solution).

Derivatise solutions (1), (2) and (4) using the following method. The solutions should be heated at the same temperature and for the same time as indicated below.

Transfer 4 mL of each solution separately into 50-mL volumetric flasks. To each solution add 10 mL of a 1% w/v solution of *1-fluoro-2,4-dinitrobenzene* in *ethanol (96%)* and 10 mL of a solution prepared by diluting 40 mL of a 1.5% w/v solution of *tris(hydroxymethyl)methylamine* in *water* to 200 mL with *dimethyl sulfoxide* and mixing. Heat in a water bath at 60° for 50 minutes. Remove the flasks, allow to stand for 10 minutes and add *acetonitrile* to about 2 mL below the meniscus. Allow to cool to room temperature and add sufficient *acetonitrile* to produce 50 mL.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 5 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 365 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 2.0 g of *tris(hydroxymethyl)aminomethane* in 800 mL of *water*, add 20 mL of 0.5M *sulfuric acid* and sufficient *acetonitrile* to produce 2000 mL. Allow to cool and filter (using a 0.2-µm, or finer, filter).

When the chromatograms are recorded under the prescribed conditions, the retention of 1-*naphtholbenzein* relative to tobramycin (retention time, about 20 minutes) is about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to 1-naphtholbenzein and tobramycin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$ in the substance being examined using the declared content of $C_{18}H_{37}N_5O_9$ in *tobramycin BPCRS*. Each mg of $C_{18}H_{37}N_5O_9$ is equivalent to 1.5245 mg of $(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$.

STORAGE

Tobramycin Sulfate should be stored in an airtight container.

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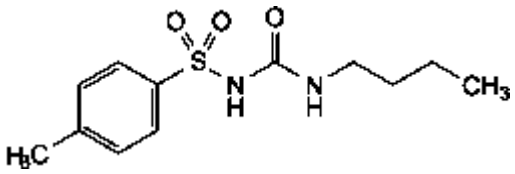
Tolbutamide

General Notices

(Ph. Eur. monograph 0304)



$C_{12}H_{18}N_2O_3S$ 270.3 *64-77-7*

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation

Tolbutamide Tablets

Ph Eur

DEFINITION

1-Butyl-3-[(4-methylphenyl)sulfonyl]urea.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, C.

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Second identification: A, B, D.

A. Melting point (2.2.14): 126 °C to 130 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution (a) Dissolve 25.0 mg in methanol R and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 10.0 mL of test solution (a) to 250.0 mL with methanol R.

Spectral range 245-300 nm for test solution (a); 220-235 nm for test solution (b).

Absorption maxima At 258 nm, 263 nm and 275 nm for test solution (a); at 228 nm for test solution (b).

Shoulder At 268 nm for test solution (a).

Specific absorbance at the absorption maximum 480 to 520 for test solution (b).

C. Infrared absorption spectrophotometry (2.2.24).

Comparison tolbutamide CRS.

D. To 0.2 g add 8 mL of a 500 g/L solution of sulfuric acid R and heat under a reflux condenser for 30 min. Allow to cool. Crystals are formed which, after recrystallisation from hot water R and drying at 105 °C, melt (2.2.14) at 135 °C to 140 °C.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.2 g in 5 mL of dilute sodium hydroxide solution R and add 5 mL of water R.

pH (2.2.3)

4.5 to 5.5.

To 2.0 g add 50 mL of carbon dioxide-free water R and heat at 70 °C for 5 min. Cool rapidly and filter.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of toluenesulfonamide R (impurity A) and 10 mg of toluenesulfonylurea R (impurity B) in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.5 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 1.5 times the retention time of tolbutamide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurities A and B.

Relative retention With reference to tolbutamide (retention time = about 18 min): impurity B = about 0.2; impurity A = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impuritites A and B.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 20 mL of *water R* and 40 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, using 1 mL of *phenolphthalein solution R* as indicator.

1 mL of *0.1 M sodium hydroxide* is equivalent to 27.03 mg of $C_{12}H_{18}N_2O_3S$.

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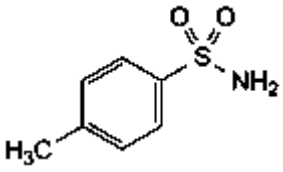
STORAGE

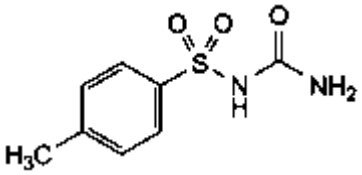
In an airtight container.

IMPURITIES

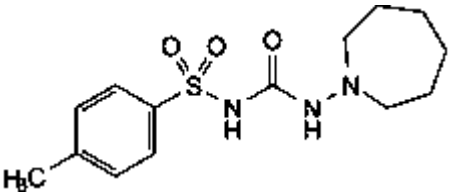
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



A. (4-methylphenyl)sulfonamide (toluenesulfonamide),



B. 1-[(4-methylphenyl)sulfonyl]urea (toluenesulfonylurea),



C. 1-azepan-1-yl-3-[(4-methylphenyl)sulfonyl]urea (tolazamide).

Ph Eur

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Tolbutamide Tablets

General Notices

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

DEFINITION

Tolbutamide Tablets contain Tolbutamide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tolbutamide, $C_{12}H_{18}N_2O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 1 g of Tolbutamide with 10 mL of *chloroform*, filter, evaporate the filtrate to dryness, scratching the side of the container, if necessary, to induce crystallisation, and dry the residue at 100° to 105° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of tolbutamide (*RS 343*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of a solution containing 2.04% w/v of *disodium hydrogen orthophosphate* and 0.135% w/v of *potassium dihydrogen orthophosphate* and rotating the basket at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium. Measure the *absorbance* of the filtered sample, suitably diluted if necessary, at the maximum at 228 nm, Appendix II B. Calculate the total content of tolbutamide, $C_{12}H_{18}N_2O_3S$, in the medium taking 417 as the value of A(1%, 1 cm) at the maximum at 228 nm.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 2 volumes of *anhydrous formic acid*, 8 volumes of *methanol* and 90 volumes of *chloroform* as the mobile phase. Apply separately to the plate 5 µL of each of solutions (1) and (2) and 10 µL of solution (3). For solution (1) shake a quantity of the powdered tablets containing 0.50 g of Tolbutamide with 10 mL of *acetone* and filter. Solution (2) contains 0.015% w/v of *toluene-p-sulfonamide* in *acetone*. Solution (3) is a mixture of equal volumes of solutions (1) and (2). After removal of the plate, dry it in a current of warm air and heat at 110° for 10 minutes. While still hot, place the plate in a chromatography tank with an evaporating dish containing a 5% w/v solution of *potassium permanganate*,

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add an equal volume of *hydrochloric acid* and close the tank. Leave the plate in the tank for 2 minutes, then place it in a current of cold air until the excess of chlorine is removed and an area of coating below the line of application gives at most a very faint blue colour with *potassium iodide and starch solution*; avoid prolonged exposure to cold air. Spray the plate with *potassium iodide and starch solution* and allow to stand for 5 minutes. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.3%). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.5 g of Tolbutamide add 50 mL of *ethanol* (*96%*) previously neutralised to *phenolphthalein solution R1*, warm to dissolve, add 25 mL of *water* and titrate with *0.1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 27.03 mg of $C_{12}H_{18}N_2O_3S$.

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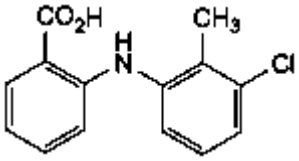
Tolfenamic Acid

General Notices

(Ph. Eur. monograph 2039)



$C_{14}H_{12}ClNO_2$ 261.7 *13710-19-5*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

2-(3-Chloro-2-methylanilino)benzoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in dimethylformamide, sparingly soluble in anhydrous ethanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

mp

About 213 °C.

IDENTIFICATION

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First identification: B.

Second identification: A, C.

A. Dissolve 20 mg in a mixture of 1 volume of *1 M hydrochloric acid* and 99 volumes of *methanol R* and dilute to 100 mL with the same mixture of solvents. Dilute 5.0 mL of the solution to 50 mL with a mixture of 1 volume of *1 M hydrochloric acid* and 99 volumes of *methanol R*. Examined between 250 nm and 380 nm (*2.2.25*), the solution shows 2 absorption maxima, at 286 nm and 345 nm. The ratio of the absorbance measured at the maximum at 286 nm to that measured at the maximum at 345 nm is 1.2 to 1.4.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *tolfenamic acid CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 25 mg of the substance to be examined in a mixture of 1 volume of *methanol R* and 3 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 25 mg of *tolfenamic acid CRS* in a mixture of 1 volume of *methanol R* and 3 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *glacial acetic acid R*, *dioxan R*, *toluene R* (1:25:90 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in 5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *2-chlorobenzoic acid R* (impurity A) and 25.0 mg of *3-chloro-2-methylaniline R* (impurity B) in 5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

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Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R*, *water for chromatography R*, *anhydrous ethanol R* (0.2:35:65 *V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 20 µL.

Run time 3 times the retention time of tolfenamic acid.

Relative retention With reference to tolfenamic acid (retention time = about 15 min): impurity A = about 0.25; impurity B = about 0.34.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity A and to impurity B.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity B*: not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.200 g with the aid of ultrasound in 100 mL of *anhydrous ethanol R*. Add 0.1 mL of *phenol red solution R* and titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 26.17 mg of $C_{14}H_{12}ClNO_2$.

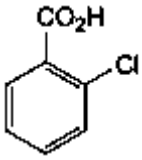
STORAGE

Protected from light.

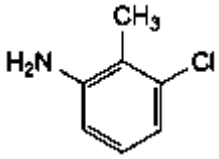
IMPURITIES

Specified impurities A, B.

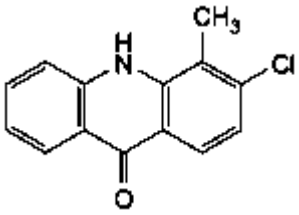
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. 2-chlorobenzoic acid,



B. 3-chloro-2-methylaniline,



C. 3-chloro-4-methylacridin-9(10*H*)-one.

Ph Eur

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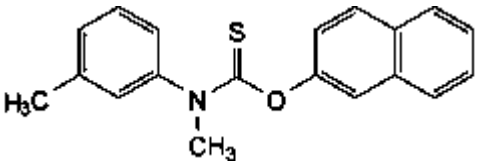
Tolnaftate

General Notices

(Ph. Eur. monograph 1158)



$C_{19}H_{17}NOS$ 307.4 *2398-96-1*

Action and use

Antifungal.

Ph Eur

DEFINITION

O-Naphthalen-2-yl methyl(3-methylphenyl)carbamothioate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in methylene chloride, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *tolnaftate CRS*.

TESTS

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Impurity D

Liquid chromatography (2.2.29).

Test solution Dissolve 0.400 g of the substance to be examined in 2 mL of *methylene chloride R*. Extract with 3 quantities, each of 3 mL, of *0.01 M hydrochloric acid*. Combine the aqueous phases and dilute to 10.0 mL with *0.01 M hydrochloric acid*.

Reference solution (a) Dissolve 20.0 mg of *N-methyl-m-toluidine R* (impurity D) in 50.0 mL of *methylene chloride R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with *methylene chloride R*. Take 2.0 mL of this solution and extract with 3 quantities, each of 3 mL, of *0.01 M hydrochloric acid*. Combine the aqueous phases and dilute to 10.0 mL with *0.01 M hydrochloric acid*.

Reference solution (c) Dissolve 10 mg of the substance to be examined in 25 mL of *methanol R*. Add 2 mL of this solution to 2 mL of reference solution (a) and dilute to 25 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *methanol R*, *water R* (0.1:10:90 *V/V/V*);

— *mobile phase B*: *trifluoroacetic acid R*, *water R*, *methanol R* (0.1:10:90 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	70	30
3 - 8	70 → 0	30 → 100
8 - 20	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 100 µL of the test solution and reference solution (b); 10 µL of reference solution (c).

Relative retention With reference to tolnaftate (retention time = about 15 min): impurity D = about 0.25.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to impurity D and tolnaftate in the chromatogram obtained with reference solution (c);

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— *symmetry factor*: maximum 1.9 for the peak due to impurity D in the chromatogram obtained with reference solution (b).

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (20 ppm).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *tolnaftate for system suitability CRS* (containing resolution component A) in 5.0 mL of *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *water R*, *methanol R* (0.1:30:70 *V/V/V*);

— *mobile phase B*: *trifluoroacetic acid R*, *water R*, *methanol R* (0.1:10:90 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	100	0
12 - 30	100 → 0	0 → 100
30 - 33	0	100

Flow rate 1.0 mL/ min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Relative retention With reference to tolnaftate (retention time = about 18 min): resolution component A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to resolution component A and tolnaftate.

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Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 50.0 mg in *methanol R* and dilute to 250.0 mL with the same solvent. Dilute 2.0 mL of this solution to 50.0 mL with *methanol R*. Measure the absorbance (2.2.25) at the absorption maximum at 257 nm.

Calculate the content of $C_{19}H_{17}NOS$ taking the specific absorbance to be 720.

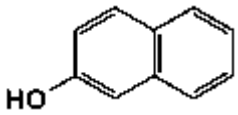
STORAGE

Protected from light.

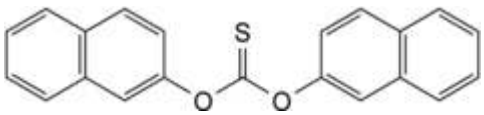
IMPURITIES

Specified impurities D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



A. naphthalen-2-ol (β-naphthol),



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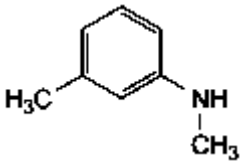
B. *O*,*O*-dinaphthalen-2-yl carbonothioate,



D. *N*,3-dimethylaniline (*N*-methyl-*m*-toluidine).

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Tolterodine Prolonged-release Capsules

General Notices

Tolterodine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Anticholinergic.

DEFINITION

Tolterodine Prolonged-release Capsules contain Tolterodine Tartrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Tolterodine Tartrate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of tolterodine tartrate, $C_{22}H_{31}NO, C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 12.5 mg of Tolterodine Tartrate with 5 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.25% w/v of *tolterodine tartrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

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1 volume of *triethylamine* 15 volumes of *ethyl acetate* and 35 volumes of *n-pentane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 10 mg of Tolterodine Tartrate with 7 mL of *methanol R1*, add sufficient *methanol R1* to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol R1*.
(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.
(4) Dilute 1 volume of solution (2) to 5 volumes with *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A To 450 volumes of 0.288% w/v *ammonium dihydrogen orthophosphate* add 5 volumes of *triethylamine R2* and adjust the mixture to pH 5.9 with a 50% v/v solution of *orthophosphoric acid*. Add 550 volumes of *methanol R1*.
Mobile phase B *methanol R1*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-45	100→80	0→20	linear gradient
45-46	80	20	isocratic
46-50	80→100	20→0	linear gradient
50-60	100	0	re-equilibration

When the chromatograms are recorded under prescribed conditions, the relative retention of impurity E with reference to tolterodine tartrate (retention time about 7 minutes) is 0.82.

SYSTEM SUITABILITY

When The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Tolterodine Tartrate comply with the requirements stated under Capsules using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake the contents of one capsule in sufficient *methanol R1* to obtain a solution containing 0.01% w/v of Tolterodine Tartrate and filter.
(2) 0.01% w/v of *tolterodine tartrate BPCRS* in *methanol R1*.
(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.

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(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

To 450 volumes of 0.288% w/v *ammonium dihydrogen orthophosphate* add 5 volumes of *triethylamine R2* and adjust the mixture to pH 5.9 with a 50% v/v solution of *orthophosphoric acid*. Add 550 volumes of *methanol R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{22}H_{31}NO, C_4H_6O_6$ in the capsules using the declared content of $C_{22}H_{31}NO, C_4H_6O_6$ in *tolterodine tartrate BPCRS*.

ASSAY

For capsules containing less than 2 mg and/or less than 2% w/w of Tolterodine Tartrate

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing 2 mg or more and 2% w/w or more of Tolterodine Tartrate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the mixed contents of 20 capsules containing 10 mg of Tolterodine Tartrate with 80 mL of *methanol R1*, dilute to 100 mL with the same solvent and filter.

(2) 0.01% w/v of *tolterodine tartrate BPCRS* in *methanol R1*.

(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{31}NO, C_4H_6O_6$ in the capsules using the declared content of $C_{22}H_{31}NO, C_4H_6O_6$ in *tolterodine tartrate BPCRS*

IMPURITIES

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Tolterodine Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Tolterodine Tablets contain Tolterodine Tartrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tolterodine tartrate, $C_{22}H_{31}NO$, $C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 12.5 mg of Tolterodine Tartrate with 5 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.25% w/v of *tolterodine tartrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *triethylamine* 15 volumes of *ethyl acetate* and 35 volumes of *n-pentane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the test for Dissolution, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a 0.68% w/v solution of *potassium dihydrogen orthophosphate* in 0.0224M *sodium hydroxide* at a temperature of 37°, as the dissolution medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Use the filtrate, diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.0001% w/v of Tolterodine Tartrate.

(2) 0.0001% w/v of *tolterodine tartrate BPCRS* in the dissolution medium.

(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

To 450 volumes of 0.288% w/v *ammonium dihydrogen orthophosphate* add 5 volumes of *triethylamine R2* and adjust the mixture to pH 5.9 with a 50% v/v solution of *orthophosphoric acid*. Add 550 volumes of *methanol R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{31}NO, C_4H_6O_6$ in the medium using the declared content of $C_{22}H_{31}NO, C_4H_6O_6$ in *tolterodine tartrate BPCRS*.

LIMITS

The amount of tolterodine tartrate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Shake a quantity of the powdered tablets containing 10 mg of Tolterodine Tartrate with 7 mL of *methanol R1*, add sufficient *methanol R1* to produce 10 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol R1*.

(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

(4) Dilute 1 volume of solution (2) to 5 volumes with *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A To 450 volumes of 0.288% w/v *ammonium dihydrogen orthophosphate* add 5 volumes of *triethylamine R2* and adjust the mixture to pH 5.9 with a 50% v/v solution of *orthophosphoric acid*. Add 550 volumes of *methanol R1*.

Mobile phase B *methanol R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	100	0	isocratic
25-45	100→80	0→20	linear gradient
45-46	80	20	isocratic
46-50	80→100	20→0	linear gradient
50-60	100	0	re-equilibration

When the chromatograms are recorded under prescribed conditions, the relative retention of impurity E with reference to tolterodine tartrate (retention time about 7 minutes) is 0.82.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Tolterodine Tartrate comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake one tablet in sufficient *methanol R1* to obtain a solution containing 0.01% w/v of Tolterodine Tartrate and filter.
(2) 0.01% w/v of *tolterodine tartrate BPCRS* in *methanol R1*.
(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{31}NO, C_4H_6O_6$ in the tablets using the declared content of $C_{22}H_{31}NO, C_4H_6O_6$ in *tolterodine tartrate BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Tolterodine Tartrate

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Tolterodine Tartrate

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 10 mg of Tolterodine Tartrate with 80 mL of *methanol R1*, dilute to 100 mL with the same solvent and filter.
(2) 0.01% w/v of *tolterodine tartrate BPCRS* in *methanol R1*.
(3) 0.02% w/v of *tolterodine tartrate BPCRS* and 0.004% w/v of *tolterodine impurity E EPCRS* in *methanol R1*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 10 µL.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity E and tolterodine tartrate is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{31}NO, C_4H_6O_6$ in the tablets using the declared content of $C_{22}H_{31}NO, C_4H_6O_6$ in *tolterodine tartrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Tolterodine Tartrate.

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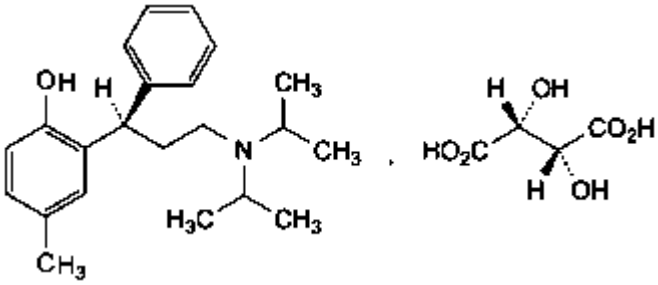
Tolterodine Tartrate

General Notices

(Ph. Eur. monograph 2781)



$C_{26}H_{37}NO_7$ 475.6 *124937-52-6*

Action and use

Anticholinergic.

Preparations

Tolterodine Prolonged-release Capsules

Tolterodine Tablets

Ph Eur

DEFINITION

2-[(1*R*)-3-[Bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison tolterodine tartrate CRS.

B. Enantiomeric purity (see Tests).

C. It gives reaction (b) of tartrates (2.3.1).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Solution A Dissolve 0.29 g of sodium dihydrogen phosphate monohydrate R and 0.47 g of disodium hydrogen phosphate dihydrate R in 1 L of water R. Dissolve 1.04 g of tetrabutylammonium bromide R in this solution.

Test solution Dissolve 4.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of tolterodine for system suitability CRS (containing impurity F) in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 0.5 mL of the test solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 2 mm;

— *stationary phase*: α1-acid-glycoprotein silica gel for chiral separation R (5 µm).

Mobile phase 2-methylpropanol R, solution A (7:93 *V/V*).

Flow rate 0.2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 1.5 times the retention time of tolterodine.

Relative retention With reference to tolterodine (retention time = about 23 min): impurity F = about 0.9.

System suitability Reference solution (a):

— peak-to-valley ratio: minimum 2.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to tolterodine.

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Calculation of percentage content:

— for impurity F, use the concentration of tolterodine tartrate in reference solution (b).

Limit:

— *impurity F*: maximum 0.6 per cent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of methanol R1, sonicate until dissolution is complete and dilute to 25.0 mL with methanol R1.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with methanol R1. Dilute 1.0 mL of this solution to 10.0 mL with methanol R1.

Reference solution (b) Dissolve 2 mg of tolterodine impurity E CRS in methanol R1 and dilute to 10.0 mL with methanol R1. Dilute 1.0 mL of the solution to 20.0 mL with methanol R1.

Reference solution (c) Dissolve 25 mg of the substance to be examined in 10 mL of methanol R1. Sonicate until dissolution is complete. Add 5 mL of reference solution (b) and dilute to 25.0 mL with methanol R1.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: mix 5 volumes of triethylamine R2 and 450 volumes of a 2.88 g/L solution of ammonium dihydrogen phosphate R; adjust to pH 5.9 with a 50 per cent *V/V* solution of phosphoric acid R; add 550 volumes of methanol R1;

— *mobile phase B*: methanol R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 45	100 → 80	0 → 20

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (a) and (c).

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Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E.

Relative retention With reference to tolterodine (retention time = about 7 min): tartaric acid = about 0.2; impurity E = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity E and tolterodine.

Calculation of percentage contents:

— for each impurity, use the concentration of tolterodine tartrate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to tartaric acid.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 30.0 mL of *anhydrous acetic acid R* and sonicate until dissolution is complete. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 47.56 mg of $C_{26}H_{37}NO_7$.

IMPURITIES

Specified impurities *F*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, G*.

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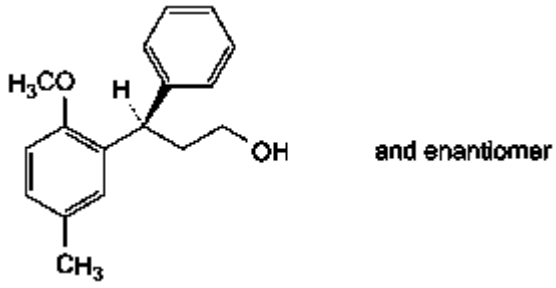
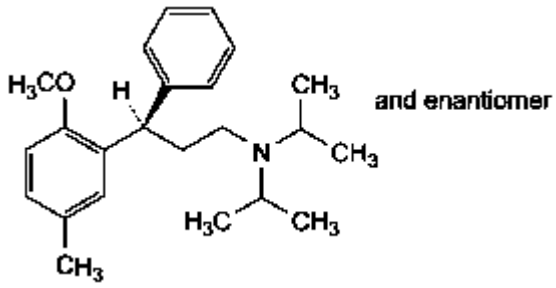
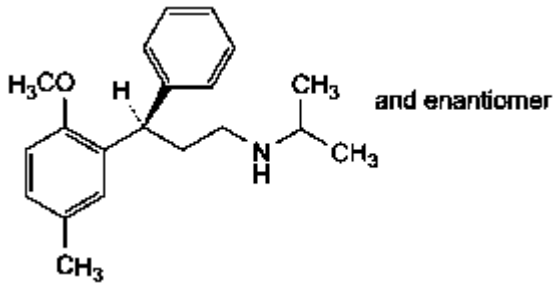


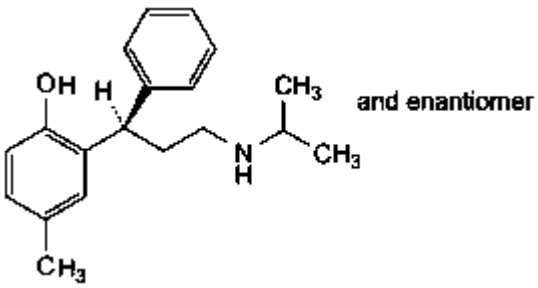
A. (3*RS*)-3-(2-methoxy-5-methylphenyl)-3-phenylpropan-1-ol,



C. (3*RS*)-3-(2-methoxy-5-methylphenyl)-*N*,*N*-bis(1-methylethyl)-3-phenylpropan-1-amine,



D. (3*RS*)-3-(2-methoxy-5-methylphenyl)-*N*-(1-methylethyl)-3-phenylpropan-1-amine,



E. 4-methyl-2-[(1*RS*)-3-[(1-methylethyl)amino]-1-phenylpropyl]phenol,

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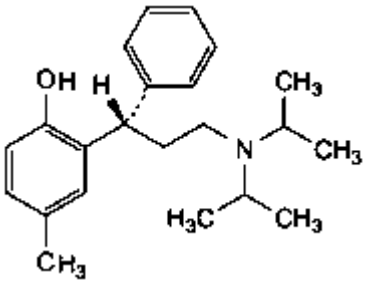
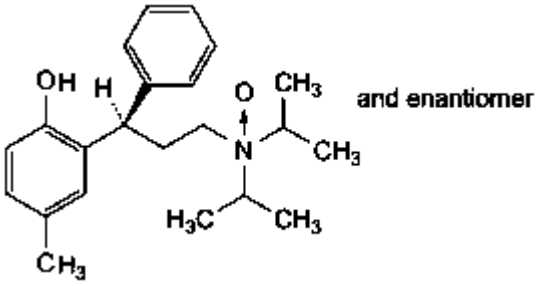


F. 2-[(1*S*)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol,



G. 2-[(1*R*)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol *N*-oxide.

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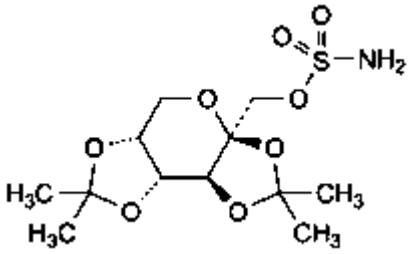
Topiramate

General Notices

(Ph. Eur. monograph 2616)



$C_{12}H_{21}NO_8S$ 339.4 *97240-79-4*

Action and use

Antiepileptic.

Ph Eur

DEFINITION

2,3:4,5-Bis-*O*-(propan-2,2-diyl)-β-D-fructopyranose 1-sulfamate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in methanol and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *topiramate CRS*.

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TESTS

Specific optical rotation (2.2.7)

-32 to -29 (anhydrous substance).

Dissolve 0.200 g in *methanol R* and dilute to 50.0 mL with the same solvent.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 40.0 mg of the substance to be examined in 1.0 mL of *methanol R*.

Reference solution (a) Dissolve 10.0 mg of *topiramate impurity A CRS* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 5.0 mL with *methanol R*.

Reference solution (b) Dissolve 40 mg of the substance to be examined in 1 mL of reference solution (a).

Plate *TLC silanised silica gel plate R*.

Pretreatment Wash the plate with *methanol R* and allow to dry in air.

Mobile phase *methanol R*, *acetonitrile R*, 29 g/L solution of *sodium chloride R* (15:35:50 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a solution prepared by dissolving 3 g of *phenol R* in 95 mL of *ethanol (96 per cent) R* and carefully adding 5 mL of *sulfuric acid R*; allow to dry in air, then heat at 125 °C for 10 min. Use transmittance mode.

Retardation factors Topiramate = about 0.43; impurity A = about 0.55.

System suitability:

— the chromatogram obtained with reference solution (b) shows 2 clearly separated spots due to topiramate and impurity A.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

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Solvent mixture acetonitrile R1, mobile phase A (20:80 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 15.0 mg of topiramate impurity E CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 200.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of the substance to be examined in 1 mL of a mixture of 2 volumes of acetonitrile R1, 4 volumes of water for chromatography R and 4 volumes of *anhydrous formic acid R*. Incubate at 60 °C for 30 min (*in situ* preparation of impurity C). Dilute 20 µL of the solution to 1 mL with a 25 mg/L solution of fructose R (impurity E).

Reference solution (d) Dissolve 25.0 mg of topiramate CRS in 10.0 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped solid core pentafluorophenylpropylsilyl silica gel for chromatography R (2.6 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1.93 g/L solution of ammonium acetate R adjusted to pH 3.5 with glacial acetic acid R;

— *mobile phase B*: acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 15	80 → 50	20 → 50
15 - 15.1	50 → 80	50 → 20

Flow rate 1.0 mL/min.

Detection Charged aerosol detector:

— *range*: 100 pA;

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— *filter*: none.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to topiramate (retention time = about 5.6 min): impurity E = about 0.18; impurity C = about 0.25.

System suitability Reference solution (c):

— *resolution*: minimum 4.5 between the peaks due to impurities E and C.

Calculation of percentage contents:

— for impurity E, use the concentration of impurity E in reference solution (b) and the height of the peak due to impurity E;

— for impurities other than E, use the concentration of topiramate in reference solution (a).

Limits:

— *impurity E*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{12}H_{21}NO_8S$ taking into account the assigned content of *topiramate CRS*.

IMPURITIES

Specified impurities *A, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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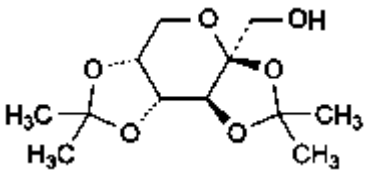
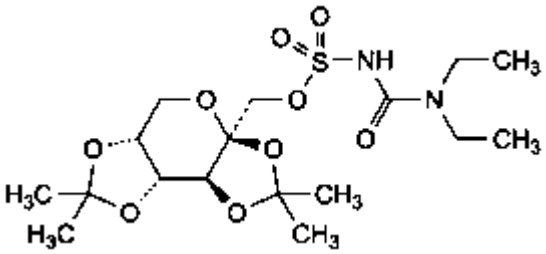
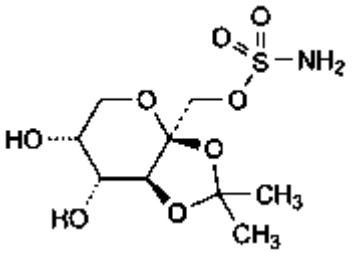
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D.*



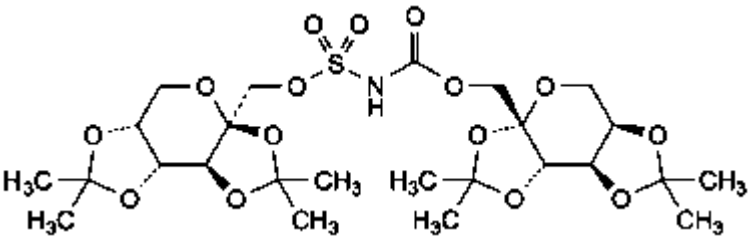
A. 2,3:4,5-bis-*O*-(propan-2,2-diyl)-β-D-fructopyranose,



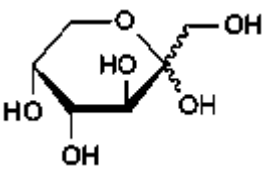
B. 2,3:4,5-bis-*O*-(propan-2,2-diyl)-β-D-fructopyranose 1-[*N*-(diethylcarbamoyl)sulfamate],



C. 2,3-*O*-(propan-2,2-diyl)-β-D-fructopyranose 1-sulfamate,



D. 2,3:4,5-bis-*O*-(propan-2,2-diyl)-β-D-fructopyranose 1-[*N*-[[[2,3:4,5-bis-*O*-(propan-2,2-diyl)-β-D-fructopyranosyl]oxy]carbamoyl]sulfamate],



E. D-fructopyranose (fructose).

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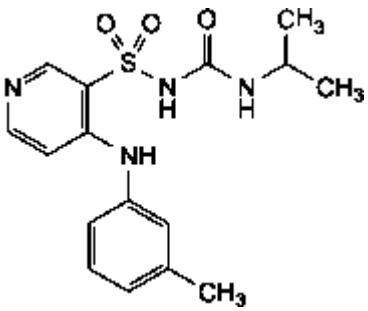
Torasemide

General Notices

Anhydrous Torasemide

(Ph. Eur. monograph 2132)



$C_{16}H_{20}N_4O_3S$ 348.4 *56211-40-6*

Action and use

Thiazide-like diuretic.

Ph Eur

DEFINITION

1-(1-Methylethyl)-3-[[4-[(3-methylphenyl)amino]pyridin-3-yl]sulfonyl]urea.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent). It is sparingly soluble in dilute solutions of alkali hydroxides and slightly soluble in dilute acids.

It shows polymorphism (*5.9*).

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison anhydrous torasemide CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 2.7 g of potassium dihydrogen phosphate R in 950 mL of water R, adjust to pH 3.5 with phosphoric acid R and dilute to 1000 mL with water R.

Test solution Dissolve 20.0 mg of the substance to be examined in 15 mL of methanol R and sonicate for 15 min. Add 22.5 mL of solution A, cool to room temperature and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of torasemide for system suitability CRS (containing impurities A, B, C and D) in 2.5 mL of methanol R and dilute to 5.0 mL with solution A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of torasemide impurity E CRS in 0.5 mL of methanol R. Add 0.5 mL of solution A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase methanol R, solution A (40:60 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 288 nm.

Injection 20 µL.

Run time 2.5 times the retention time of torasemide.

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Identification of impurities Use the chromatogram supplied with *torasemide for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E.

Relative retention With reference to torasemide (retention time = about 10 min): impurity A = about 0.3; impurity B = about 0.4; impurity C = about 0.5; impurity E = about 0.7; impurity D = about 2.3.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to impurities B and C in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 100 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 5.1; impurity B = 0.76;

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities A, C, D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 34.84 mg of $C_{16}H_{20}N_4O_3S$.

STORAGE

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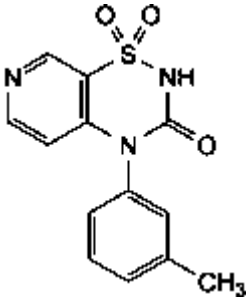
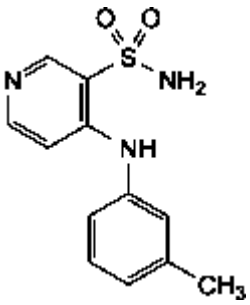
Protected from light.

IMPURITIES

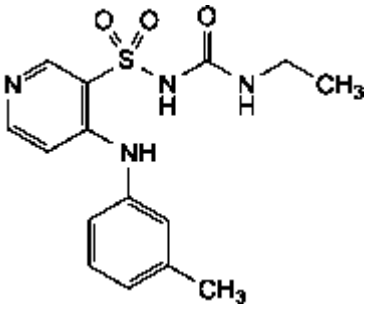
Specified impurities *A, B, C, D, E.*



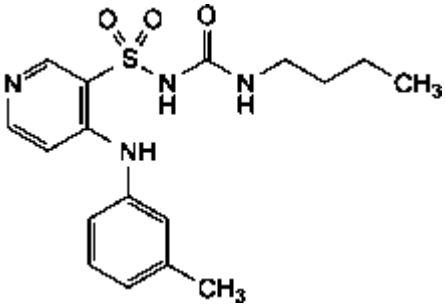
A. 4-(3-methylphenyl)-2*H*-pyrido[4,3-*e*]-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide,



B. 4-[(3-methylphenyl)amino]pyridine-3-sulfonamide,



C. 1-ethyl-3-[[4-[(3-methylphenyl)amino]pyridin-3-yl]sulfonyl]urea,



D. 1-butyl-3-[[4-[(3-methylphenyl)amino]pyridin-3-yl]sulfonyl]urea,

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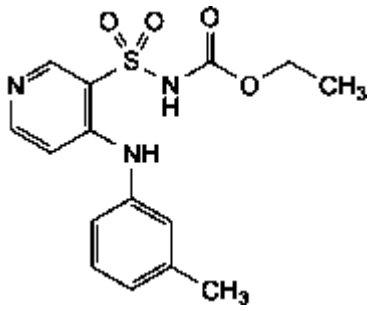

E. ethyl [[4-[(3-methylphenyl)amino]pyridin-3-yl]sulfonyl]carbamate.

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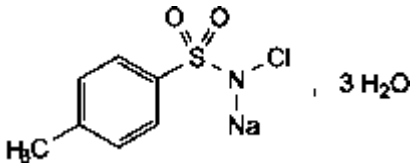
Tosylchloramide Sodium

General Notices

(Ph. Eur. monograph 0381)



$C_7H_7ClNNaO_2S,3H_2O$ 281.7

Action and use

Antiseptic.

Ph Eur

DEFINITION

Sodium *N*-chloro-4-methylbenzene-sulfonimidate trihydrate.

Content

98.0 per cent to 103.0 per cent of $C_7H_7ClNNaO_2S,3H_2O$.

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) turns *red litmus paper R* blue and then bleaches it.

B. To 10 mL of solution S add 10 mL of *dilute hydrogen peroxide solution R*. A white precipitate is formed which dissolves on heating. Filter the hot solution and allow to cool. White crystals are formed which, when washed and dried at 100-105 °C, melt (*2.2.14*) at 137 °C to 140 °C.

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C. Ignite cautiously 1 g, because of the risk of deflagration. Dissolve the residue in 10 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

D. The solution prepared for identification test C gives reaction (a) of sulfates (*2.3.1*).

E. The solution prepared for identification test C gives reaction (b) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

8.0 to 10.0 for solution S.

Ortho compound

To 2 g add 10 mL of *water R*, mix, add 1 g of *sodium metabisulfite R* and heat to boiling. Cool to 0 °C, filter rapidly and wash with 3 quantities, each of 5 mL, of iced *water R*. The precipitate, dried *in vacuo* (*2.2.32*) at a pressure not exceeding 0.6 kPa, melts (*2.2.14*) at a minimum of 134 °C.

Residue insoluble in anhydrous ethanol

Maximum 2 per cent.

Shake 1.00 g with 20 mL of *anhydrous ethanol R* for 30 min, filter on a tared filter, wash any residue with 5 mL of *anhydrous ethanol R* and dry at 100-105 °C. The residue weighs a maximum of 20 mg.

ASSAY

Dissolve 0.125 g in 100 mL of *water R* in a ground-glass-stoppered flask. Add 1 g of *potassium iodide R* and 5 mL of *dilute sulfuric acid R*. Allow to stand for 3 min. Titrate with *0.1 M sodium thiosulfate*, using 1 mL of *starch solution R* as indicator.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 14.08 mg of $C_7H_7ClNNaO_2S,3H_2O$.

STORAGE

In an airtight container, protected from light.

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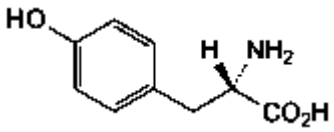
Tyrosine

General Notices

(Ph. Eur. monograph 1161)



$C_9H_{11}NO_3$ 181.2 *60-18-4*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-(4-hydroxyphenyl)propanoic acid.

Product of fermentation or of protein hydrolysis.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D, E.

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *tyrosine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 1 mL of *dilute ammonia R2* and dilute to 50 mL with *water R*.

Reference solution Dissolve 10 mg of *tyrosine CRS* in 1 mL of *dilute ammonia R2* and dilute to 50 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R1*, *propanol R* (30:70 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. To about 50 mg add 1 mL of *dilute nitric acid R*. A dark red colour is produced within 15 min.

E. Dissolve about 30 mg in 2 mL of *dilute sodium hydroxide solution R*. Add 3 mL of a freshly prepared mixture of equal volumes of a 100 g/L solution of *sodium nitrite R* and a solution of 0.5 g of *sulfanilic acid R* in a mixture of 6 mL of *hydrochloric acid R1* and 94 mL of *water R*. An orange-red colour is produced.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Dissolve 0.5 g in *dilute hydrochloric acid R* and dilute to 20 mL with the same acid.

Specific optical rotation (2.2.7)

-12.3 to -11.0 (dried substance).

Dissolve 1.25 g in a mixture of equal volumes of *dilute hydrochloric acid R* and *water R* and dilute to 25.0 mL with the same mixture of solvents.

Ninhydrin-positive substances

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Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A dilute hydrochloric acid R1 or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of phenylalanine R (impurity A) in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dissolve 30.0 mg of proline R in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (d) Dilute 6.0 mL of ammonium standard solution (100 ppm NH_4) R to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (e) Dissolve 30 mg of isoleucine R and 30 mg of leucine R in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (e):

— resolution: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (b);

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of tyrosine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (c); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *impurity A at 570 nm*: maximum 0.5 per cent;

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

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— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.25 g in 3 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*. The solution, without further addition of nitric acid, complies with the test.

Sulfates (2.4.13)

Maximum 300 ppm.

Dissolve, with gentle heating, 0.5 g in 5 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (d) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (2.4.9)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 5 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

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1 mL of *0.1 M perchloric acid* is equivalent to 18.12 mg of $C_9H_{11}NO_3$.

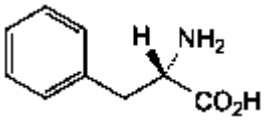
STORAGE

Protected from light.

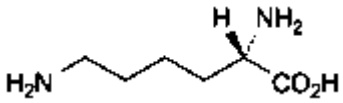
IMPURITIES

Specified impurities A.

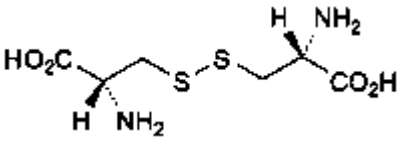
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. (2*S*)-2-amino-3-phenylpropanoic acid (phenylalanine),



B. (2*S*)-2,6-diaminohexanoic acid (lysine),



C. 3,3′-disulfanediylbis[(2*R*)-2-aminopropanoic acid] (cystine).

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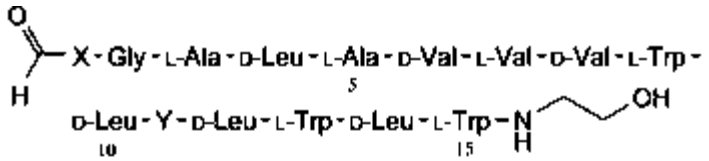
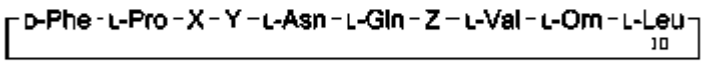
Tyrothricin

General Notices

(Ph. Eur. monograph 1662)



Gramicidin	Mol. formula	M_r	X	Y
A1	$C_{99}H_{140}N_{20}O_{17}$	1882	L-Val	L-Trp
A2	$C_{100}H_{142}N_{20}O_{17}$	1896	L-Ile	L-Trp
C1	$C_{97}H_{139}N_{19}O_{18}$	1859	L-Val	L-Tyr
C2	$C_{98}H_{141}N_{19}O_{18}$	1873	L-Ile	L-Tyr



Tyrocidin	Mol. formula	M_r	X	Y	Z
A	$C_{66}H_{88}N_{13}O_{13}$	1271	L-Phe	D-Phe	L-Tyr
B	$C_{68}H_{89}N_{14}O_{13}$	1311	L-Trp	D-Phe	L-Tyr
C	$C_{70}H_{90}N_{15}O_{13}$	1350	L-Trp	D-Trp	L-Tyr
D	$C_{72}H_{91}N_{16}O_{12}$	1373	L-Trp	D-Trp	L-Trp
E	$C_{66}H_{88}N_{13}O_{12}$	1255	L-Phe	D-Phe	L-Phe

Action and use

Polypeptide antibacterial.

Ph Eur

DEFINITION

Mixture of antimicrobial linear and cyclic polypeptides, isolated from the fermentation broth of *Brevibacillus brevis* Dubos. It consists mainly of gramicidins and tyrocidins as described above; other related compounds may be present in smaller amounts.

Potency

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180 IU/mg to 280 IU/mg (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in 4.0 mL of *ethanol (96 per cent) R*.

Reference solution Dissolve 5 mg of *tyrothricin CRS* in 4.0 mL of *ethanol (96 per cent) R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *butanol R*, *water R*, *acetic acid R*, *butyl acetate R* (2.5:7.5:12:20:40 *V/V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spots or groups of principal spots in the chromatogram obtained with the test solution are similar in position and size to the principal spots or groups of principal spots in the chromatogram obtained with the reference solution. The upper group corresponds to gramicidins, the lower group to tyrocidins.

Detection B Spray with *dimethylaminobenzaldehyde solution R2*. Heat the plate in a current of warm air until the spots appear.

System suitability Reference solution:

— the chromatogram shows 2 clearly separated spots or groups of spots.

Results B The principal spots or groups of principal spots in the chromatogram obtained with the test solution are similar in position, colour and size to the principal spots or groups of principal spots in the chromatogram obtained with the reference solution. The upper group corresponds to gramicidins, the lower group to tyrocidins.

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B. Composition (see Tests).

TESTS

Composition

Liquid chromatography (2.2.29): use the normalisation procedure. *Prepare the solutions immediately before use.*

Test solution Dissolve 5 mg of the substance to be examined in 2 mL of methanol R and dilute to 5.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of tyrothricin CRS in 2 mL of methanol R and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm),

— *temperature*: 60 °C.

Mobile phase 0.79 g/L solution of ammonium sulfate R, methanol R (25:75 *V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 25 µL.

Run time 6 times the retention time of gramicidin A1. Use the chromatogram obtained with reference solution (a) and the chromatogram supplied with tyrothricin CRS to identify the peaks due to gramicidin A1, gramicidin A2 and the tyrocidins.

Relative retention With reference to gramicidin A1 (retention time = about 10 min): gramicidin C1 = about 0.8; gramicidin C2 = about 0.9; gramicidin A2 = about 1.1; tyrocidins = about 1.5 to 6.

System suitability Reference solution (a):

— peak-to-valley ratio: minimum 3.0, where H_p = height above the baseline of the peak due to gramicidin A2 and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to gramicidin A1.

Limits:

— *sum of gramicidins*: 25 per cent to 50 per cent,

— *sum of tyrocidins*: 50 per cent to 70 per cent,

— *total*: minimum 85 per cent,

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— *disregard limit*: the sum of the areas of the peaks due to gramicidins in the chromatogram obtained with reference solution (b).

Loss on drying (2.2.32)

Maximum 4.0 per cent, determined on 1.000 g by drying under high vacuum at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 1.5 per cent, determined on 1.0 g.

ASSAY

Carry out the microbiological assay of antibiotics (2.7.2) using the turbidimetric method. Use *gramicidin CRS* as the reference substance.

Test solution Prepare a solution of tyrothricin containing about the same amount of gramicidin as the corresponding solution of *gramicidin CRS* i.e. 5 times more concentrated.

STORAGE

In an airtight container, protected from light.

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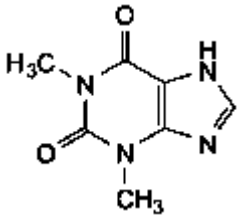
Theophylline

General Notices

(Ph. Eur. monograph 0299)



$C_7H_8N_4O_2$ 180.2 *58-55-9*

Action and use

Non-selective phosphodiesterase inhibitor (xanthine); treatment of reversible airways obstruction.

Preparations

Aminophylline Injection

Theophylline Prolonged-release Tablets

Ph Eur

DEFINITION

1,3-Dimethyl-3,7-dihydro-1*H*-purine-2,6-dione.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides, in ammonia and in mineral acids.

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IDENTIFICATION

First identification: B, D.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 270 °C to 274 °C, determined after drying at 100-105 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of theophylline*.

C. Heat 10 mg with 1.0 mL of a 360 g/L solution of *potassium hydroxide R* in a water-bath at 90 °C for 3 min, then add 1.0 mL of *diazotised sulfanilic acid solution R*. A red colour slowly develops. Carry out a blank test.

D. Loss on drying (see Tests).

E. It gives the reaction of xanthines (2.3.1).

TESTS

Solution S

Dissolve 0.5 g with heating in *carbon dioxide-free water R*, cool and dilute to 75 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity

To 50 mL of solution S add 0.1 mL of *methyl red solution R*. The solution is red. Not more than 1.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *theobromine R* in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase. Dilute 5 mL of this solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (7 µm).

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Mobile phase Mix 7 volumes of *acetonitrile for chromatography R* and 93 volumes of a 1.36 g/L solution of *sodium acetate R* containing 5.0 mL/L of *glacial acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL.

Run time 3.5 times the retention time of theophylline.

Relative retention With reference to theophylline (retention time = about 6 min): impurity C = about 0.3; impurity B = about 0.4; impurity D = about 0.5; impurity A = about 2.5.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to theobromine and theophylline.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 100 mL of *water R*, add 20 mL of *0.1 M silver nitrate* and shake. Add 1 mL of *bromothymol blue solution R1*. Titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

IMPURITIES

Specified impurities *A, B, C, D.*

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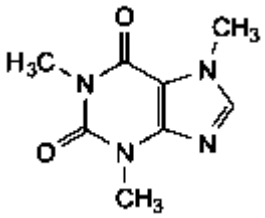
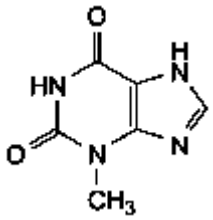
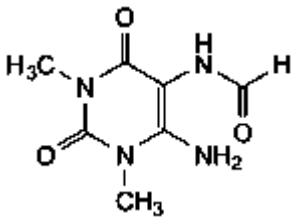
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E, F.



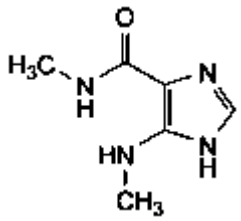
A. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),



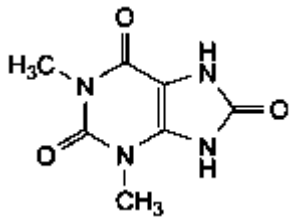
B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



C. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



D. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide (theophyllidine),



E. 1,3-dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione,

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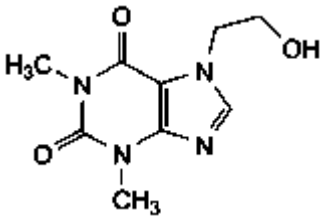

F. 7-(2-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (etofylline).

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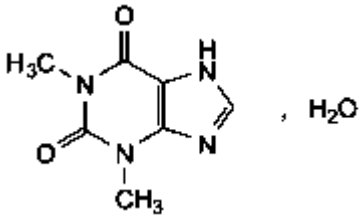
Theophylline Hydrate

General Notices

(Theophylline Monohydrate, Ph. Eur. monograph 0302)



$C_7H_8N_4O_2,H_2O$ 198.2 *5967-84-0*

Action and use

Non-selective phosphodiesterase inhibitor (xanthine); treatment of reversible airways obstruction.

Preparations

Aminophylline Injection

Theophylline Prolonged-release Tablets

Ph Eur

DEFINITION

1,3-Dimethyl-3,7-dihydro-1*H*-purine-2,6-dione monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides, in ammonia and in mineral acids.

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IDENTIFICATION

First identification: B, D.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 270 °C to 274 °C, determined after drying at 100-105 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Dry the substance to be examined at 100-105 °C before use.

Comparison *Ph. Eur. reference spectrum of theophylline*.

C. Heat 10 mg with 1.0 mL of a 360 g/L solution of *potassium hydroxide R* in a water-bath at 90 °C for 3 min, then add 1.0 mL of *diazotised sulfanilic acid solution R*. A red colour slowly develops. Carry out a blank test.

D. Water (see Tests).

E. It gives the reaction of xanthines (2.3.1).

TESTS

Solution S

Dissolve 0.5 g with heating in *carbon dioxide-free water R*, cool and dilute to 75 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity

To 50 mL of solution S add 0.1 mL of *methyl red solution R*. The solution is red. Not more than 1.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *theobromine R* in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase. Dilute 5 mL of this solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

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— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 7 volumes of *acetonitrile for chromatography R* and 93 volumes of a 1.36 g/L solution of *sodium acetate R* containing 5.0 mL/L of *glacial acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL.

Run time 3.5 times the retention time of theophylline.

Relative retention With reference to theophylline (retention time = about 6 min): impurity C = about 0.3; impurity B = about 0.4; impurity D = about 0.5; impurity A = about 2.5.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to theobromine and theophylline.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

8.0 per cent to 9.5 per cent, determined on 0.20 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.160 g in 100 mL of *water R*, add 20 mL of *0.1 M silver nitrate* and shake. Add 1 mL of *bromothymol blue solution R1*. Titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

IMPURITIES

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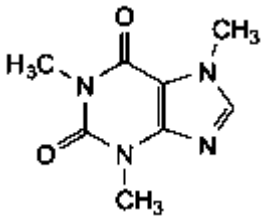
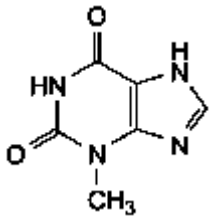
Specified impurities *A, B, C, D.*

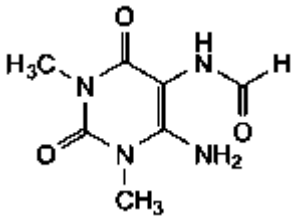
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F.*



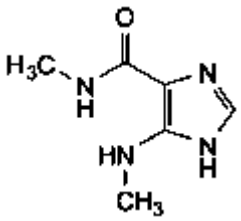
A. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),



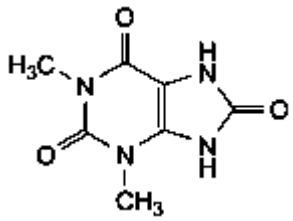
B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



C. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



D. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide (theophyllidine),



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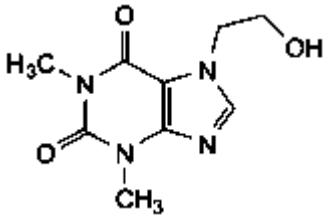
E. 1,3-dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione,



F. 7-(2-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (etofylline).

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Theophylline Prolonged-release Tablets

General Notices

Prolonged-release Theophylline Tablets

Theophylline Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Non-selective phosphodiesterase inhibitor (xanthine); treatment of reversible airways obstruction.

DEFINITION

Theophylline Prolonged-release Tablets contain Theophylline or Theophylline Hydrate. The are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Theophylline. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of theophylline, $C_7H_8N_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. Extract a quantity of the powdered tablets containing the equivalent of 0.2 g of theophylline with 10 mL of a mixture of 60 volumes of *chloroform* and 40 volumes of *methanol*, filter and evaporate the filtrate to dryness. The residue yields the reaction characteristic of *xanthines*, Appendix VI.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel F_{254} plate* and a mixture of 10 volumes of *concentrated ammonia*, 30 volumes of *acetone*, 30 volumes of *chloroform* and 40 volumes of *butan-1-ol* as the mobile phase. Apply

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separately to the plate 10 µL of each of the following solutions. For solution (1) mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 0.2 g of theophylline with 10 mL of a mixture of 60 volumes of *chloroform* and 40 volumes of *methanol* and centrifuge. For solution (2) dilute 1 volume of solution (1) to 200 volumes with a mixture of 60 volumes of *chloroform* and 40 volumes of *methanol*. After removal of the plate, allow it to dry in air and view under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the principal spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 1 mL of *methanol* to a quantity of the powdered tablets containing the equivalent of 0.1 g of theophylline, mix and add 50 mL of *water*. Dissolve with the aid of ultrasound, swirling occasionally, dilute to 100 mL with *water* and mix thoroughly. Dilute 5 mL to 50 mL with *water*. Solution (2) contains 0.01% w/v of *theophylline BPCRS* in water.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) as the mobile phase with a flow rate of 1.8 mL per minute a mixture of 250 volumes of *methanol* and 750 volumes of *water* and (c) a detection wavelength of 270 nm.

Calculate the content of $C_7H_8N_4O_2$ in the tablets using the declared content of $C_7H_8N_4O_2$ in *theophylline BPCRS*.

LABELLING

When the active ingredient is Theophylline Hydrate the quantity is stated in terms of the equivalent amount of theophylline.

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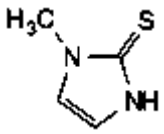
Thiamazole

General Notices

(Ph. Eur. monograph 1706)



$C_4H_6N_2S$ 114.2 *60-56-0*

Action and use

Thionamide antithyroid.

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DEFINITION

1-Methyl-1,3-dihydro-2*H*-imidazole-2-thione.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or pale brown, crystalline powder.

Solubility

Freely soluble in water, freely soluble in methylene chloride, freely soluble or soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 143 °C to 146 °C.

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B. Dissolve 25 mg in 10 mL of a 0.28 per cent *V/V* solution of *sulfuric acid R* and dilute to 50.0 mL with the same solution. Dilute 1.0 mL of this solution to 100.0 mL with a 0.28 per cent *V/V* solution of *sulfuric acid R*. Examined between 200 nm and 300 nm (2.2.25), the solution shows 2 absorption maxima, at 211 nm and 251 nm. The ratio of the absorbance measured at the absorption maximum at 251 nm to that measured at the absorption maximum at 211 nm is 2.5 to 2.7.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *thiamazole CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5.0 mg of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *thiamazole CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 5.0 mg of *2-methylimidazole R* in *methanol R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of this solution to 2.0 mL with the test solution.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R1*, *2-propanol R*, *toluene R* (1:24:75 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— expose the plate to iodine vapour for 30 min; the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 2.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_6 (2.2.2, *Method II*).

Related substances

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Gas chromatography (2.2.28).

Test solution Dissolve 0.100 g of the substance to be examined in chloroform R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with chloroform R. Dilute 1.0 mL of this solution to 10.0 mL with chloroform R.

Reference solution (b) Dissolve 5.0 mg of thiamazole impurity A CRS, 5.0 mg of 1-methylimidazole R1 and 5.0 mg of thiamazole impurity C CRS in chloroform R and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with chloroform R.

Column:

— *material*: fused silica,

— *size*: *l* = 30.0 m, Ø = 0.25 mm,

— *stationary phase*: base-deactivated phenyl(5)methyl(95)polysiloxane R (film thickness 0.5 µm).

Carrier gas helium for chromatography R.

Flow rate 1.5 mL/min.

Split ratio 3:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	100
	2 - 7	100 → 250
	7 - 22	250
Injection port		150
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to thiamazole (retention time = about 6.5 min): impurity A = about 0.3; impurity B = about 0.4; impurity C = about 0.7.

System suitability Reference solution (b):

— resolution: minimum 1.5 between the peaks due to impurity A and impurity B.

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Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

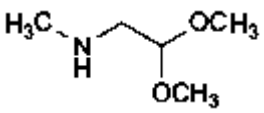
ASSAY

Dissolve 0.250 g in 75 mL of *water R*. Add 15.0 mL of *0.1 M sodium hydroxide*, mix and add with stirring, about 30 mL of *0.1 M silver nitrate*. Continue the titration with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

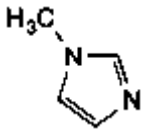
1 mL of *0.1 M sodium hydroxide* is equivalent to 11.42 mg of $C_4H_6N_2S$.

IMPURITIES

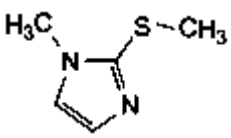
Specified impurities *A, B, C.*



A. 2,2-dimethoxy-*N*-methylethanamine,



B. 1-methyl-1*H*-imidazole,



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C. 1-methyl-2-(methylsulfanyl)-1*H*-imidazole.

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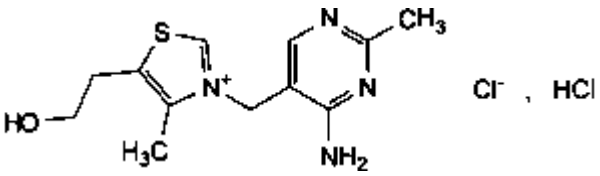
Thiamine Hydrochloride

General Notices

(Ph. Eur. monograph 0303)



$C_{12}H_{18}Cl_2N_4OS$ 337.3 *67-03-8*

Action and use

Vitamin B_1.

Preparations

Thiamine Injection

Thiamine Tablets

Vitamins B and C Injection

Ph Eur

DEFINITION

3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium chloride hydrochloride.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, soluble in glycerol, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

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IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *thiamine hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *water R*, evaporate to dryness and record new spectra using the residues.

B. Dissolve about 20 mg in 10 mL of *water R*, add 1 mL of *dilute acetic acid R* and 1.6 mL of *1 M sodium hydroxide*, heat on a water-bath for 30 min and allow to cool. Add 5 mL of *dilute sodium hydroxide solution R*, 10 mL of *potassium ferricyanide solution R* and 10 mL of *butanol R* and shake vigorously for 2 min. The upper alcoholic layer shows an intense light-blue fluorescence, especially in ultraviolet light at 365 nm. Repeat the test using 0.9 mL of *1 M sodium hydroxide* and 0.1 g of *anhydrous sodium sulfite R* instead of 1.6 mL of *1 M sodium hydroxide*. Practically no fluorescence is seen.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 or GY_7 (2.2.2, *Method II*).

Dilute 2.5 mL of solution S to 5 mL with *water R*.

pH (2.2.3)

2.7 to 3.3.

Dilute 2.5 mL of solution S to 10 mL with *water R*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.35 g of the substance to be examined in 15.0 mL of a 5 per cent *V/V* solution of *glacial acetic acid R* and dilute to 100.0 mL with *water R*.

Reference solution (a) Dissolve the contents of a vial of *thiamine for system suitability CRS* (containing impurities A, B and C) in 1 mL of a 0.75 per cent *V/V* solution of *glacial acetic acid R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: 3.764 g/L solution of *sodium hexanesulfonate R* adjusted to pH 3.1 with *phosphoric acid R*;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 27	90 → 70	10 → 30
27 - 35	70 → 50	30 → 50
35 - 42	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 248 nm.

Injection 25 µL.

Identification of impurities Use the chromatogram supplied with *thiamine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to thiamine (retention time = about 30 min): impurity A = about 0.3; impurity B = about 0.9; impurity C = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity B and thiamine; minimum 2.0 between the peaks due to thiamine and impurity C.

Calculation of percentage contents:

— for each impurity, use the concentration of thiamine hydrochloride in reference solution (b).

Limits:

— *impurity B*: maximum 0.3 per cent;

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— *impurities A, C*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.400 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.110 g in 5 mL of *anhydrous formic acid R* and add 50 mL of *acetic anhydride R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*) and carrying out the titration within 2 min. Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 16.86 mg of $C_{12}H_{18}Cl_2N_4OS$.

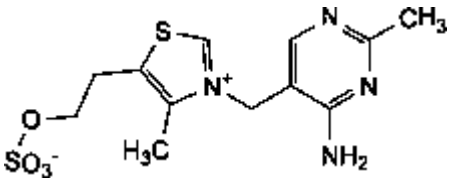
STORAGE

In a non-metallic container, protected from light.

IMPURITIES

Specified impurities *A, B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, F, G, H.*



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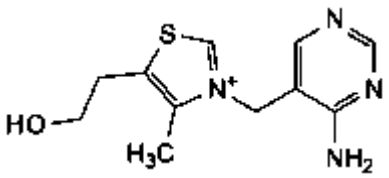
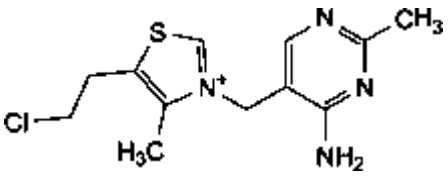
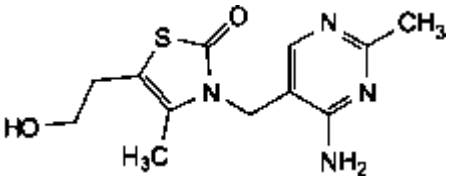
A. 2-[3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium-5-yl]ethyl sulfate (thiamine sulfate ester),



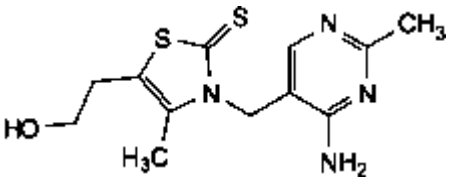
B. 3-[(4-aminopyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium (desmethylthiamine),



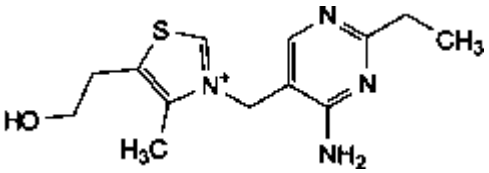
C. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-chloroethyl)-4-methyl-1,3-thiazol-3-ium (chlorothiamine),



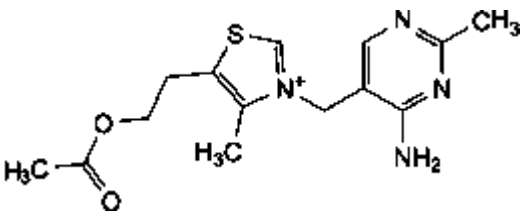
D. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-2(3*H*)-one (oxothiamine),



E. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-2(3*H*)-thione (thioxothiamine),



F. 3-[(4-amino-2-ethylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium (ethylthiamine),



G. 5-[2-(acetyloxy)ethyl]-3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium (acetylthiamine),

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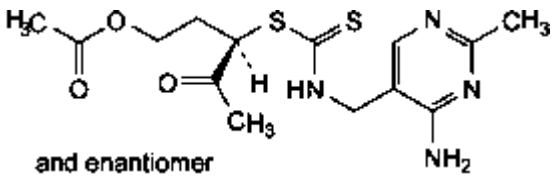

H. (3*RS*)-3-[[[(4-amino-2-methylpyrimidin-5-yl)methyl]thiocarbamoyl]sulfanyl]-4-oxopentyl acetate (ketodithiocarbamate).

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Thiamine Injection

General Notices

Action and use

Vitamin B_1.

DEFINITION

Thiamine Injection is a sterile solution of Thiamine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of thiamine hydrochloride, $C_{12}H_{17}ClN_4OS,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the injection, diluted with *water*, if necessary, to contain 0.1% w/v of Thiamine Hydrochloride.

(2) 0.1% w/v of *thiamine mononitrate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 105° for 30 minutes, spray with a mixture of equal volumes of a 0.3% w/v solution of *potassium hexacyanoferrate*(*III*) and a 10% w/v solution of *sodium hydroxide* and examine under *ultraviolet light* (*365 nm*).

MOBILE PHASE

15 volumes of *glacial acetic acid*, 25 volumes of *water* and 60 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. To a volume containing 20 mg of Thiamine Hydrochloride diluted, if necessary, to 10 mL with *water*, add 2 mL of 1M *acetic acid* and 1.6 mL of 1M *sodium hydroxide*, heat in a water bath for 30 minutes and cool. Add 5 mL of 5M *sodium hydroxide*, 10 mL of *dilute potassium hexacyano-ferrate(III) solution* and 10 mL of *butan-1-ol* and shake vigorously for 2 minutes. The upper layer shows an intense light blue fluorescence on exposure to ultraviolet light. Repeat the test but adding 0.9 mL of 1M *sodium hydroxide* and 0.2 g of *sodium sulfite* in place of the 1.6 mL of 1M *sodium hydroxide*. Not more than a slight fluorescence is produced.

C. To a mixture of 0.1 mL of *nitrobenzene* and 0.2 mL of *sulfuric acid* add a volume of the injection containing 5 mg of Thiamine Hydrochloride. Allow to stand for 10 minutes, cool in ice and add slowly with stirring 5 mL of *water* followed by 5 mL of 10M *sodium hydroxide*. Add 5 mL of *acetone* and allow to stand. No violet colour is produced in the upper layer.

TESTS

Acidity

pH, 2.8 to 3.4, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection containing 0.1 g of Thiamine Hydrochloride to 100 mL with 0.1M *hydrochloric acid* and further dilute 5 mL to 100 mL with *water*.

(2) 0.005% w/v of *thiamine mononitrate BPCRS* in 0.005M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 244 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 1 g of *sodium heptane sulfonate* in a mixture of 180 mL of *methanol* and 10 mL of *triethylamine*, diluting to 1000 mL with *water* and adjusting the pH to 3.2 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{12}H_{17}ClN_4OS,HCl$ using the declared content of $C_{12}H_{17}N_5O_4S$ in *thiamine mononitrate BPCRS*. Each mg of $C_{12}H_{17}N_5O_4S$ is equivalent to 1.030 mg of $C_{12}H_{17}ClN_4OS,HCl$.

STORAGE

Thiamine Injection should be protected from light.

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When vitamin B_1 injection is prescribed or demanded, Thiamine Injection shall be dispensed or supplied.

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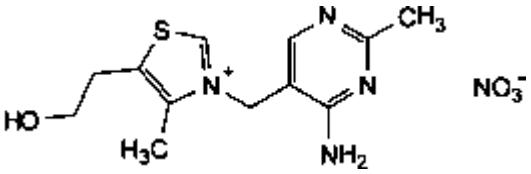
Thiamine Nitrate

General Notices

(Ph. Eur. monograph 0531)



$C_{12}H_{17}N_5O_4S$ 327.4 *532-43-4*

Action and use

Vitamin B_1.

Ph Eur

DEFINITION

3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium nitrate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or small, colourless crystals.

Solubility

Sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *thiamine nitrate CRS*.

B. Dissolve about 20 mg in 10 mL of *water R*, add 1 mL of *dilute acetic acid R* and 1.6 mL of *1 M sodium hydroxide*, heat on a water-bath for 30 min and allow to cool. Add 5 mL of *dilute sodium hydroxide solution R*, 10 mL of *potassium ferricyanide solution R* and 10 mL of *butanol R* and shake vigorously for 2 min. The upper alcoholic layer shows an intense light-blue fluorescence, especially in ultraviolet light at 365 nm. Repeat the test using 0.9 mL of *1 M sodium hydroxide* and 0.2 g of *sodium sulfite heptahydrate R* instead of 1.6 mL of *1 M sodium hydroxide*. Practically no fluorescence is produced.

C. About 5 mg gives the reaction of nitrates (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

6.8 to 7.6 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.35 g of the substance to be examined in 15.0 mL of a 5 per cent *V/V* solution of *glacial acetic acid R* and dilute to 100.0 mL with *water R*.

Reference solution (a) Dissolve the contents of a vial of *thiamine for system suitability CRS* (containing impurities A, B and C) in 1 mL of a 0.75 per cent *V/V* solution of *glacial acetic acid R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: 3.764 g/L solution of *sodium hexanesulfonate R* adjusted to pH 3.1 with *phosphoric acid R*;

— *mobile phase B*: *methanol R1*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 27	90 → 70	10 → 30
27 - 35	70 → 50	30 → 50
35 - 42	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 248 nm.

Injection 25 µL.

Identification of impurities Use the chromatogram supplied with *thiamine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to thiamine (retention time = about 30 min): impurity A = about 0.3; impurity B = about 0.9; impurity C = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity B and thiamine; minimum 2.0 between the peaks due to thiamine and impurity C.

Calculation of percentage contents:

— for each impurity, use the concentration of thiamine nitrate in reference solution (b).

Limits:

— *impurity B*: maximum 0.6 per cent;

— *impurity C*: maximum 0.4 per cent;

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to the nitrate ion at the beginning of the chromatogram.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.140 g in 5 mL of *anhydrous formic acid R* and add 50 mL of *acetic anhydride R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*) and carrying out the titration within 2 min. Carry out a blank titration.

1.0 mL of *0.1 M perchloric acid* is equivalent to 16.37 mg of $C_{12}H_{17}N_5O_4S$.

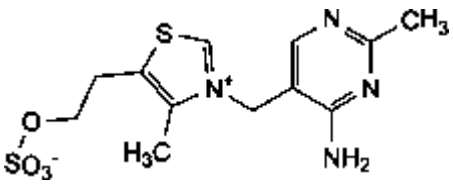
STORAGE

In a non-metallic container, protected from light.

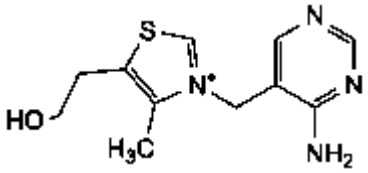
IMPURITIES

Specified impurities A, B, C.

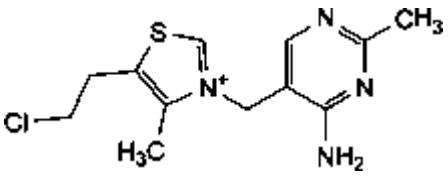
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, E, F, G, H.



A. 2-[3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium-5-yl]ethyl sulfate (thiamine sulfate ester),



B. 3-[(4-aminopyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium (desmethylthiamine),



C. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-chloroethyl)-4-methyl-1,3-thiazol-3-ium (chlorothiamine),

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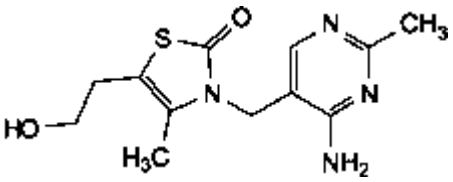
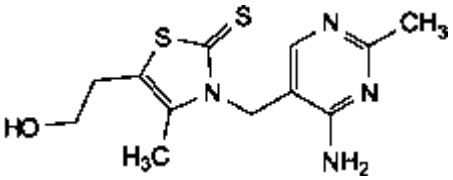
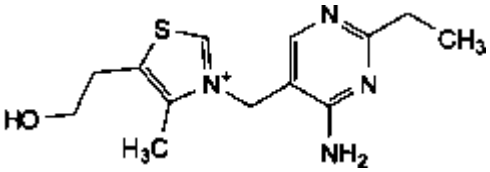


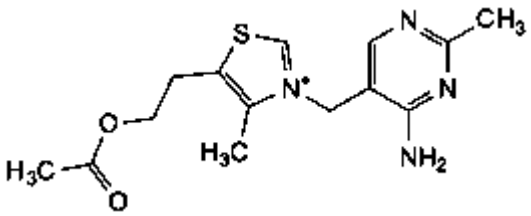
D. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-2(3*H*)-one (oxothiamine),



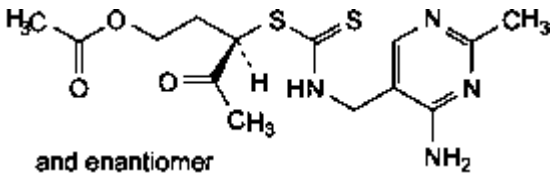
E. 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-2(3*H*)-thione (thioxothiamine),



F. 3-[(4-amino-2-ethylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium (ethylthiamine),



G. 5-[2-(acetyloxy)ethyl]-3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium (acetylthiamine),



H. (3*RS*)-3-[[[(4-amino-2-methylpyrimidin-5-yl)methyl]thiocarbamoyl]sulfanyl]-4-oxopentyl acetate (ketodithiocarbamate).

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Thiamine Tablets

General Notices

Action and use

Vitamin B_1.

DEFINITION

Thiamine Tablets contain Thiamine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of thiamine hydrochloride, $C_{12}H_{17}ClN_4OS,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Thiamine Hydrochloride with 20 mL of *water* and filter.

(2) 0.1% w/v of *thiamine mononitrate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 105° for 30 minutes and spray with a mixture of equal volumes of a 0.3% w/v solution of *potassium hexacyanoferrate*(III) and a 10% w/v solution of *sodium hydroxide*. Examine under *ultraviolet light* (*365 nm*).

MOBILE PHASE

15 volumes of *glacial acetic acid*, 25 volumes of *water* and 60 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. Dissolve a quantity of the powdered tablets containing 20 mg of Thiamine Hydrochloride as completely as possible in 10 mL of *water* and 2 mL of 1M *acetic acid*, filter, add 1.6 mL of 1M *sodium hydroxide*, heat in a water bath for 30 minutes and cool. Add 5 mL of 5M *sodium hydroxide*, 10 mL of *dilute potassium hexacyanoferrate*(*III*) *solution* and 10 mL of *butan-1-ol* and shake vigorously for 2 minutes. The

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alcohol layer shows an intense light blue fluorescence on exposure to ultraviolet light. Repeat the test but adding 0.9 mL of 1M *sodium hydroxide* and 0.2 g of *sodium sulfite* in place of the 1.6 mL of 1M sodium hydroxide; not more than a slight fluorescence is produced.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For tablets containing less than 10 mg of Thiamine Hydrochloride:

(1) Add 5 mL of 0.1M *hydrochloric acid* and 50 mL of *water* to a quantity of the powdered tablets containing 6 mg of Thiamine Hydrochloride, shake for 20 minutes, dilute to 100 mL with *water* and filter.
(2) 0.006% w/v of *thiamine mononitrate BPCRS* in 0.005M *hydrochloric acid*.

For tablets containing 10 mg or more of Thiamine Hydrochloride:

(1) Add 50 mL of 0.1M *hydrochloric acid* and 500 mL of *water* to a quantity of the powdered tablets containing 60 mg of Thiamine Hydrochloride, shake for 20 minutes, dilute to 1000 mL with *water* and filter.
(2) 0.006% w/v of *thiamine mononitrate BPCRS* in 0.005M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 244 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 1 g of *sodium heptane sulfonate* in a mixture of 180 mL of *methanol* and 10 mL of *triethylamine*, diluting to 1000 mL with *water* and adjusting the pH to 3.2 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{12}H_{17}ClN_4OS,HCl$ using the declared content of $C_{12}H_{17}N_5O_4S$ in *thiamine mononitrate BPCRS*. Each mg of $C_{12}H_{17}N_5O_4S$ is equivalent to 1.030 mg of $C_{12}H_{17}ClN_4OS,HCl$.

STORAGE

Thiamine Tablets should be kept free from contact with metal and protected from light.

When vitamin B_1 tablets are prescribed or demanded, Thiamine Tablets shall be dispensed or supplied.

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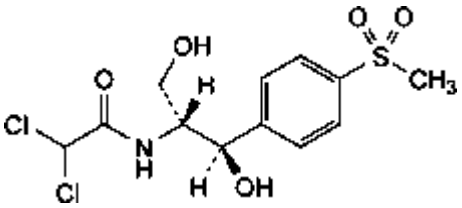
Thiamphenicol

General Notices

(Ph. Eur. monograph 0109)



$C_{12}H_{15}Cl_2NO_5S$ 356.2 *15318-45-3*

Action and use

Antibacterial.

Ph Eur

DEFINITION

2,2-Dichloro-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)-2-[4- (methylsulfonyl)phenyl]ethyl]acetamide.

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

Fine, white or yellowish-white, crystalline powder or crystals.

Solubility

Slightly soluble in water, very soluble in dimethylacetamide, freely soluble in acetonitrile and in dimethylformamide, soluble in methanol, sparingly soluble in acetone and in anhydrous ethanol, slightly soluble in ethyl acetate.

A solution in anhydrous ethanol is dextrorotatory and a solution in dimethylformamide is laevorotatory.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Preparation Dry the substance to be examined and the reference substance at 100-105 °C for 2 h; examine as discs of *potassium bromide R*.

Comparison *thiamphenicol CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.1 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.1 g of *thiamphenicol CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *silica gel GF_{254} R* as the coating substance.

Mobile phase *methanol R*, *ethyl acetate R* (3:97 *V/V*).

Application 5 µL.

Development Over a path of 10 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the spot in the chromatogram obtained with the reference solution.

C. To 50 mg in a porcelain crucible add 0.5 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Acidity or alkalinity

Shake 0.1 g with 20 mL of *carbon dioxide-free water R* and add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.1 mL of *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*)

-24 to -21 (dried substance).

Dissolve 1.25 g in *dimethylformamide R* and dilute to 25.0 mL with the same solvent.

Melting point (*2.2.14*)

163 °C to 167 °C.

Absorbance (*2.2.25*)

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Test solution (a) Dissolve 20 mg in *water R*, heating to about 40 °C, and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 2.5 mL of test solution (a) to 50.0 mL with *water R*.

Spectral range 240-300 nm for test solution (a); 200-240 nm for test solution (b).

Absorption maxima At 266 nm and 273 nm for test solution (a); at 224 nm for test solution (b).

Specific absorbances at the absorption maxima:

— at 266 nm: 25 to 28 for test solution (a);

— at 273 nm: 21.5 to 23.5 for test solution (a);

— at 224 nm: 370 to 400 for test solution (b).

Chlorides (*2.4.4*)

Maximum 200 ppm.

Shake 0.5 g with 30 mL of *water R* for 5 min and filter.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Dissolve 0.300 g in 30 mL of *ethanol (96 per cent) R*, add 20 mL of a 500 g/L solution of *potassium hydroxide R*, mix and heat under a reflux condenser for 4 h. Cool, add 100 mL of *water R*, neutralise with *dilute nitric acid R* and add 5 mL of the same acid in excess. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank test.

1 mL of *0.1 M silver nitrate* is equivalent to 17.81 mg of $C_{12}H_{15}Cl_2NO_5S$.

STORAGE

In an airtight container, protected from light.

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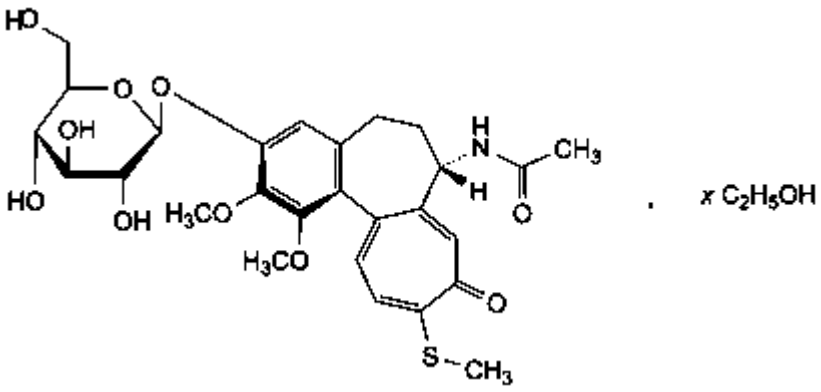
Thiocolchicoside Crystallised from Ethanol

General Notices

(Ph. Eur. monograph 2896)



$C_{27}H_{33}NO_{10}S,xC_2H_6O$ 563.6 (ethanol-free substance)

Anhydrous thiocolchicoside *602-41-5*

Action and use

Muscle relaxant.

Ph Eur

DEFINITION

N-[(7*S*,12aR_a)-3-(β-D-Glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of ethanol.

CHARACTERS

Appearance

Yellow crystalline powder, hygroscopic.

Solubility

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Sparingly soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

mp

About 208 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *thiocolchicoside crystallised from ethanol CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*).

Dissolve 0.100 g in *methanol R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-600 to -570 (anhydrous substance).

Dissolve 0.500 g in *water R* and dilute to 100.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution (a) Dissolve 20.0 mg of the substance to be examined in *methanol R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *thiocolchicoside for system suitability CRS* (containing impurities D, E, G, H, K and L) in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (c) Dissolve 20.0 mg of *thiocolchicoside hydrate CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 25 °C.

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Mobile phase:

— *mobile phase A*: dissolve 0.22 g of *ammonium formate R* in 350 mL of *water for chromatography R* and mix with 25 mL of *tetrahydrofuran R*;

— *mobile phase B*: dilute 45 µL of *anhydrous formic acid R* in 900 mL of *acetonitrile R* and mix with 100 mL of *tetrahydrofuran R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	99	1
2 - 6	99 → 92	1 → 8
6 - 7.5	92 → 70	8 → 30
7.5 - 8.8	70 → 50	30 → 50
8.8 - 9.2	50 → 2	50 → 98
9.2 - 10	2	98

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 370 nm.

Injection 1.0 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *thiocolchicoside for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities D, E, H and L.

Relative retention With reference to thiocolchicoside (retention time = about 6 min): impurity D = about 0.2; impurity H = about 0.4; impurity E = about 1.05; impurity L = about 1.11.

System suitability:

— *signal-to-noise ratio*: minimum 50 for the principal peak in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to thiocolchicoside in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factor*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity H = 2.8;

— for each impurity, use the concentration of the substance to be examined in reference solution (a).

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Limits:

— *impurity D*: maximum 0.4 per cent;

— *impurities E, H*: for each impurity, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to impurity L.

Ethanol (*2.4.24*)

Maximum 1.5 per cent.

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{27}H_{33}NO_{10}S$ taking into account the assigned content of *thiocolchicoside hydrate CRS*.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *D, E, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, G, J, K, L.*

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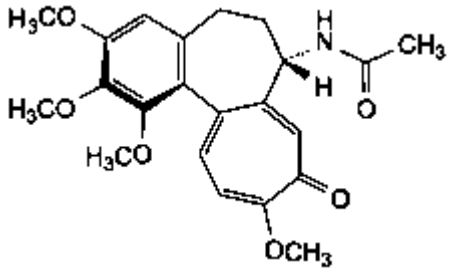
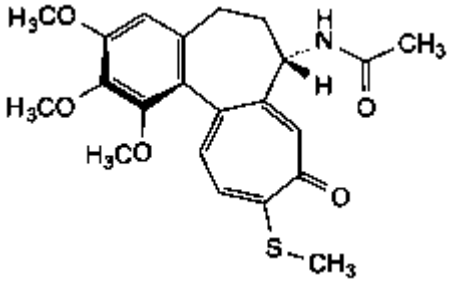
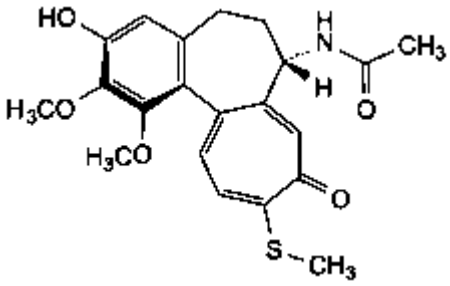


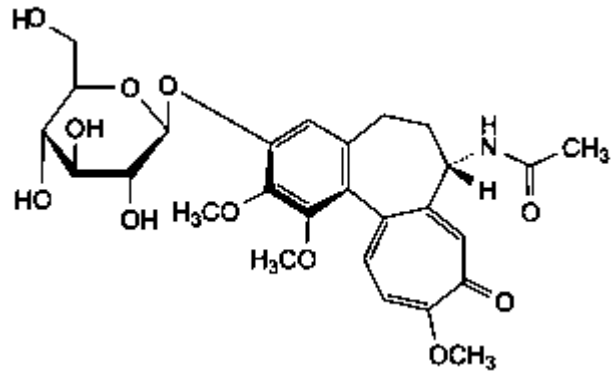
A. *N*-[(7*S*,12aR_a)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (colchicine),



B. *N*-[(7*S*,12aR_a)-1,2,3-trimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (thiocolchicine),



C. *N*-[(7*S*,12aR_a)-3-hydroxy-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (3-*O*-demethylthiocolchicine),



D. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (colchicoside),

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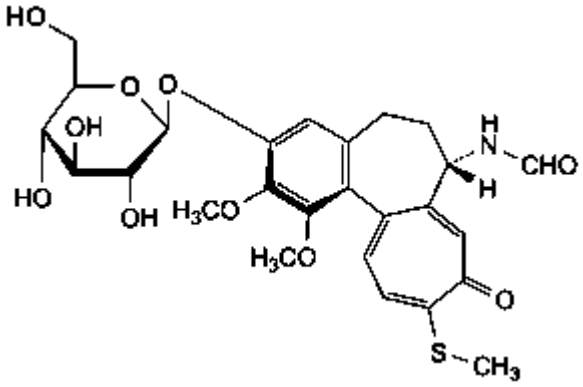
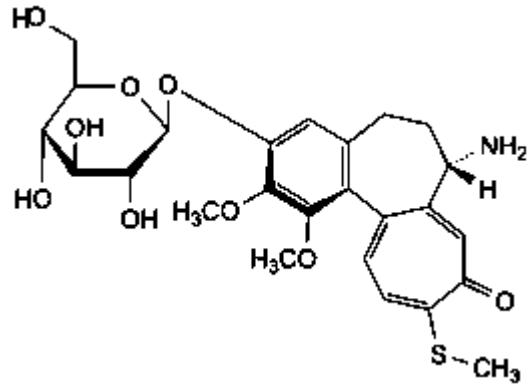
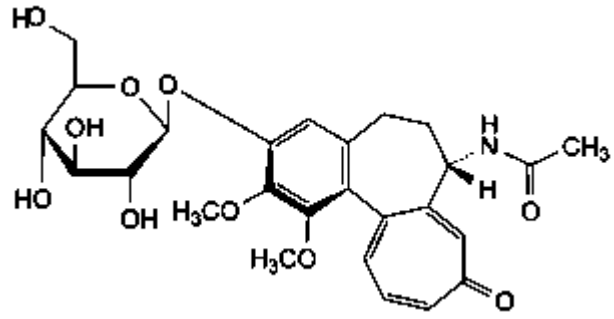


E. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]formamide (*N*-deacetyl-*N*-formylthiocolchicoside),



G. (7*S*,12aR_a)-7-amino-3(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-6,7-dihydrobenzo[*a*]heptalen-9(5*H*)-one (*N*-deacetylthiocolchicoside),



H. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (10-demethoxycolchicoside),

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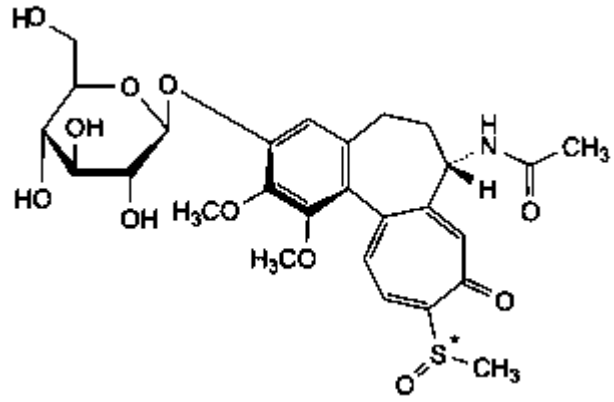
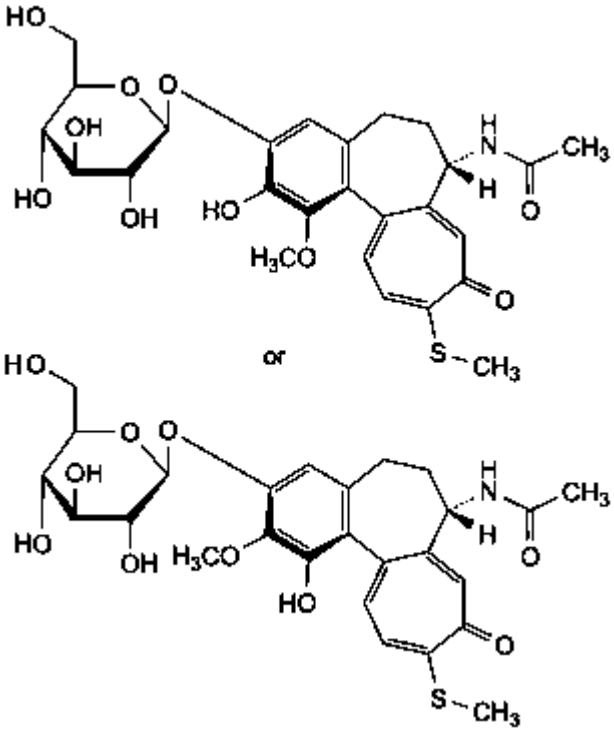


J. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfinyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (thiocolchicoside *S*-oxide),



K. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-2-hydroxy-1-methoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide or *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1-hydroxy-2-methoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide,

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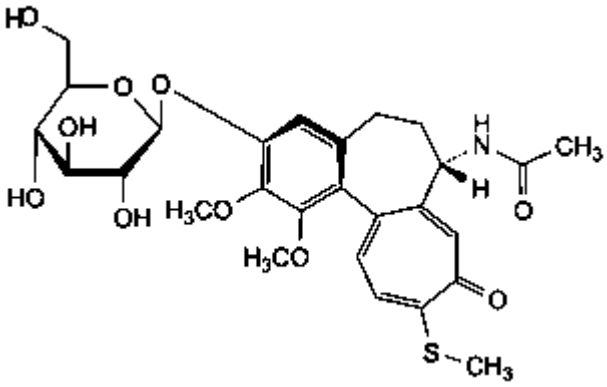

L. *N*-[(7*S*,12aS_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (12aS_a-thiocolchicoside).

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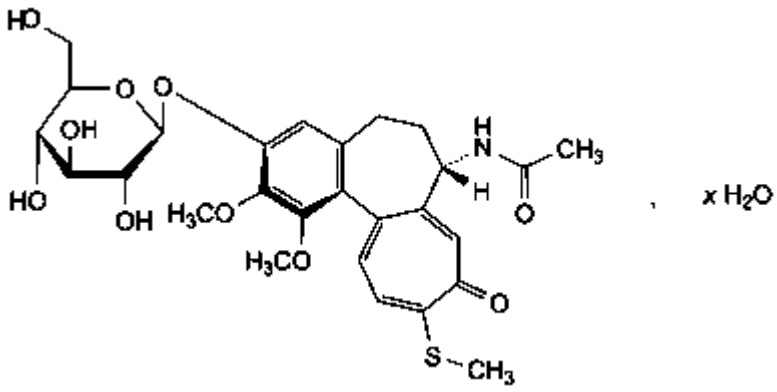
Thiocolchicoside Hydrate

General Notices

(Ph. Eur. monograph 2814)



$C_{27}H_{33}NO_{10}S,xH_2O$ 563.6 (anhydrous substance) *1622135-03-8*

Action and use

Muscle relaxant.

Ph Eur

DEFINITION

N-[(7*S*,12aR_a)-3-(β-D-Glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

Yellow crystalline powder, slightly hygroscopic.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

mp

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m.p.

About 272 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *thiocolchicoside hydrate CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 0.100 g in *methanol R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

-600 to -570 (anhydrous substance).

Dissolve 0.500 g in *water R* and dilute to 100.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution (a) Dissolve 20.0 mg of the substance to be examined in *methanol R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *thiocolchicoside for system suitability CRS* (containing impurities D, E, G, H, K and L) in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (c) Dissolve 20.0 mg of *thiocolchicoside hydrate CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 25 °C.

Mobile phase:

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— *mobile phase A*: dissolve 0.22 g of *ammonium formate R* in 350 mL of *water for chromatography R* and mix with 25 mL of *tetrahydrofuran R*;

— *mobile phase B*: dilute 45 µL of *anhydrous formic acid R* in 900 mL of *acetonitrile R* and mix with 100 mL of *tetrahydrofuran R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	99	1
2 - 6	99 → 92	1 → 8
6 - 7.5	92 → 70	8 → 30
7.5 - 8.8	70 → 50	30 → 50
8.8 - 9.2	50 → 2	50 → 98
9.2 - 10	2	98

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 370 nm.

Injection 1.0 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *thiocolchicoside for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities D, E, G, H, K and L.

Relative retention With reference to thiocolchicoside (retention time = about 6 min): impurity D = about 0.2; impurity H = about 0.4; impurity G = about 0.7; impurity K = about 0.8; impurity E = about 1.05; impurity L = about 1.11.

System suitability:

— *signal-to-noise ratio*: minimum 50 for the principal peak in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to thiocolchicoside in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity H = 2.8;

— for each impurity, use the concentration of thiocolchicoside hydrate in reference solution (a).

Limits:

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— *impurity E*: maximum 1.0 per cent;

— *impurity H*: maximum 0.7 per cent;

— *impurity K*: maximum 0.3 per cent;

— *impurities D, G*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 2.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to impurity L.

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{27}H_{33}NO_{10}S$ taking into account the assigned content of *thiocolchicoside hydrate CRS*.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *D, E, G, H, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, J, L.*

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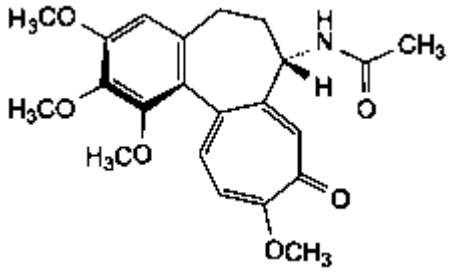
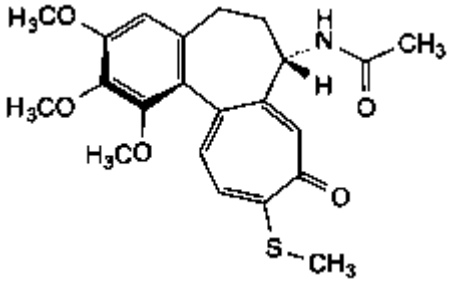
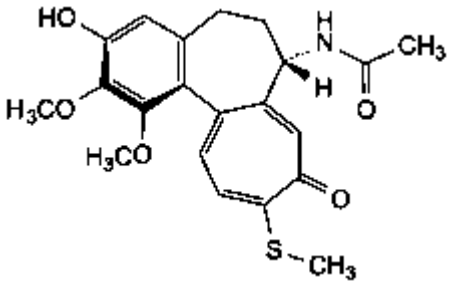


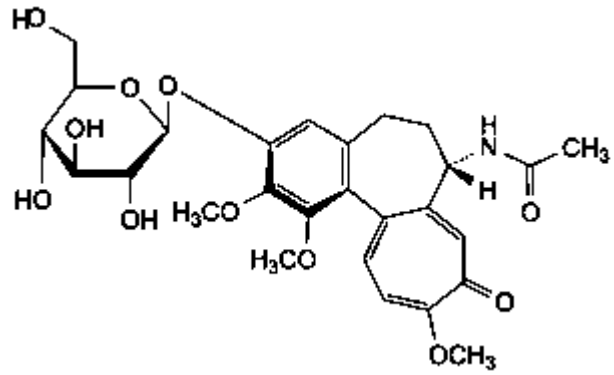
A. *N*-[(7*S*,12aR_a)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (colchicine),



B. *N*-[(7*S*,12aR_a)-1,2,3-trimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (thiocolchicine),



C. *N*-[(7*S*,12aR_a)-3-hydroxy-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (3-*O*-demethylthiocolchicine),



D. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (colchicoside),

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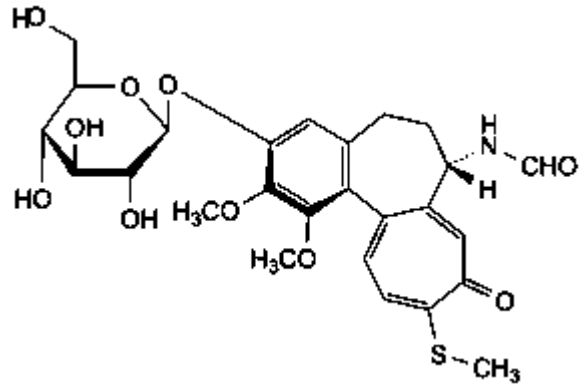
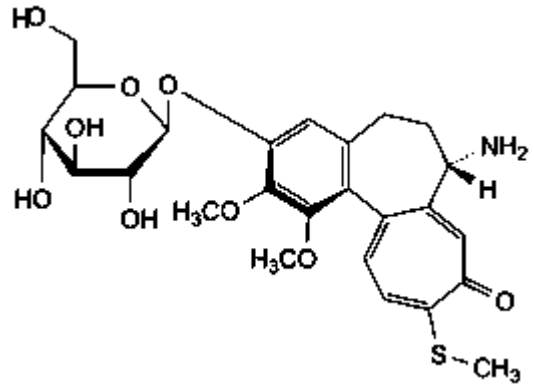
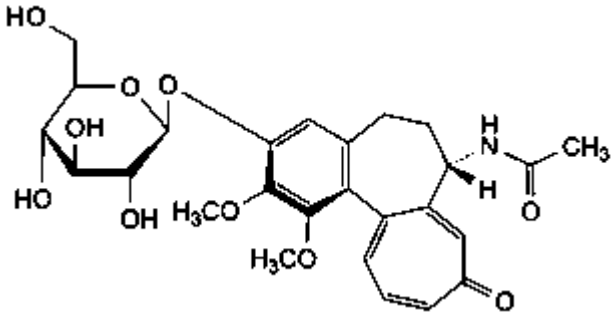


E. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]formamide (*N*-deacetyl-*N*-formylthiocolchicoside),



G. (7*S*,12aR_a)-7-amino-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-6,7-dihydrobenzo[*a*]heptalen-9(5*H*)-one (*N*-deacetylthiocolchicoside),



H. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (10-demethoxycolchicoside),

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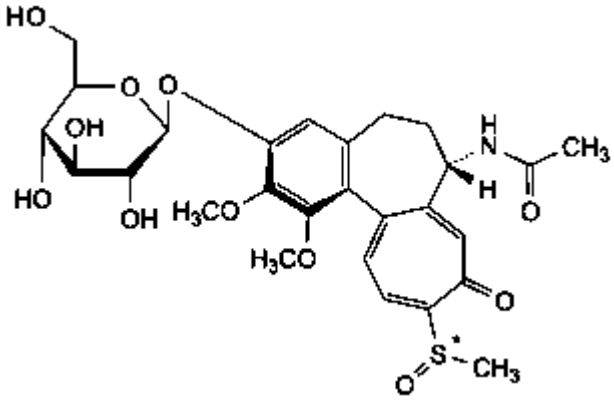
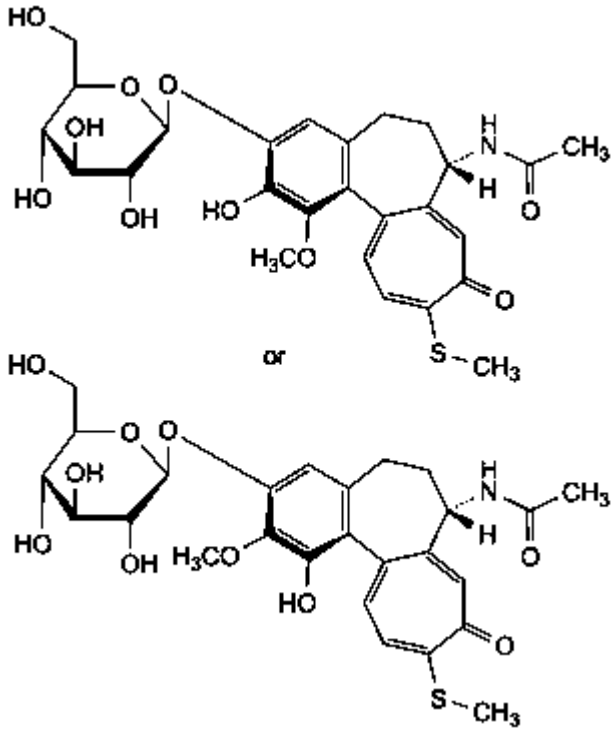


J. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfinyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (thiocolchicoside *S*-oxide),



K. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-2-hydroxy-1-methoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide or *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1-hydroxy-2-methoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide,

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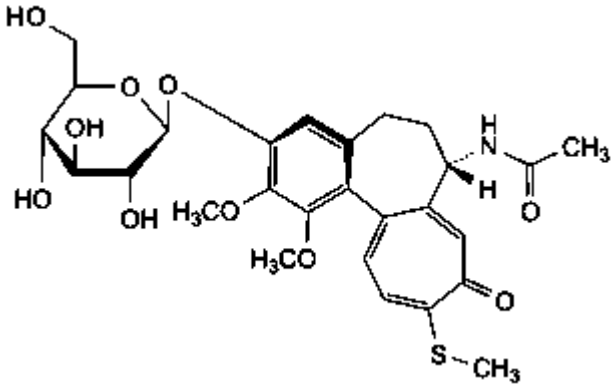

L. *N*-[(7*S*,12aS_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (12aS_a-thiocolchicoside).

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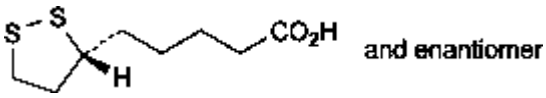
Thioctic Acid

General Notices

(Ph. Eur. monograph 1648)



and enantiomer

$C_8H_{14}O_2S_2$ 206.3 *1077-28-7*

Action and use

Antioxidant.

Ph Eur

DEFINITION

5-[(3*RS*)-1,2-Dithiolan-3-yl]pentanoic acid.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Very slightly soluble in water, very soluble in dimethylformamide, freely soluble in methanol.

mp

About 61 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *thioctic acid CRS*.

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TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 0.50 g in a 20 g/L solution of *sodium hydroxide R* and dilute to 10 mL with the same solution.

Impurity B

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in *dimethylformamide R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *thioctic acid containing impurity B CRS* in *dimethylformamide R* and dilute to 1.0 mL with the same solvent (1.0 per cent impurity B solution).

Plate *TLC silica gel plate R*.

Mobile phase 25 per cent *V/V* solution of *ammonia R*, *water R*, *ethyl acetate R*, *propanol R* (5:10:40:40 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 50 °C for 20 min.

Detection Expose to iodine vapour for 30 min or until the spots appear.

System suitability Reference solution:

— the chromatogram shows 2 clearly separated principal spots due to impurity B (R_F = 0.0) and thioctic acid (R_F = about 0.3).

Limit:

— *impurity B*: any spot due to impurity B is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (1.0 per cent).

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light.*

Solvent mixture A mixture of equal volumes of *acetonitrile R1* and a 0.7 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.6 with *phosphoric acid R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *thioctic acid for system suitability CRS* (containing impurity A) in the solvent mixture and dilute to 5 mL with the solvent mixture.

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Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *thioctic acid CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Blank solution Solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 8 volumes of *acetonitrile R1*, 41 volumes of a 0.7 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*, and 51 volumes of *methanol R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 2.5 times the retention time of thioctic acid.

Relative retention With reference to thioctic acid (retention time = about 6 min): impurity A = about 2.2.

System suitability:

— *resolution*: minimum 6.0 between the peaks due to thioctic acid and impurity A in the chromatogram obtained with reference solution (a);

— *symmetry factor*: maximum 2.0 for the peak due to thioctic acid in the chromatogram obtained with reference solution (c).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.6;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

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Maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 40 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

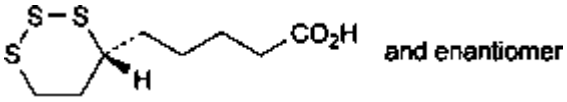
Calculate the percentage content of $C_8H_{14}O_2S_2$ from the peak areas and the declared content of *thioctic acid CRS*.

STORAGE

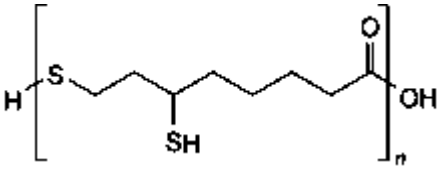
Protected from light.

IMPURITIES

Specified impurities *A, B.*



A. 5-[(4*RS*)-1,2,3-trithian-4-yl]pentanoic acid,



B. α-hydro-ω-hydroxypoly[sulfanediyl(3-sulfanyl-8-oxooctane-1,8-diyl)] (mixture of thioctic acid polymers).

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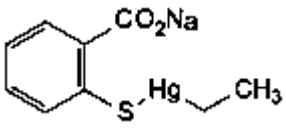
Thiomersal

General Notices

Thimerosal

(Ph. Eur. monograph 1625)



$C_9H_9HgNaO_2S$ 404.8 *54-64-8*

Action and use

Antiseptic; adjuvant in vaccine formulations.

Ph Eur

DEFINITION

Sodium ethyl[2-sulfanylbenzoato(2-)-*O*,*S*]mercurate(1-).

Content

97.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble or soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 103 °C to 115 °C.

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Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent. Add 2 mL of *dilute hydrochloric acid R*. A white precipitate is formed. Wash the precipitate with *water R* and dry *in vacuo* (2.2.32) at a pressure not exceeding 0.7 kPa.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *thiomersal CRS*.

C. Treat 50 mg by the oxygen-flask method (2.5.10). Use a mixture of 1 mL of *strong hydrogen peroxide solution R* and 50 mL of *water R* to absorb the combustion products. To the solution add 5 mL of *dilute nitric acid R*. 0.1 mL of this solution gives reaction (a) of mercury (2.3.1). To the remaining part of the solution add 10 mL of *dilute hydrochloric acid R* and filter. 5 mL of the filtrate, without further addition of acid, gives reaction (a) of sulfates (2.3.1).

D. Solution S (see Tests) gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution B_6 (2.2.2, *Method II*).

pH (2.2.3)

6.0 to 8.0.

Dilute 5 mL of solution S to 50 mL with *carbon dioxide-free water R*.

Inorganic mercury compounds

Maximum 0.70 per cent.

Protect the solutions from light throughout the procedure.

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution Dissolve 95.0 mg of *mercuric chloride R* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with *water R*.

Test, reference and blank preparations Label five 10 mL volumetric flasks A, B, C, D and E. Place 5 mL of the test solution in flasks A, B, C and D. To each of the flasks C and D add 0.5 mL of the reference solution. Dilute the contents of flasks A and C to 10 mL with *water R* (blank preparations A and C). Dilute the contents of flasks B and D to 10 mL with a freshly prepared 332 g/L solution of *potassium iodide R* (test preparation B and reference preparation D). Place 5 mL of a 332 g/L solution of *potassium iodide R* in flask E. Dilute to 10 mL with *water R* (blank preparation E).

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Measure the absorbance (2.2.25) of each solution (A_a, A_b, A_c, A_d and A_e) at 323 nm using water R as the compensation liquid. Calculate the content of inorganic mercury compounds, expressed as Hg from the expression:

$$\frac{\left(A_b - A_a - A_e\right) \times m_R \times 0.1847}{\left(A_d - A_c - A_b + A_a\right) \times m_T}$$

m_R = mass of mercuric chloride in the reference solution in milligrams,

m_T = mass of the substance to be examined in milligrams.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator at a pressure not exceeding 0.7 kPa for 24 h.

ASSAY

Place 0.5 g in a 100 mL long-necked combustion flask, add 5 mL of sulfuric acid R and heat gently until charring occurs, continue to heat and add dropwise strong hydrogen peroxide solution R until the mixture is colourless. Dilute with water R, evaporate until slight fuming occurs, dilute to 10 mL with water R, cool down and titrate with 0.1 M ammonium thiocyanate using ferric ammonium sulfate solution R2 as indicator.

1 mL of 0.1 M ammonium thiocyanate is equivalent to 20.24 mg of $C_9H_9HgNaO_2S$.

STORAGE

Protected from light.

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Thiopental Injection

General Notices

Action and use

Intravenous barbiturate; general anaesthetic.

DEFINITION

Thiopental Injection is a sterile solution of Thiopental Sodium in Water for Injections. It is prepared by dissolving Thiopental Sodium for Injection in the requisite amount of Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Thiopental Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

THIOPENTAL SODIUM FOR INJECTION

DEFINITION

Thiopental Sodium for Injection is a sterile material consisting of Thiopental Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of $C_{11}H_{18}N_2O_2S$

77.0 to 92.0% of the stated amount of Thiopental Sodium.

Content of Na

9.4 to 11.8% of the stated amount of Thiopental Sodium.

IDENTIFICATION

A. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) corresponds to the peak due to thiopental in the chromatogram obtained with solution (4).

B. Yield the reaction characteristic of *non-nitrogen substituted barbiturates*, Appendix VI.

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C. Yield reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Clarity and colour of solution

A 10.0% w/v solution in *carbon dioxide-free water* is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* GY_3, Appendix IV B, Method II.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Dissolve a quantity of the contents of a sealed container containing 0.1 g of Thiopental Sodium in 80 mL of the mobile phase, add sufficient mobile phase to produce 100 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with mobile phase.
(3) Dilute 1 volume of solution (2) to 5 volumes with mobile phase.
(4) 0.03% w/v of *thiopental for system suitability EPCRS* in mobile phase.
(5) Dilute 1 volume of solution (3) to 2 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS 3 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of thiopental.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.02M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to thiopental (retention time = about 19 minutes) are: impurity A = about 0.3; impurity B = about 0.4; impurity C = about 0.9; impurity D = about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution factor* between the peaks due to thiopental impurity A and thiopental impurity B is at least 4.0;

the *resolution factor* between the peaks due to thiopental impurity C and thiopental is at least 1.5.

LIMITS

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Identify any peak in the chromatogram obtained with solution (1) corresponding to thiopental impurity B using solution (4) and multiply the area of the peak by 1.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to thiopental impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to thiopental impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to thiopental impurity C is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to thiopental impurity D is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

Loss on drying

When dried at 100° at a pressure not exceeding 2.7 kPa for 4 hours, lose not more than 2.5% of their weight. Use 0.5 g.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration. Carry out the following procedures using the mixed contents of the 10 containers.

For sodium

Dissolve a quantity of the powder for injection containing 0.6 g of Thiopental Sodium in 20 mL of *water* and titrate with *0.1M hydrochloric acid VS*, using *methyl red solution* as indicator, until the yellow colour changes to pink; boil gently for 1 or 2 minutes, cool and if necessary continue the titration with *0.1M hydrochloric acid VS* until the pink colour is restored. Each mL of *0.1M hydrochloric acid VS* is equivalent to 2.299 mg of Na.

For thiopental

To the liquid from the completed Assay for Na add a further 5 mL of 0.1M *hydrochloric acid* and extract with successive quantities of 25, 25, 20, 15, 15 and 10 mL of *chloroform*, washing each extract with the same 5 mL of *water*. Evaporate the chloroform from the mixed extracts and dry the residue of $C_{11}H_{18}N_2O_2S$ to constant weight at 105°. Calculate the content of $C_{11}H_{18}N_2O_2S$ in a container of average content weight.

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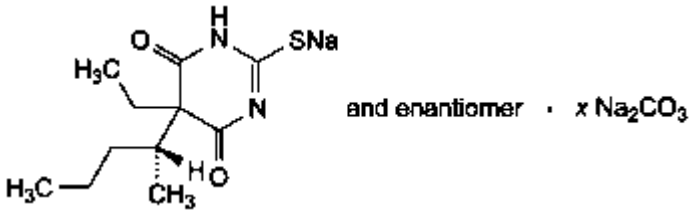
Thiopental Sodium

General Notices

(Thiopental Sodium and Sodium Carbonate, Ph. Eur. monograph 0212)



$C_{11}H_{17}N_2NaO_2S,xNa_2CO_3$ 264.3 (thiopental sodium)

Thiopental sodium *71-73-8*

Action and use

Intravenous barbiturate; general anaesthetic.

Preparation

Thiopental Injection

Ph Eur

DEFINITION

Mixture of sodium 5-ethyl-4,6-dioxo-5-[(2*RS*)-pentan-2-yl]-1,4,5,6-tetrahydropyrimidine-2-thiolate and anhydrous sodium carbonate.

Content

— *thiopental*: 84.0 per cent to 87.0 per cent (dried substance);

— *sodium*: 10.2 per cent to 11.2 per cent (dried substance).

CHARACTERS

Appearance

Yellowish-white, hygroscopic powder.

Solubility

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Solubility

Freely soluble in water, partly soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

First identification *A, B, D.*

Second identification *A, C, D.*

A. Melting point (2.2.14).

Determination A Acidify 10 mL of solution S (see Tests) with *dilute hydrochloric acid R*. An effervescence is produced. Shake with 20 mL of *1,1-dimethylethyl methyl ether R*. Separate the upper layer, wash with 10 mL of *water R*, dry over *anhydrous sodium sulfate R* and filter. Evaporate the filtrate to dryness and dry the residue at 100-105 °C. Determine the melting point of the residue.

Result A About 160 °C.

Determination B Mix equal parts of the residue obtained in determination A and *thiopental for ID and assay CRS* and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Use the residue obtained in Identification test A.

Comparison *thiopental for ID and assay CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.1 g of the substance to be examined in *water R* and dilute to 100 mL with the same solvent.

Reference solution Dissolve 85 mg of *thiopental for ID and assay CRS* in 10 mL of *dilute sodium hydroxide solution R* and dilute to 100 mL with *water R*.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *concentrated ammonia R*, *ethanol (96 per cent) R*, *methylene chloride R* (5:15:80 *V/V/V*); use the lower layer.

Application 10 µL.

Development Over 3/4 of the plate.

Detection Examine immediately in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of sodium (2.3.1).

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TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution GY_3 (*2.2.2, Method II*).

pH (*2.2.3*)

10.6 to 11.2.

Dissolve 0.800 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 17.0 mg of *thiopental for ID and assay CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *thiopental impurity mixture CRS* (impurities A, B, C and D) in 1 mL of the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, 1 g/L solution of *phosphoric acid R* (35:65 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time Twice the retention time of thiopental.

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Identification of impurities Use the chromatogram supplied with *thiopental impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to thiopental (retention time = about 19 min): impurity A = about 0.40; impurity B = about 0.45; impurity C = about 0.92; impurity D = about 1.34.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B; minimum 1.5 between the peaks due to impurity C and thiopental.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.6; impurity D = 1.9;

— for each impurity, use the concentration of thiopental sodium and sodium carbonate in reference solution (a).

Limits:

— *impurity B*: maximum 1.0 per cent;

— *impurity D*: maximum 0.5 per cent;

— *unspecified impurities*: maximum 0.10 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 330 ppm.

To 5 mL of solution S add 35 mL of *water R* and 10 mL of *dilute nitric acid R*. Shake with 3 quantities, each of 25 mL, of *1,1-dimethylethyl methyl ether R* and discard the upper layer. Eliminate the organic solvent from the lower layer by heating on a water-bath. 15 mL of this solution complies with the test for chlorides.

Loss on drying (2.2.32)

Maximum 2.5 per cent, determined on 0.500 g by drying *in vacuo* at 100 °C for 4 h.

ASSAY

Sodium

Dissolve 0.400 g in 30 mL of *water R*. Add 0.1 mL of *methyl red solution R* and titrate with *0.1 M hydrochloric acid* until a red colour is obtained. Boil gently for 2 min. Allow to cool and, if necessary, continue the titration with *0.1 M hydrochloric acid* until the red colour is again obtained.

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1 mL of *0.1 M hydrochloric acid* is equivalent to 2.299 mg of Na.

Thiopental

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{11}H_{18}N_2O_2S$ taking into account the assigned content of *thiopental for ID and assay CRS*.

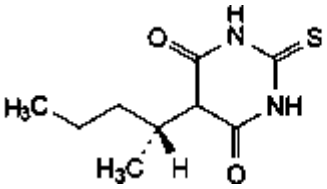
STORAGE

In an airtight container, protected from light.

IMPURITIES

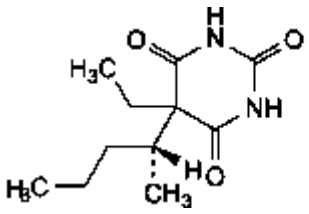
Specified impurities *B, D*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C*.



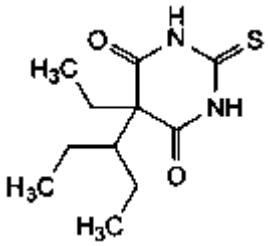
and enantiomer

A. 5-[(2*RS*)-pentan-2-yl]-2-sulfanylidene-1,3-diazinane-4,6-dione,



and enantiomer

B. 5-ethyl-5-[(2*RS*)-pentan-2-yl]-1,3-diazinane-2,4,6-trione (pentobarbital),



C. 5-ethyl-5-(pentan-3-yl)-2-sulfanylidene-1,3-diazinane-4,6-dione,

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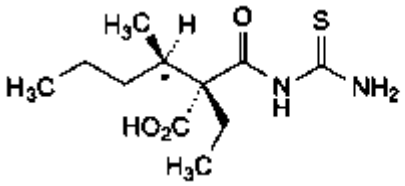
https://thuocngocanh.com/



D. mixture of the 4 stereoisomers of (2Ξ,3Ξ)-2-(carbamothioylcarbamoyl)-2-ethyl-3-methylhexanoic acid.

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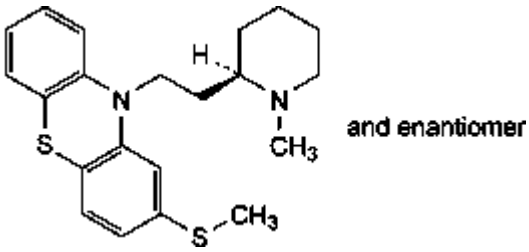
Thioridazine

General Notices

(Ph. Eur. monograph 2005)



and enantiomer

$C_{21}H_{26}N_2S_2$ 370.6 *50-52-2*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

10-[2-[(2*RS*)-1-Methylpiperidin-2-yl]ethyl]-2-(methylsulfanyl)-10*H*-phenothiazine

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, freely soluble in methanol, soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *thioridazine CRS*.

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TESTS

Solution S

Dissolve 1.25 g in *methanol R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test as quickly as possible and protected from light.*

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 100 mL with the same solvent.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve the contents of a vial of *thioridazine for system suitability CRS* (containing impurities A, B, C, D and E) in 1.0 mL of *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* resistant to bases up to pH 11.

Mobile phase:

— *mobile phase A*: *triethylamine R1*, *acetonitrile R*, *water R* (2:400:600 *V/V/V*);

— *mobile phase B*: *triethylamine R1*, *acetonitrile R* (2:1000 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 35	100 → 5	0 → 95
35 - 40	5	95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 25 µL.

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Identification of impurities Use the chromatogram supplied with *thioridazine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to thioridazine (retention time = about 30 min): impurity D = about 0.1; impurity A = about 0.3; impurity C = about 0.4; impurity B = about 0.5; impurity E = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to impurities C and B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity B = 2.4; impurity C = 0.5; impurity D = 1.5;

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g *in vacuo* at 50 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 37.06 mg of $C_{21}H_{26}N_2S_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E*.

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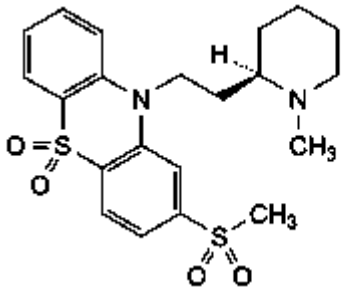
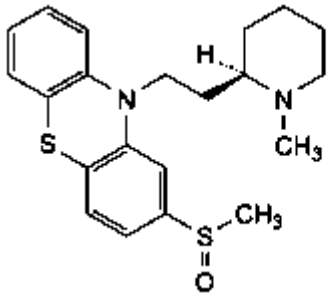
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) F.



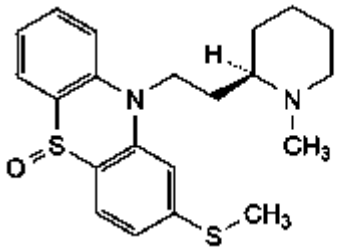
and enantiomer

A. 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulfonyl)-10*H*-phenothiazine 5,5-dioxide,



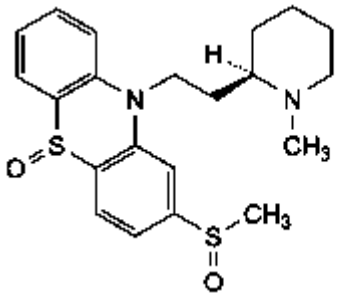
and enantiomer

B. 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulfinyl)-10*H*-phenothiazine (mesoridazine),



and enantiomer

C. 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulfanyl)-10*H*-phenothiazine 5-oxide,



and enantiomer

D. 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulfinyl)-10*H*-phenothiazine 5-oxide,

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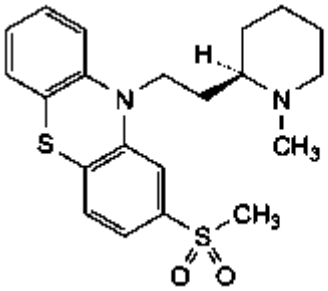
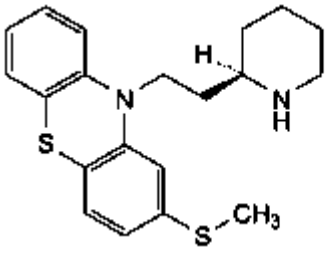


and enantiomer

E. 10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulfonyl)-10*H*-phenothiazine (sulforidazine),



and enantiomer

F. 2-(methylsulfanyl)-10-[2-[(2*RS*)-piperidin-2-yl]ethyl]-10*H*-phenothiazine (northioridazine).

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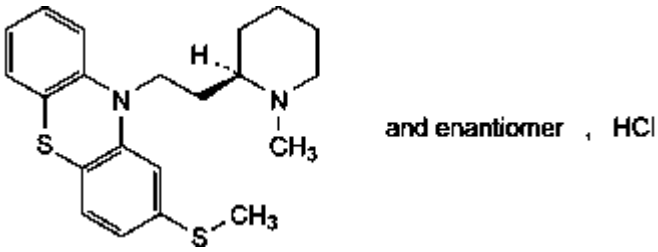
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Thioridazine Hydrochloride

General Notices

(Ph. Eur. monograph 0586)



$C_{21}H_{27}ClN_2S_2$ 407.0 *130-61-0*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

10-[2-[(2*RS*)-1-Methylpiperidin-2-yl]ethyl]-2-(methylsulfanyl)-10*H*-phenothiazine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, soluble in ethanol 96 per cent.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *thioridazine hydrochloride CRS*.

B. Dissolve about 23 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*); use *methanol R* instead of *water R* to wash the precipitate.

TESTS

Carry out all operations protected from light.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dissolve 1.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Optical rotation (*2.2.7*)

-0.10° to + 0.10°.

Dissolve 1.0 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test as quickly as possible and protected from light.*

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve the contents of a vial of *thioridazine for system suitability CRS* (containing impurities A, B, C, D and E) in 1 mL of *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm) resistant to bases up to pH 11.

Mobile phase:

— *mobile phase A*: *triethylamine R1*, *acetonitrile R*, *water for chromatography R* (2:400:600 *V/V/V*);

— *mobile phase B*: *triethylamine R1*, *acetonitrile R* (2:1000 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 35	100 → 5	0 → 95
35 - 40	5	95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 25 µL.

Identification of impurities Use the chromatogram supplied with *thioridazine for system suitability CRS* to identify the peaks due to impurities A, B, C, D and E .

Relative retention With reference to thioridazine (retention time = about 30 min): impurity D = about 0.1; impurity A = about 0.3; impurity C = about 0.4; impurity B = about 0.5; impurity E = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to impurities C and B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity B = 2.4; impurity C = 0.5; impurity D = 1.5;

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.300 g in a mixture of 10 mL of *anhydrous acetic acid R* and 60 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 40.70 mg of $C_{21}H_{27}ClN_2S_2$.

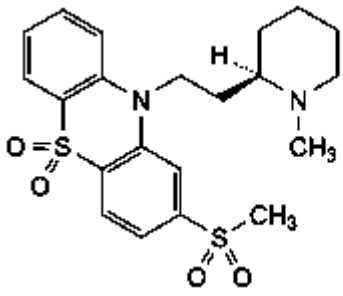
STORAGE

Protected from light.

IMPURITIES

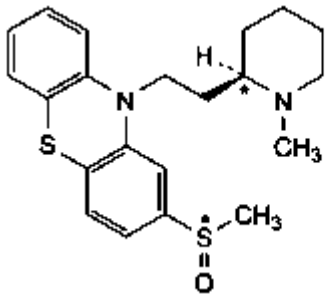
Specified impurities *A, B, C, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F.*



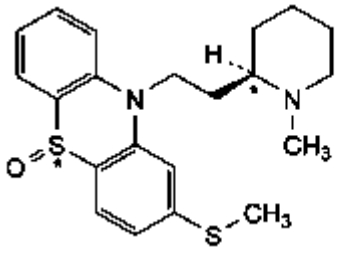
and enantiomer

A. 2-(methanesulfonyl)-10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-5λ^6-phenothiazine-5,5(10*H*)-dione,



and epimer at C*

B. 2-[(Ξ)-methanesulfinyl]-10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-10*H*-phenothiazine (mesoridazine),



and epimer at C*

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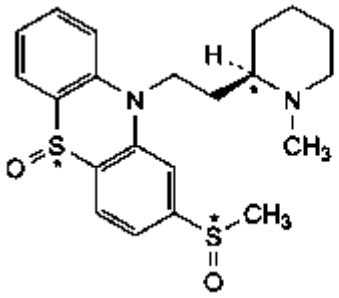
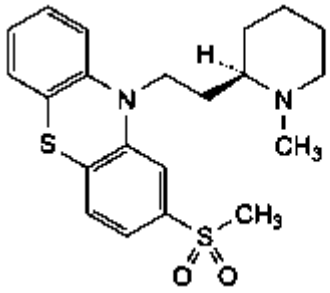
C. (5Ξ)-10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-2-(methylsulfanyl)-5λ^4-phenothiazin-5(10*H*)-one,



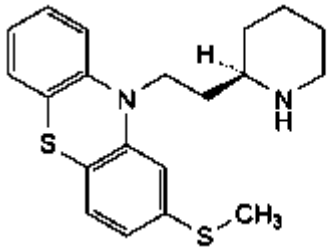
and epimer at C*

D. (5Ξ)-2-[(Ξ)-methanesulfinyl]-10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-5λ^4-phenothiazin-5(10*H*)-one,



and enantiomer

E. 2-(methanesulfonyl)-10-[2-[(2*RS*)-1-methylpiperidin-2-yl]ethyl]-10*H*-phenothiazine (sulforidazine),



and enantiomer

F. 2-(methylsulfanyl)-10-[2-[(2*RS*)-piperidin-2-yl]ethyl]-10*H*-phenothiazine (northioridazine).

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Thiotepa

General Notices

$C_6H_{12}N_3PS$ 189.2 *52-24-4*

Action and use

Cytotoxic alkylating agent.

Preparation

Thiotepa Injection

DEFINITION

Thiotepa is phosphorothioic tri(ethyleneamide). It contains not less than 97.0% and not more than 102.0% of $C_6H_{12}N_3PS$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

Fine, white crystalline flakes.

Freely soluble in *water*, in *chloroform* and in *ethanol (96%)*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of thiotepa *(RS 337)*.

B. Burn 20 mg by the method for *oxygen-flask combustion*, Appendix VIII C, using 5 mL of 1.25M *sodium hydroxide* as the absorbing liquid. When the process is complete, dilute to 25 mL with *water*. To 5 mL of the resulting solution add 0.1 mL of *hydrogen peroxide solution (100 vol)* and 1 mL of 1M *hydrochloric acid*, mix and add 0.05 mL of *barium chloride solution*. The solution becomes turbid.

C. To 2 mL of the solution obtained in test B add 40 mL of *water* and 4 mL of *ammonium molybdate-sulfuric acid solution*, mix, add 0.1 g of L-*ascorbic acid* and boil for 1 minute. A blue colour is produced.

TESTS

Melting point

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52° to 57°, Appendix V A.

Clarity of solution

A 2.0% w/v solution is *clear*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions. Solutions (1) and (2) are solutions of the substance being examined in *water* containing 0.350% w/v and 0.00035% w/v, respectively. For solution (3) dissolve 10 mg of the substance being examined in 2 mL of *methanol* in a ground-glass-stoppered tube, add 50 µL of a 0.1% v/v solution of *orthophosphoric acid*, stopper the tube and heat in a water bath at 65° for 50 seconds (generation of methoxythiotepa). Allow the solution to cool and add 1 mL of *methanol*. For solution (4) dissolve 15 mg of the substance being examined in 10 mL of *water*, add 1 g of *sodium chloride*, boil in a water bath for 10 minutes and cool (generation of chloro-adduct).

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable), (b) 15 volumes of *acetonitrile* and 85 volumes of 0.1M *mixed phosphate buffer pH 7.0* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 215 nm.

The chromatogram obtained with solution (3) shows a peak corresponding to methoxythiotepa with a retention time relative to thiotepa of about 1.3 and the chromatogram obtained with solution (4) shows a peak due to the chloro-adduct with a retention time relative to thiotepa of about 3.75. The test is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (3) is at least 3.

For solution (1) allow the chromatography to proceed for 4 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to the ‘chloro-adduct’ (identified from the peak in the chromatogram obtained with solution (4)) is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%), the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%) and the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Water

Not more than 0.5% w/w, Appendix IX C. Cool the reagents and titration vessel in ice throughout the procedure and use 1.2 g. Complete the procedure as quickly as possible.

ASSAY

Transfer 0.2 g to an iodine flask with the aid of 50 mL of a 20% w/v solution of *sodium thiosulfate* and titrate immediately with *0.1M hydrochloric acid VS*, using 0.05 mL of *methyl orange solution* as indicator, until a faint red colour persists for 10 seconds. Stopper the flask, allow to stand for 30 minutes and titrate with *0.1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Subtract the volume of *0.1M sodium hydroxide VS* used from the volume of *0.1M hydrochloric acid VS* used. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of hydrochloric acid required. Each mL of *0.1M hydrochloric acid VS* is equivalent to 6.307 mg of $C_6H_{12}N_3PS$.

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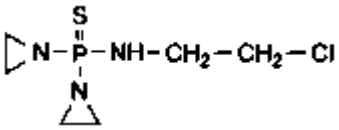
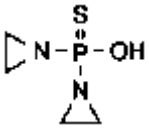
STORAGE

Thiotepa should be stored at a temperature of 2° to 8°. At higher temperatures it polymerises and becomes inactive.

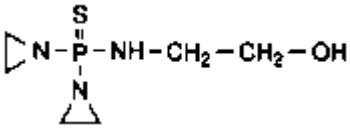
IMPURITIES



A. ‘chloro-adduct’,



B. ‘hydroxythiotepa A’,



C. ‘hydroxythiotepa B’.

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Thiotepa Injection

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Thiotepa Injection is a sterile solution of Thiotepa in Water for Injections. It is prepared by dissolving Thiotepa for Injection in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Thiotepa Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions. If solid matter separates, the solution should not be used.

THIOTEPA FOR INJECTION

DEFINITION

Thiotepa for Injection is a sterile material consisting of Thiotepa with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of thiotepa, $C_6H_{12}N_3PS$

95.0 to 110.0% of the stated amount.

CHARACTERISTICS

A white powder.

IDENTIFICATION

Burn 20 mg by the method for *oxygen-flask combustion*, Appendix VIII C, using 5 mL of 1.25M *sodium hydroxide* as the absorbing liquid. When the process is complete, dilute to 25 mL with *water*. The resulting solution complies with the following tests.

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A. To 5 mL add 0.1 mL of *hydrogen peroxide solution (100 vol)* and 1 mL of 1M *hydrochloric acid*, mix and add 0.05 mL of *barium chloride solution*. The solution becomes turbid.

B. To 2 mL add 40 mL of *water* and 4 mL of *ammonium molybdate-sulfuric acid solution*, mix, add 0.1 g of L-*ascorbic acid* and boil for 1 minute. A blue colour is produced.

TESTS

Acidity or alkalinity

Dissolve a quantity containing 20 mg of Thiotepa in 2 mL of *carbon dioxide-free water*. The pH of the resulting solution is 5.5 to 7.5, Appendix V L.

Clarity of solution

Dissolve a quantity containing 15 mg of Thiotepa in 4 mL of *water*. The solution is *clear*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions.

(1) Dissolve, with shaking, a quantity of the contents of the sealed container containing 15 mg of Thiotepa in 4 mL of *water*, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water* and further dilute 1 volume to 10 volumes with *water*.

(3) Dissolve 10 mg of *thiotepa BPCRS* in 2 mL of *methanol* in a ground-glass-stoppered tube, add 50 µL of a 0.1% v/v solution of *orthophosphoric acid*, stopper the tube and heat in a water bath at 65° for 50 seconds (generation of methoxy-thiotepa). Allow the solution to cool and add 1 mL of *methanol*.

(4) Dissolve 15 mg of *thiotepa BPCRS* in 10 mL of *water*, add 1 g of *sodium chloride*, boil in a water bath for 10 minutes and cool (generation of chloro-adduct impurity).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 4 times the retention time of the principal peak.

The chromatogram obtained with solution (3) shows a peak corresponding to methoxy-thiotepa with a retention time relative to thiotepa of about 1.3 and the chromatogram obtained with solution (4) shows a peak corresponding to the chloro-adduct impurity with a retention time relative to thiotepa of about 3.1.

MOBILE PHASE

15 volumes of *acetonitrile* and 85 volumes of 0.1M *mixed phosphate buffer pH 7.0*.

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SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to the chloro-adduct impurity (identified from the peak in the chromatogram obtained with solution (4)) is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of not more than two such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing 0.15% w/v of Thiotepa.
(2) 0.15% w/v of *thiotepa BPCRS* in *water*.
(3) Dissolve 10 mg of *thiotepa BPCRS* in 2 mL of *methanol* in a ground-glass-stoppered tube, add 50 µL of a 0.1% v/v solution of *orthophosphoric acid*, stopper the tube and heat in a water bath at 65° for 50 seconds (to produce a sufficient quantity of methoxy-thiotepa). Allow the solution to cool and add 1 mL of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 20 µL of each solution.
The chromatogram obtained with solution (3) shows a peak corresponding to methoxy-thiotepa with a retention time relative to thiotepa of about 1.3.

MOBILE PHASE

15 volumes of *acetonitrile* and 85 volumes of *0.1M mixed phosphate buffer pH 7.0*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.

DETERMINATION OF CONTENT

Calculate the amount of $C_6H_{12}N_3PS$ in the sealed container using the declared content of $C_6H_{12}N_3PS$ in *thiotepa BPCRS*.

Repeat the procedure with a further nine sealed containers. Calculate the average content of $C_6H_{12}N_3PS$ per container from the 10 individual results thus obtained.

STORAGE

The sealed container should be stored at a temperature of 2° to 8°.

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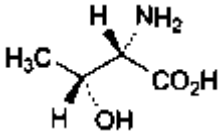
Threonine

General Notices

(Ph. Eur. monograph 1049)



$C_4H_9NO_3$ 119.1 *72-19-5*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*,3*R*)-2-Amino-3-hydroxybutanoic acid.

Product of fermentation or of protein hydrolysis.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *threonine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 1 per cent *V*/*V* solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Reference solution Dissolve 10 mg of *threonine CRS* in a 1 per cent *V*/*V* solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V*/*V*/*V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Mix 1 mL of a 2 g/L solution of the substance to be examined and 1 mL of a 20 g/L solution of *sodium periodate R*. Add 0.2 mL of *piperidine R* and 0.1 mL of a 25 g/L solution of *sodium nitroprusside R*. A blue colour develops that changes to yellow after a few minutes.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

pH (2.2.3)

5.0 to 6.5 for solution S.

Specific optical rotation (2.2.7)

-29.0 to -27.6 (dried substance).

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Dissolve 1.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Ninhydrin-positive substances

Amino acid analysis (*2.2.56*). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter *2.2.46* are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A *dilute hydrochloric acid R1* or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* (impurity D) and 30 mg of *leucine R* in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity D and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of threonine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

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— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dissolve 0.5 g in *distilled water R* and dilute to 15 mL with the same solvent.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 5 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 11.91 mg of $C_4H_9NO_3$.

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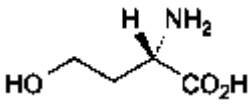
STORAGE

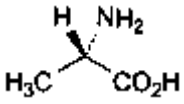
Protected from light.

IMPURITIES

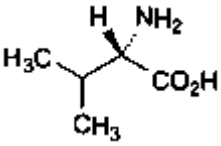
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E.*



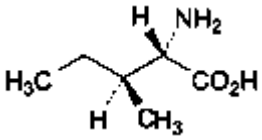
A. (2*S*)-2-amino-4-hydroxybutanoic acid (homoserine),



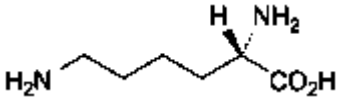
B. (2*S*)-2-aminopropanoic acid (alanine),



C. (2*S*)-2-amino-3-methylbutanoic acid (valine),



D. (2*S*,3*S*)-2-amino-3-methylpentanoic acid (isoleucine),



E. (2*S*)-2,6-diaminohexanoic acid (lysine).

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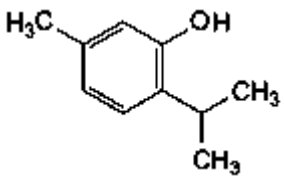
Thymol

General Notices

(Ph. Eur. monograph 0791)



$C_{10}H_{14}O$ 150.2 *89-83-8*

Ph Eur

DEFINITION

5-Methyl-2-(methylethyl)phenol.

CHARACTERS

Appearance

Colourless crystals.

Solubility

Very slightly soluble in water, very soluble in ethanol (96 per cent), freely soluble in essential oils and in fatty oils, sparingly soluble in glycerol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (2.2.14): 48 °C to 52 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *thymol CRS*.

C. Dissolve 0.2 g with heating in 2 mL of *dilute sodium hydroxide solution R* and add 0.2 mL of *chloroform R*. Heat on a water-bath. A violet colour develops.

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D. Dissolve about 2 mg in 1 mL of *anhydrous acetic acid R*. Add 0.15 mL of *sulfuric acid R* and 0.05 mL of *nitric acid R*. A bluish-green colour develops.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension IV (*2.2.1*) and not more intensely coloured than reference solution R_6 (*2.2.2, Method II*).

Dissolve 1.0 g in 10 mL of *dilute sodium hydroxide solution R*.

Acidity

To 1.0 g in a 100 mL glass-stoppered conical flask add 20 mL of *water R*. Boil until dissolution is complete, cool and stopper the flask. Shake vigorously for 1 min. Add a few crystals of the substance to be examined to initiate crystallisation. Shake vigorously for 1 min and filter. To 5 mL of the filtrate add 0.05 mL of *methyl red solution R* and 0.05 mL of *0.01 M sodium hydroxide*. The solution is yellow.

Related substances

Gas chromatography (*2.2.28*).

Test solution Dissolve 0.100 g of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 100 mL with *ethanol (96 per cent) R*.

Reference solution (b) Dilute 1 mL of reference solution (a) to 10 mL with *ethanol (96 per cent) R*.

Reference solution (c) Dilute 5 mL of reference solution (b) to 10 mL with *ethanol (96 per cent) R*.

Column:

— *material*: glass or steel;

— *size*: *l* = 4 m, Ø = 2 mm;

— *stationary phase*: diatomaceous earth for gas chromatography R, impregnated with a mixture suitable for the separation of free fatty acids.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 2	80
	2 - 22	80 → 240
	22 - 37	240
Injection port		250
Detector		300

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 5 for the principal peak.

Limits:

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Residue on evaporation

Maximum 0.05 per cent.

Evaporate 2.00 g on a water-bath and heat in an oven at 100-105 °C for 1 h. The residue weighs not more than 1.0 mg.

STORAGE

Protected from light.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Tragacanth

General Notices

(Ph. Eur. monograph 0532)

When Powdered Tragacanth is prescribed or demanded, material complying with the requirements below with the exception of Identification test A shall be dispensed or supplied.

9000-65-1

Ph Eur

DEFINITION

Air-hardened, gummy exudate, flowing naturally or obtained by incision from the trunk and branches of *Astragalus gummifer* Labill. and certain other species of *Astragalus* from western Asia.

IDENTIFICATION

A. Tragacanth occurs in thin, flattened, ribbon-like, white or pale yellow, translucent strips, about 30 mm long and 10 mm wide and up to 1 mm thick, more or less curved, horny, with a short fracture; the surface is marked by fine longitudinal striae and concentric transverse ridges. It may also contain pieces similar in shape but somewhat thicker, more opaque and more difficult to fracture.

B. Microscopic examination (2.8.23). The powder is white or almost white and forms a mucilaginous gel with about 10 times its mass of *water R*. Examine under a microscope using a 50 per cent *V/V* solution of *glycerol R*. The powder shows in the gummy mass numerous stratified cellular membranes that turn slowly violet when treated with *iodinated zinc chloride solution R*. The gummy mass includes starch granules, isolated or in small groups, usually rounded in shape and sometimes deformed, with diameters varying between 4 µm and 10 µm, occasionally up to 20 µm, and a central hilum visible between crossed nicol prisms.

C. Examine the chromatograms obtained in the test for acacia.

Results The chromatogram obtained with the test solution shows 3 zones due to galactose, arabinose and xylose. A faint yellowish zone at the solvent front and a greyish-green zone between the zones due to galactose and arabinose may be present.

D. Moisten 0.5 g of the powdered herbal drug (355) (2.9.12) with 1 mL of *ethanol (96 per cent) R* and add gradually, while shaking, 50 mL of *water R* until a homogeneous mucilage is obtained. To 5 mL of the mucilage add 5 mL of *water R* and 2 mL of *barium hydroxide solution R*. A slight flocculent precipitate is formed. Heat on a water-bath for 10 min. An intense yellow colour develops.

TESTS

Acacia

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Thin-layer chromatography (2.2.27).

Test solution To 100 mg of the powdered herbal drug (355) (2.9.12) in a thick-walled centrifuge test-tube, add 2 mL of a 100 g/L solution of *trifluoroacetic acid R*, shake vigorously to dissolve the forming gel, stopper the test-tube and heat the mixture at 120 °C for 1 h. Centrifuge the resulting hydrolysate, transfer the clear supernatant carefully into a 50 mL flask, add 10 mL of *water R* and evaporate the solution to dryness under reduced pressure. To the resulting clear film add 0.1 mL of *water R* and 0.9 mL of *methanol R*. Centrifuge to separate the amorphous precipitate, collect the supernatant and, if necessary, dilute to 1 mL with *methanol R*.

Reference solution Dissolve 10 mg of *arabinose R*, 10 mg of *galactose R*, 10 mg of *rhamnose R* and 10 mg of *xylose R* in 1 mL of *water R* and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase 16 g/L solution of *sodium dihydrogen phosphate R*, *butanol R*, *acetone R* (10:40:50 *V/V/V*).

Application 10 µL as bands.

Development A Over a path of 10 cm.

Drying A In a current of warm air for a few minutes.

Development B Over a path of 15 cm using the same mobile phase.

Drying B At 110 °C for 10 min.

Detection Spray with *anisaldehyde solution R* and dry at 110 °C for 10 min.

Results The chromatogram obtained with the reference solution shows 4 clearly separated coloured zones due to galactose (greyish-green or green), arabinose (yellowish-green), xylose (greenish-grey or yellowish-grey) and rhamnose (yellowish-green), in order of increasing R_F value; the chromatogram obtained with the test solution does not show a yellowish-green zone corresponding to the zone of rhamnose in the chromatogram obtained with the reference solution.

Methylcellulose

Examine the chromatograms obtained in the test for acacia.

Results The chromatogram obtained with the test solution does not show a red zone near the solvent front.

Sterculia gum

A. Place 0.2 g of the powdered herbal drug (355) (2.9.12) in a 10 mL ground-glass-stoppered cylinder graduated in 0.1 mL. Add 10 mL of *ethanol (60 per cent V/V) R* and shake. Any gel formed occupies not more than 1.5 mL.

B. To 1.0 g of the powdered herbal drug (355) (2.9.12) add 100 mL of *water R* and shake. Add 0.1 mL of *methyl red solution R*. Not more than 5.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Foreign matter

Maximum 1.0 per cent.

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Place 2.0 g of the powdered herbal drug (355) (2.9.12) in a 250 mL round-bottomed flask and add 95 mL of *methanol R*. Swirl to moisten the powder and add 60 mL of *hydrochloric acid R1*. Add a few glass beads about 4 mm in diameter and heat on a water-bath under a reflux condenser for 3 h, shaking occasionally. Remove the glass beads and filter the hot suspension *in vacuo* through a sintered-glass filter (160) (2.1.2). Rinse the flask with a small quantity of *water R* and pass the rinsings through the filter. Wash the residue on the filter with about 40 mL of *methanol R* and dry to constant mass at 110 °C (about 1 h). Allow to cool in a desiccator and weigh. The residue weighs a maximum of 20 mg.

Flow time

Minimum 10 s, or minimum 50 s if the substance to be examined is to be used for the preparation of emulsions.

Place 1.0 g of the powdered herbal drug (125-250) (2.9.12) in a 1000 mL round-bottomed flask with a ground-glass stopper, add 8.0 mL of *ethanol (96 per cent) R* and close the flask. Disperse the suspension over the inner surface of the flask by shaking, taking care not to wet the stopper. Open the flask and add as a single portion 72.0 mL of *water R*. Stopper the flask and shake vigorously for 3 min. Allow to stand for 24 h and shake vigorously again for 3 min. Eliminate air bubbles by applying vacuum above the mucilage for 5 min. Transfer the mucilage to a 50 mL cylinder. Dip in the mucilage a piece of glass tubing 200 mm long and 6.0 mm in internal diameter and graduated at 20 mm and 120 mm from the lower end; the tubing must not be rinsed with surface-active substances. When the mucilage has reached the upper mark, close the tube with a finger. Withdraw the closed tube, remove the finger and measure with a stop-watch the time needed for the meniscus to reach the lower graduation. Carry out this operation 4 times and determine the average value of the last 3 determinations.

Total ash (2.4.16)

Maximum 4.0 per cent.

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

LABELLING

The label states whether or not the contents are suitable for preparing emulsions.

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Tramadol Capsules

General Notices

Action and use

μ-Opioid receptor (OP_3, MOR) agonist and noradrenaline reuptake inhibitor; analgesic.

DEFINITION

Tramadol Capsules contain Tramadol Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of tramadol hydrochloride, $C_{16}H_{25}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the capsules containing 50 mg of Tramadol Hydrochloride with 25 mL of *methanol* for 5 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the reference spectrum of tramadol hydrochloride *(RS 465)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.0056% w/v of Tramadol Hydrochloride, at the maximum at 272 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0056% w/v solution of *tramadol hydrochloride BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of tramadol hydrochloride, $C_{16}H_{25}NO_2$,HCl in the medium using the declared content of $C_{16}H_{25}NO_2$,HCl in *tramadol hydrochloride BPCRS*.

LIMITS

The amount of tramadol hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Mix with the aid of ultrasound, a quantity of the contents of the capsules containing 0.5 g of Tramadol Hydrochloride with 80 mL. Dilute to produce 100 mL and filter through a glass-fibre filter (Whatman GF/A is suitable).
(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and further dilute 1 volume to 10 volumes with the mobile phase.
(3) 0.0015% w/v of *tramadol impurity A BPCRS* in the mobile phase.
(4) 0.0015% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 271 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for four times the retention time of the principal peak.

MOBILE PHASE

1 volume of *trifluoroacetic acid*, 30 volumes of *acetonitrile* and 69 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

CALCULATION OF IMPURITIES

For impurity A, use the concentration of impurity A in solution (3).

For each unspecified impurity, use the concentration of tramadol hydrochloride in solution (2).

For the reporting threshold, use the concentration of tramadol hydrochloride in solution (2).

For peak identification, use solution (3).

Tramadol retention time: about 5 minutes.

Relative retention: impurity A, about 0.9.

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LIMITS

— impurity A: not more than 0.3%;

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 1.0%;

— reporting threshold: 0.1%.

ASSAY

Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound, a quantity of the mixed capsule contents containing 50 mg of Tramadol Hydrochloride with 150 mL of the mobile phase, cool, add sufficient mobile phase to produce 200 mL and filter through a glass-fibre filter (Whatman GF/A is suitable).
(2) 0.025% w/v of *tramadol hydrochloride BPCRS* in the mobile phase.
(3) 0.0015% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{25}NO_2$,HCl in the capsules from the chromatograms obtained and using the declared content of $C_{16}H_{25}NO_2$,HCl in *tramadol hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to D listed under Tramadol Hydrochloride.

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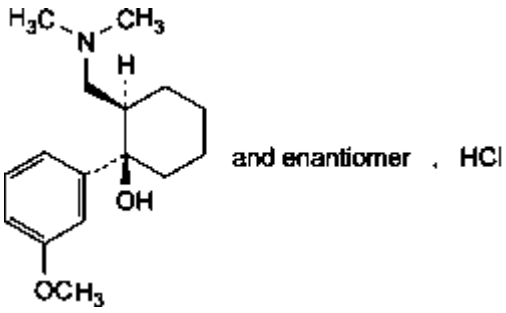
Tramadol Hydrochloride

General Notices

(Ph. Eur. monograph 1681)



$C_{16}H_{26}ClNO_2$ 299.8 *36282-47-0*

Action and use

μ-Opioid receptor (OP3, MOR) agonist and noradrenaline reuptake inhibitor; analgesic.

Preparations

Tramadol Capsules

Tramadol Prolonged-release Capsules

Tramadol Injection

Tramadol Oral Drops

Tramadol Prolonged-release Tablets

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DEFINITION

(1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, very slightly soluble in acetone.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 180 °C to 184 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *tramadol hydrochloride CRS*.

C. Examine the chromatograms obtained in the test for impurity E.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity

To 10 mL of solution S, add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M hydrochloric acid*. The solution is red. Not more than 0.4 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Impurity E

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 2.0 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

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Reference solution (a) Dissolve 25 mg of *tramadol hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 5.0 mg of *tramadol impurity E CRS* in *methanol R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 5 mg of *tramadol impurity A CRS* in 1 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Pretreatment Wash the plate with *methanol R*.

Mobile phase *concentrated ammonia R*, *2-propanol R*, *toluene R* (1:19:80 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate. Add *concentrated ammonia R* to one trough of a twin trough tank then saturate the plate for 20 min. Just before developing, add the mobile phase to the other trough. Place the plate in the trough, ensuring that the layer of silica gel faces the middle of the tank.

Drying In air.

Detection Expose to iodine vapour for 1 h, then examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (c) shows 2 clearly separated spots.

Limit Test solution (a):

— *impurity E*: any spot due to impurity E is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.15 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *tramadol impurity A CRS* in 4 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 295 volumes of *acetonitrile R* and 705 volumes of a mixture of 0.2 mL of *trifluoroacetic acid R* and 100 mL of *water for chromatography R*.

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Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL.

Run time 4 times the retention time of tramadol.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to tramadol (retention time = about 6 min): impurity A = about 0.85.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and tramadol.

Calculation of percentage contents:

— for each impurity, use the concentration of tramadol hydrochloride in reference solution (a).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.02 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 50 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M ethanolic sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 29.98 mg of $C_{16}H_{26}ClNO_2$.

STORAGE

Protected from light.

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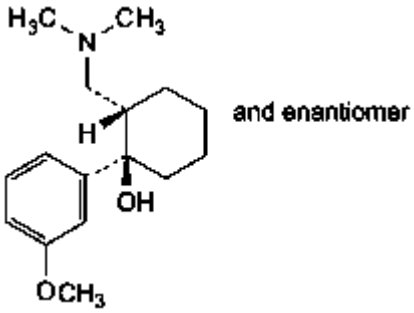
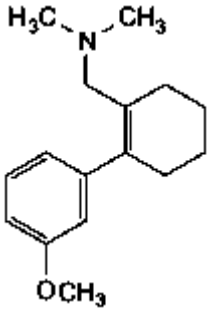
IMPURITIES

Specified impurities A, E.

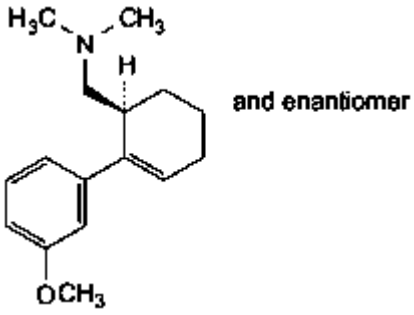
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D.



A. (1*RS*,2*SR*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol,



B. [2-(3-methoxyphenyl)cyclohex-1-en-1-yl]-*N*,*N*-dimethylmethanamine,



C. [(1*RS*)-2-(3-methoxyphenyl)cyclohex-2-en-1-yl]-*N*,*N*-dimethylmethanamine,

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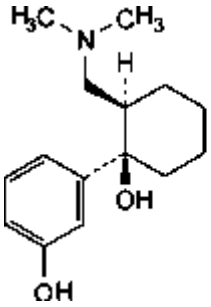
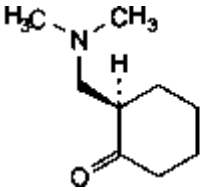


and enantiomer

D. (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-hydroxyphenyl)cyclohexan-1-ol,



and enantiomer

E. (2*RS*)-2-[(dimethylamino)methyl]cyclohexan-1-one.

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Tramadol Injection

General Notices

Action and use

μ-Opioid receptor (OP_3, MOR) agonist and noradrenaline reuptake inhibitor; analgesic.

DEFINITION

Tramadol Injection contains Tramadol Hydrochloride.

The Injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of tramadol hydrochloride, $C_{16}H_{25}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH of a solution containing 5% w/v of Tramadol Hydrochloride, 6.0 to 7.0, Appendix V L.

Clarity and colour of solution

The injection is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method I.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection with sufficient mobile phase to produce a solution containing 0.05% w/v of Tramadol Hydrochloride.

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(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and further dilute 1 volume to 10 volumes with the mobile phase.

(3) 0.005% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-5 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for five times the retention time of the principal peak.

MOBILE PHASE

295 volumes of *acetonitrile* and 705 volumes of 0.2% w/v of *trifluoroacetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of tramadol hydrochloride in solution (2).

For the reporting threshold, use the concentration of tramadol hydrochloride in solution (2).

For the reporting threshold, use the concentration of tramadol hydrochloride in solution (2).

Tramadol retention time: about 5 minutes.

Relative retention: impurity D, about 0.7; impurity A, about 0.9; impurity 1, about 1.2; impurity 2, about 1.9; impurity C, about 2.4; impurity B, about 2.7 and impurity 3, about 4.2.

LIMITS

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 1.0%;

— reporting threshold: 0.1%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection with sufficient mobile phase to produce a solution containing 0.05% w/v of Tramadol Hydrochloride.

(2) 0.05% w/v of *tramadol hydrochloride BPCRS* in the mobile phase.

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(3) 0.005% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS* in the mobile phase.

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

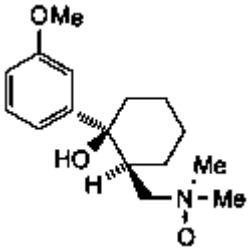
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

DETERMINATION OF CONTENT

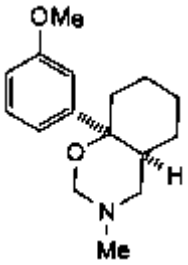
Calculate the content of $C_{16}H_{25}NO_2$,HCl in the injection from the chromatograms obtained and using the declared content of $C_{16}H_{25}NO_2$,HCl in *tramadol hydrochloride BPCRS*.

IMPURITIES

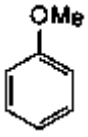
The impurities limited by the requirements of this monograph include impurities A to D listed under Tramadol Hydrochloride and:



1. (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol N-oxide



2. 8*a*-(3-methoxyphenyl)-3-methyloctahydro-2*H*-1,3-benzoxazine



3. methoxybenzene (anisole).

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Tramadol Oral Drops

General Notices

Action and use

μ-Opioid receptor (OP_3, MOR) agonist and noradrenaline reuptake inhibitor; analgesic.

DEFINITION

Tramadol Oral Drops contain Tramadol Hydrochloride in a suitable vehicle.

The Oral Drops comply with the requirements stated under Oral Liquids and with the following requirements.

Content of tramadol hydrochloride, $C_{16}H_{25}NO_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the oral drops with sufficient mobile phase to produce a solution containing 0.1% w/v of Tramadol Hydrochloride.
(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and further dilute 1 volume to 10 volumes with the mobile phase.
(3) 0.0002% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 μm) (LiChrospher 60 RP Select B is suitable).
(b) Use isocratic elution and the mobile phase described below.

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(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use detection wavelengths of 213 nm and 273 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 6 times the retention time of tramadol.

MOBILE PHASE

15 volumes of *acetonitrile R1* and 85 volumes of a solution containing 0.12% w/v of *diammonium hydrogen orthophosphate* in a mixture of 0.9 volumes of *triethylamine* and 100 volumes of *water*, adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of tramadol hydrochloride in solution (2).

For the reporting threshold, use the concentration of tramadol hydrochloride in solution (2).

Tramadol retention time: about 4 minutes.

Relative retention: impurity D, about 0.5; impurity A, about 0.9; impurity 1, about 1.1; impurity C, about 3.7 and impurity B, about 4.5.

LIMITS

At 213 nm

— impurities B and C: not more than 0.2% of each.

At 273 nm

— unspecified impurities: for each impurity, not more than 0.2%;

— total unspecified impurities: not more than 1.0%;

— reporting threshold: 0.1%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the oral drops with sufficient mobile phase to produce a solution containing 0.1% w/v of Tramadol Hydrochloride.

(2) 0.1% w/v of *tramadol hydrochloride BPCRS* in the mobile phase.

(3) 0.0002% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

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SYSTEM SUITABILITY

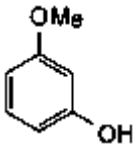
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{25}NO_2$,HCl in the oral drops from the chromatograms obtained and using the declared content of $C_{16}H_{25}NO_2$,HCl in *tramadol hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to D listed under Tramadol Hydrochloride and:



1. 3-methoxyphenol.

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Tramadol Prolonged-release Capsules

General Notices

Prolonged-release Tramadol Capsules

Tramadol Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

μ-Opioid receptor (OP_3, MOR) agonist; noradrenaline reuptake inhibitor; analgesic.

DEFINITION

Tramadol Prolonged-release Capsules contain Tramadol Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Tramadol Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of tramadol hydrochloride, $C_{16}H_{25}NO_2$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered capsule contents containing 50 mg of Tramadol Hydrochloride with 25 mL of *methanol* for 5 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of tramadol hydrochloride (*RS 465*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix, with the aid of ultrasound, a quantity of the powdered capsule contents containing 0.5 g of Tramadol Hydrochloride with 80 mL, cool, add sufficient mobile phase to produce 100 mL and filter through a glass-fibre filter (Whatman GF/A is suitable).

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(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume to 10 volumes.

(3) 0.0015% w/v of *tramadol impurity A BPCRS*.

(4) 0.0015% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 271 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for four times the retention time of the principal peak.

MOBILE PHASE

1 volume of *trifluoroacetic acid*, 30 volumes of *acetonitrile* and 69 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

CALCULATION OF IMPURITIES

For impurity A, use the concentration of impurity A in solution (3).

For each unspecified impurity, use the concentration of tramadol hydrochloride in solution (2).

For the reporting threshold, use the concentration of tramadol hydrochloride in solution (2).

For peak identification, use solution (3).

Tramadol retention time: about 5 minutes.

Relative retention: impurity A, about 0.9.

LIMITS

— impurity A: not more than 0.3%;

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 1.0%;

— reporting threshold: 0.1%.

ASSAY

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Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix, with the aid of ultrasound, a quantity of the powdered capsule contents containing 50 mg of Tramadol Hydrochloride with 150 mL, cool, add sufficient mobile phase to produce 200 mL and filter through a glass-fibre filter (Whatman GF/A is suitable).

(2) 0.025% w/v of *tramadol hydrochloride BPCRS*.

(3) 0.0015% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{25}NO_2$,HCl in the capsules using the declared content of $C_{16}H_{25}NO_2$,HCl in *tramadol hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to D listed under Tramadol Hydrochloride.

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Tramadol Prolonged-release Tablets

General Notices

Prolonged-release Tramadol Tablets

Tramadol Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

μ-Opioid receptor (OP_3, MOR) agonist; noradrenaline reuptake inhibitor; analgesic.

DEFINITION

Tramadol Prolonged-release Tablets contain Tramadol Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Tramadol Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tramadol hydrochloride, $C_{16}H_{25}NO_2$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 25 mL of *methanol* to a quantity of the powdered tablets containing 50 mg of Tramadol Hydrochloride, shake for 10 minutes and filter through a glass-fibre filter (Whatman GF/A is suitable).

(2) 0.2% w/v of *tramadol hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F* (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 μL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

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MOBILE PHASE

1 volume of *anhydrous formic acid*, 50 volumes of *acetone* and 50 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 0.5 g of Tramadol Hydrochloride with 80 mL, cool, add sufficient mobile phase to produce 100 mL and filter through a glass-fibre filter (Whatman GF/A is suitable).
(2) Dilute 1 volumes of solution (1) to 50 volumes and further dilute 1 volume to 10 volumes.
(3) 0.0015% w/v of *tramadol impurity A BPCRS*.
(4) 0.0015% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 271 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for four times the retention time of the principal peak.

MOBILE PHASE

1 volume of *trifluoroacetic acid*, 30 volumes of *acetonitrile* and 69 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

CALCULATION OF IMPURITIES

For impurity A, use the concentration of impurity A in solution (3).

For each unspecified impurity, use the concentration of tramadol hydrochloride in solution (2).

For the reporting threshold, use the concentration of tramadol hydrochloride in solution (2).

For peak identification, use solution (3).

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Tramadol retention time: about 5 minutes.

Relative retention: impurity A, about 0.9.

LIMITS

— impurity A: not more than 0.3%;

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 1.0%;

— reporting threshold: 0.1%.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 50 mg of Tramadol Hydrochloride in 150 mL, cool, add sufficient mobile phase to produce 200 mL and filter through a glass-fibre filter (Whatman GF/A is suitable).
(2) 0.025% w/v of *tramadol hydrochloride BPCRS*.
(3) 0.0015% w/v each of *tramadol hydrochloride BPCRS* and *tramadol impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and tramadol is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{25}NO_2$,HCl in the tablets using the declared content of $C_{16}H_{25}NO_2$,HCl in *tramadol hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to D listed under Tramadol Hydrochloride.

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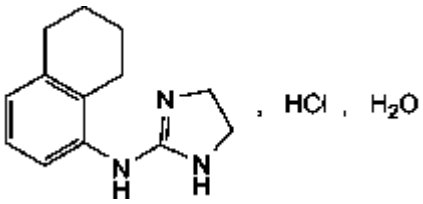
Tramazoline Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 1597)



$C_{13}H_{18}ClN_3,H_2O$ 269.8 *74195-73-6*

Action and use

Alpha-adrenoceptor agonist.

Ph Eur

DEFINITION

N-(5,6,7,8-Tetrahydronaphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride monohydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tramazoline hydrochloride monohydrate CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

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TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*)

4.9 to 6.3 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5.0 mg of *tramazoline impurity A CRS* and 5.0 mg of *tramazoline impurity B CRS* in 5 mL of the solvent mixture and add 5 mL of the test solution.

Reference solution (b) Dilute 0.2 mL of reference solution (a) to 100 mL with the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 2.0 g/L solution of *sodium dodecyl sulfate R* in a mixture of 6 volumes of *2-propanol R*, 42 volumes of *acetonitrile R1* and 52 volumes of *water for chromatography R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 5 µL.

Run time 3 times the retention time of tramazoline.

Relative retention With reference to tramazoline (retention time = about 6.5 min): impurity A = about 0.71; impurity B = about 0.86.

System suitability Reference solution (a):

— the chromatogram obtained shows 3 clearly separated peaks;

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— *resolution*: minimum 1.5 between the peak due to impurity B and tramazoline.

Limits:

— *impurities A, B*: for each impurity, not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *sum of impurities other than A and B*: not more than twice the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.02 per cent).

Water (*2.5.12*)

6.2 per cent to 7.2 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

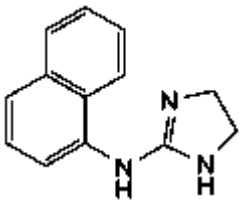
Dissolve 2.000 g in a mixture of 5 mL of *0.1 M hydrochloric acid* and 75 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*) using *1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *1 M sodium hydroxide* is equivalent to 251.8 mg of $C_{13}H_{18}ClN_3$.

IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



A. *N*-(naphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine,

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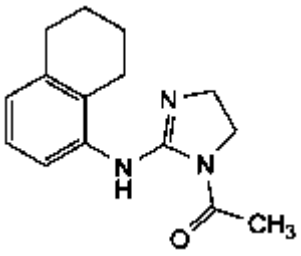
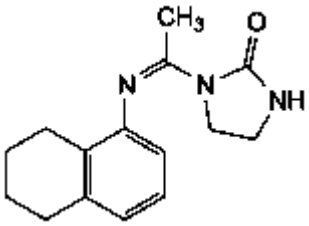


B. 1-[2-[(5,6,7,8-tetrahydronaphthalen-1-yl)amino]-4,5-dihydro-1*H*-imidazol-1-yl]ethan-1-one,



C. 1-[(1*Z*)-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)ethanimidoyl]imidazolidin-2-one.

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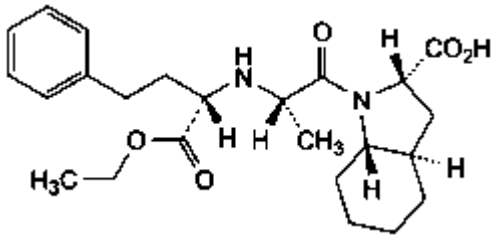
Trandolapril

General Notices

(Ph. Eur. monograph 2245)



$C_{24}H_{34}N_2O_5$ 430.5 *87679-37-6*

Action and use

Angiotensin converting enzyme inhibitor.

Preparation

Trandolapril Capsules

Ph Eur

DEFINITION

(2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *trandolapril CRS*.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Dissolve 1.0 g in *methanol R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

-18.5 to -16.5 (anhydrous substance).

Dissolve 1.0 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *trandolapril impurity C CRS* and 5 mg of *trandolapril impurity D CRS* in mobile phase A and dilute to 5 mL with mobile phase A. Dilute 1 mL of the solution to 20 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 25 volumes of *acetonitrile R1* and 75 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.5 ± 0.1 with *phosphoric acid R*;

— *mobile phase B*: mix equal volumes of *acetonitrile R1* and a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.2 ± 0.1 with *phosphoric acid R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	95	5
20 - 35	95 → 5	5 → 95
35 - 45	5	95

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and D.

Relative retention With reference to trandolapril (retention time = about 14.5 min): impurity C = about 2.1; impurity D = about 2.5.

System suitability Reference solution (b):

— *resolution*: minimum 4 between the peaks due to impurities C and D.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2.2;

— *impurity D*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than D*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.2 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g in a porcelain or quartz crucible.

ASSAY

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Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 43.05 mg of $C_{24}H_{34}N_2O_5$.

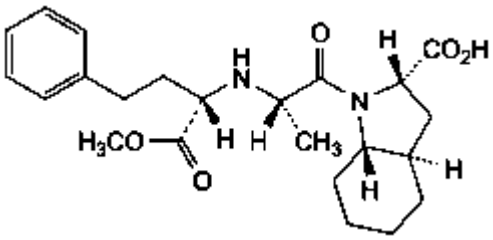
STORAGE

Protected from light.

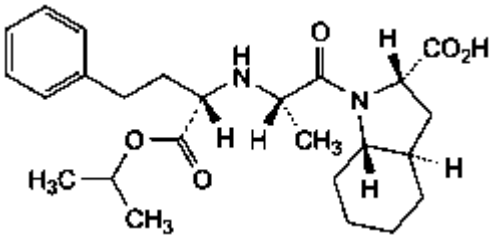
IMPURITIES

Specified impurities C, D.

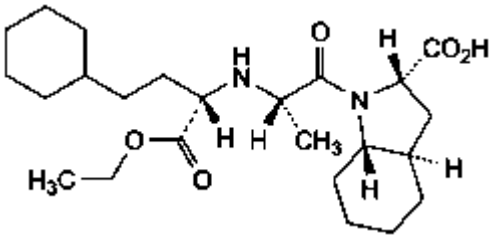
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, E, F.



A. (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-methoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (methyl ester derivative),



B. (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-oxo-4-phenyl-1-[(propan-2-yl)oxy]butan-2-yl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (isopropyl ester derivative),



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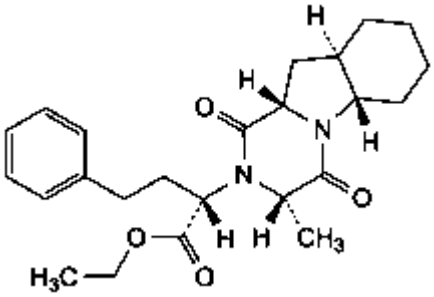
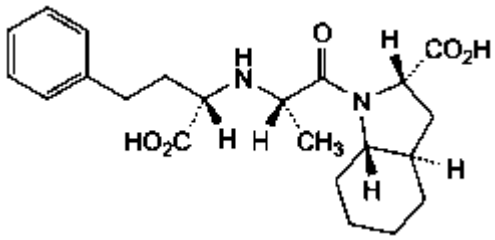
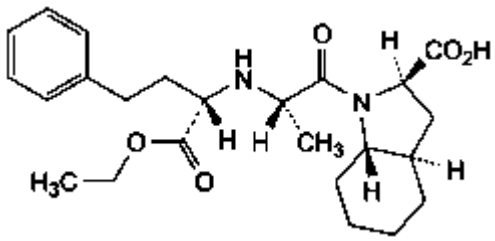
C. (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-4-cyclohexyl-1-ethoxy-1-oxobutan-2-yl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (hexahydrotrandolapril),



D. ethyl (2*S*)-2-[(3*S*,5a*S*,9a*R*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]-4-phenylbutanoate (trandolapril diketopiperazine),



E. (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (trandolaprilate),



F. (2*R*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid.

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Trandolapril Capsules

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Trandolapril Capsules contain Trandolapril.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of trandolapril, $C_{24}H_{34}N_2O_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the contents of the capsules containing 26 mg of Trandolapril add 10 mL of *water* and centrifuge. Discard the supernatant liquid and dissolve the residue in 10 mL of *dichloromethane*, shake and filter (Whatman GF/C is suitable). Evaporate the filtrate to dryness under a stream of nitrogen and dry under vacuum at 60° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of trandolapril (*RS 468*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute with *water*, if necessary, to produce a solution expected to contain 0.000055% w/v of Trandolapril.

(2) 0.000055% w/v of *trandolapril BPCRS* in *water*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher 60 RP-Select B is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 400 µL of each solution.

MOBILE PHASE

3 volumes of *acetonitrile R1* and 7 volumes of a 0.05M solution of *potassium dihydrogen orthophosphate* in *water* adjusted to pH 5.3 using 1M *sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the total content of trandolapril, $C_{24}H_{34}N_2O_5$, in the medium from the chromatograms obtained and using the declared content of $C_{24}H_{34}N_2O_5$ in *trandolapril BPCRS*.

LIMITS

The amount of trandolapril released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 3 volumes of *acetonitrile R1* and 7 volumes of *water* (solvent A).

(1) Dissolve a quantity of the capsule contents in sufficient solvent A to produce a solution containing 0.02% w/v of Trandolapril, mix and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.0002% w/v of *trandolapril BPCRS*, 0.0001% w/v of *trandolapril impurity D EPCRS* and 0.00004% w/v of *trandolapril impurity E BPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (HyperClone ODS is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 80 µL of each solution.

MOBILE PHASE

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Mobile phase A 0.05M of *potassium dihydrogen orthophosphate*, adjusted to pH 2.0 using *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-3	70	30	isocratic
3-45	70→50	30→50	linear gradient
45-50	50	50	isocratic

Use the chromatogram obtained with solution (3) to identify the peaks due to impurities D and E. When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to trandolapril (retention time about 20 minutes) are: impurity D, about 1.9; impurity E, about 0.35.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *column efficiency*, determined using the peak due to trandolapril, is not less than 10,000 and the *symmetry factor* of the peak due to trandolapril is between 0.8 and 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 8 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

the area of any peak corresponding to impurity E is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* excluding impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Trandolapril comply with the requirement stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To the contents of one capsule add sufficient *methanol (40%)* to produce a solution containing 0.002% w/v of Trandolapril.

(2) 0.002% w/v of *trandolapril BPCRS* in *methanol (40%)*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Assay may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{34}N_2O_5$ in each capsule using the declared content of $C_{24}H_{34}N_2O_5$ in *trandolapril BPCRS*.

ASSAY

For capsules containing less than 2 mg and/or less than 2% w/w of Trandolapril

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing 2 mg or more and 2% w/w or more of Trandolapril

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the mixed contents of 20 capsules containing 10 mg of Trandolapril with sufficient *methanol (50%)* to produce a solution containing 0.0025% w/v of Trandolapril. Dilute 4 volumes of this solution to 5 volumes with *water*.

(2) 0.002% w/v of *trandolapril BPCRS* in *methanol (40%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *propylsilyl silica gel for chromatography* (3.5 µm) (Zorbax SB C3 300A is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *tetrahydrofuran*, 12.5 volumes of *acetonitrile R1* and 82.5 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate*.

Mobile phase B 5 volumes of *tetrahydrofuran*, 35 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* and 60 volumes of *acetonitrile R1*.

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Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0 – 1.5	90	10	isocratic
1.5 – 1.6	90→0	10→100	linear gradient
1.6 – 3.9	0	100	isocratic
3.9 – 4.0	0→100	100→0	linear gradient
4.0 – 5.0	100	0	isocratic

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{34}N_2O_5$ in the capsules using the declared content of $C_{24}H_{34}N_2O_5$ in *trandolapril BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities D and E listed under Trandolapril.

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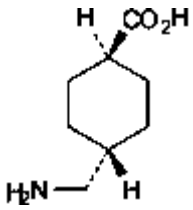
Tranexamic Acid

General Notices

(Ph. Eur. monograph 0875)



$C_8H_{15}NO_2$ 157.2 *1197-18-8*

Action and use

Antifibrinolytic.

Preparations

Tranexamic Acid Injection

Tranexamic Acid Mouthwash

Tranexamic Acid Oral Solution

Tranexamic Acid Tablets

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DEFINITION

(1*r*,4*r*)-4-(Aminomethyl)cyclohexane-1-carboxylic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Freely soluble in water and in glacial acetic acid, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *tranexamic acid CRS*.

TESTS

pH (*2.2.3*)

7.0 to 8.0.

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (b) Dissolve 5.0 mg of *tranexamic acid impurity D CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 100.0 mL with *water R*.

Reference solution (d) Dissolve 2.5 mg of *tranexamic acid impurity E CRS* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solution (e) Dissolve 2.5 mg of *tranexamic acid impurity C CRS*, 2.5 mg of *tranexamic acid impurity F CRS* and 7.5 mg of *tranexamic acid impurity B CRS* in 25 mL of *water R*. Mix 1 mL of the solution, 1 mL of reference solution (b) and 18 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 11.0 g of *anhydrous sodium dihydrogen phosphate R* in 500 mL of *water for chromatography R* and add 5 mL of *triethylamine R* and 1.4 g of *sodium laurilsulfate R1*; adjust to pH 2.0 with *phosphoric acid R* and dilute to 600 mL with *water for chromatography R*; add 400 mL of *methanol R2*.

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 40 µL of the test solution and reference solutions (a), (c), (d) and (e).

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Run time 2.5 times the retention time of tranexamic acid.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (e) to identify the peaks due to impurities B, C and F.

Relative retention With reference to tranexamic acid (retention time = about 10 min): impurity F = about 0.3; impurity C = about 1.1; impurity D = about 1.2; impurity E = about 1.3; impurity B = about 1.5.

System suitability Reference solution (e):

— *resolution*: minimum 2.0 between the peaks due to tranexamic acid and impurity C; minimum 1.5 between the peaks due to impurities C and D.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.3; impurity C = 0.4; impurity F = 0.6;

— for impurities C and D, use the concentration of impurity D in reference solution (c);

— for impurities E and F, use the concentration of impurity E in reference solution (d);

— for impurities other than C, D, E and F, use the concentration of tranexamic acid in reference solution (a).

Limits:

— *impurity B*: maximum 0.15 per cent;

— *impurities C, D, E, F*: for each impurity, maximum 0.05 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Halides expressed as chlorides (2.4.4)

Maximum 140 ppm.

Dissolve 1.2 g in *water R* and dilute to 50 mL with the same solvent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

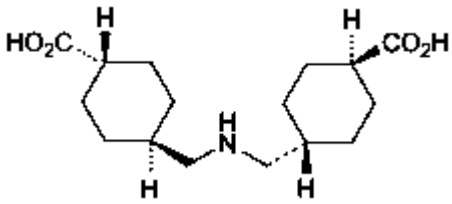
Dissolve 0.140 g in 20 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 15.72 mg of $C_8H_{15}NO_2$.

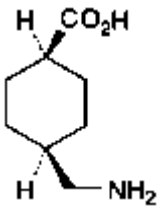
IMPURITIES

Specified impurities *B, C, D, E, F.*

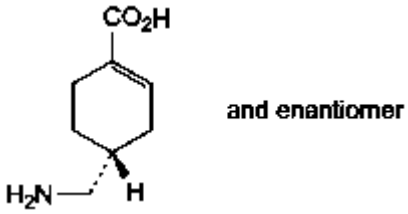
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



A. (1*r*,4*r*,1′*r*,4′*r*)-4,4′-[azanediylbis(methylene)]di(cyclohexane-1-carboxylic acid),



B. (1*s*,4*s*)-4-(aminomethyl)cyclohexane-1-carboxylic acid,



C. (4*RS*)-4-(aminomethyl)cyclohex-1-ene-1-carboxylic acid,

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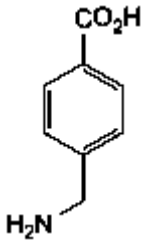
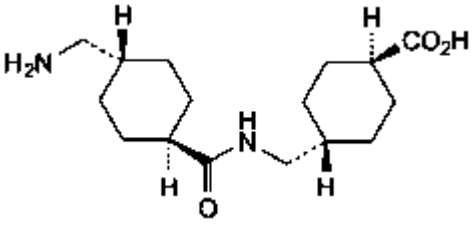
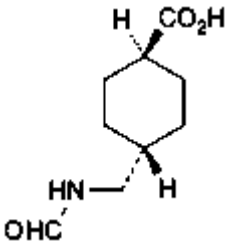


D. 4-(aminomethyl)benzoic acid,



E. (1*r*,4*r*)-4-[[(1*r*,4*r*)-4-(aminomethyl)cyclohexane-1-carboxamido]methyl]cyclohexane-1-carboxylic acid,



F. (1*r*,4*r*)-4-(formamidomethyl)cyclohexane-1-carboxylic acid.

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Tranexamic Acid Injection

General Notices

Action and use

Antifibrinolytic.

DEFINITION

Tranexamic Acid Injection is a sterile solution of Tranexamic Acid in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of tranexamic acid, $C_8H_{15}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume containing 0.4 g of Tranexamic Acid add 2 mL of *ether*, stir, add 5 mL of *methanol*, stir again and allow to crystallise. After drying, the *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of tranexamic acid (*RS 344*).

TESTS

Acidity or alkalinity

pH, 6.5 to 8.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *water*.

(1) Dilute the injection, if necessary, with sufficient *water* to produce a solution containing 1% w/v of Tranexamic Acid.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.001% w/v of *4-aminomethylbenzoic acid* (impurity D).
(4) 1% w/v of *tranexamic acid impurity standard BPCRS*.
(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.9 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of tranexamic acid.

MOBILE PHASE

Dissolve 11.0 g of *anhydrous sodium dihydrogen orthophosphate* in 500 mL of *water*, add 5 mL of *triethylamine* and 1.4 g of *sodium dodecyl sulfate*, adjust the pH to 2.5 with 2M *orthophosphoric acid* and add sufficient *water* to produce 600 mL. Add 400 mL of *methanol* and mix.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to tranexamic acid (retention time about 13 minutes) are: impurity C, about 1.1; impurity D, about 1.2; impurity B, about 1.4 and impurity A, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *tranexamic acid impurity standard BPCRS*;

in the chromatogram obtained with solution (4) the *resolution* between the peaks due to tranexamic acid and impurity C is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity B is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity C or impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%);

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

The total impurity content is not greater than 2.0%.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 35 IU per mL.

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *water*.

(1) Dilute the injection, if necessary, with sufficient *water* to produce a solution containing 0.2% w/v of Tranexamic Acid.

(2) 0.2% w/v of *tranexamic acid BPCRS*.

(3) 1% w/v of *tranexamic acid impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks corresponding to tranexamic acid and impurity C is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of tranexamic acid, $C_8H_{15}NO_2$, in the injection from the chromatograms obtained and using the declared content of $C_8H_{15}NO_2$ in *tranexamic acid BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C and D listed under Tranexamic Acid.

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Tranexamic Acid Mouthwash

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Antifibrinolytic.

DEFINITION

Tranexamic Acid Mouthwash contains Tranexamic Acid in a suitable vehicle.

The mouthwash complies with the requirements stated under Oromucosal Preparations and with the following requirements. Where appropriate, the mouthwash also complies with the requirements stated under Unlicensed Medicines.

Content of tranexamic acid, $C_8H_{15}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume of the mouthwash containing 0.25 g of Tranexamic Acid add 25 mL of *ethanol (96%)* and shake mechanically for 15 minutes; a cloudy white solution is produced, which may contain white lumps. Remove any lumps and filter the remaining solution using a glass fibre filter (Whatman GF/C filter is suitable). Wash the residue with 50 mL of *ethanol (96%)* and dry under vacuum at 35° for 30 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of tranexamic acid (*RS 344*).

TESTS

Acidity or alkalinity

pH, 6.5 to 8.0, Appendix V L.

ASSAY

To a volume of the mouthwash containing 0.1 g of Tranexamic Acid add 50 mL of *water* and adjust the pH of the solution to 7.0 with either 0.1M *sodium hydroxide* or 0.1M *hydrochloric acid*. Add 25 mL of *formaldehyde solution*, previously adjusted to pH 7.0, and 20 mL of *0.1M sodium hydroxide VS*. Titrate immediately with *0.1M hydrochloric acid VS*, determining the end point potentiometrically. Repeat the operation without the preparation being examined. The difference between the titrations represents the amount of sodium hydroxide required. Each mL of *0.1M sodium hydroxide VS* is equivalent to 15.72 mg of $C_8H_{15}NO_2$.

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Tranexamic Acid Oral Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Antifibrinolytic.

DEFINITION

Tranexamic Acid Oral Solution contains Tranexamic Acid in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of tranexamic acid, $C_8H_{15}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume of the oral solution containing 0.25 g of Tranexamic Acid add 25 mL of *ethanol (96%)* and shake mechanically for 15 minutes; a cloudy white solution is produced, which may contain white lumps. Remove any lumps and filter the remaining solution using a glass fibre filter (Whatman GF/C filter is suitable). Wash the residue with 50 mL of *ethanol (96%)* and dry under vacuum at 35° for 30 minutes. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of tranexamic acid (*RS 344*).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute the oral solution to contain 0.05% w/v of Tranexamic Acid.

(2) 0.05% w/v of *tranexamic acid BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS or Luna C18 (2) are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.9 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 220 nm.

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(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 11.0 g of *anhydrous sodium dihydrogen orthophosphate* in 500 mL of *water*, add 5 mL of *triethylamine* and 1.4 g of *sodium dodecyl sulfate*, adjust the pH to 2.5 with 2M *orthophosphoric acid* and add sufficient *water* to produce 600 mL. Add 400 mL of *methanol* and mix.

When the chromatograms are recorded under the prescribed conditions, the retention time of tranexamic acid is about 12 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}NO_2$ in the oral solution using the declared content of $C_8H_{15}NO_2$ in *tranexamic acid BPCRS*.

STORAGE

Tranexamic Acid Oral Solution should not be refrigerated.

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Tranexamic Acid Tablets

General Notices

Action and use

Antifibrinolytic.

DEFINITION

Tranexamic Acid Tablets contain Tranexamic Acid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tranexamic acid, $C_8H_{15}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Tranexamic Acid with 5 mL of *water* for 15 minutes, filter and add 2 mL of *ether* to the filtrate. Stir, add 10 mL of *methanol*, stir again and allow to crystallise. The crystals, after drying, comply with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of tranexamic acid (*RS 344*).

B. To 1 mL of a 1% w/v solution add 1 mL of a 0.2% w/v solution of *ninhydrin* in *ethanol* (*96%*) and heat on a water bath for 2 minutes. A dark bluish violet colour is produced.

C. Dissolve 0.2 g in 10 mL of 5M *sodium hydroxide*, add 0.2 mL of *benzoyl chloride* and shake vigorously for 10 minutes. Acidify to pH 4 with 2M *hydrochloric acid*, filter, wash the residue with 5 mL of *ether* and dry at 50° at a pressure of 2 kPa. The *melting point* of the residue is about 186°, Appendix V A.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 1 g of Tranexamic Acid with 100 mL of *water* for 10 minutes, filter and use the filtrate.

(2) 0.01% w/v of *tranexamic acid EPCRS* in *water*.

(3) 0.001% w/v of *4-aminomethylbenzoic acid* in *water*.

(4) 1% w/v of *tranexamic acid impurity standard BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a Stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.9 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

Inject solution (1) and allow the chromatography to proceed for 3 times the retention time of tranexamic acid (about 13 minutes). Identify the impurities from the chromatogram obtained with solution (4) and from the reference chromatogram supplied with *tranexamic acid impurity standard BPCRS*.

MOBILE PHASE

Dissolve 11.0 g of *anhydrous sodium dihydrogen orthophosphate* in 500 mL of *water*, add 5 mL of *triethylamine* and 1.4 g of *sodium dodecyl sulfate*, adjust the pH to 2.5 with 2M *orthophosphoric acid* and add sufficient *water* to produce 600 mL. Add 400 mL of *methanol* and mix.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *tranexamic acid impurity standard BPCRS;*

the *resolution factor* between the peaks corresponding to tranexamic acid and impurity C in the chromatogram obtained with solution (4) is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity B is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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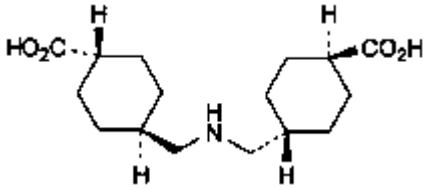
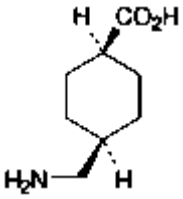
Weigh and powder 20 tablets. Dissolve a quantity of the powdered tablets containing 0.25 g of Tranexamic Acid in 50 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 15.72 mg of $C_8H_{15}NO_2$.

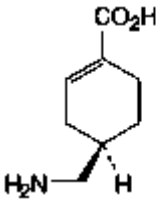
IMPURITIES



A. *trans,trans*-4,4′-(iminodimethylene)di(cyclohexanecarboxylic) acid,

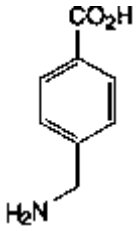


B. *cis*-4-(aminomethyl)cyclohexanecarboxylic acid,



and enantiomer

C. (*RS*)-4-(aminomethyl)cyclohex-1-enecarboxylic acid,



D. 4-aminomethylbenzoic acid.

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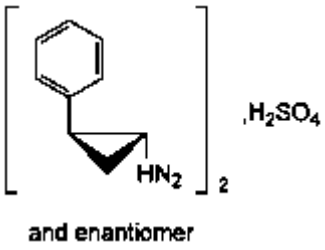
Tranylcypromine Sulfate

General Notices



$(C_9H_{11}N)_2,H_2SO_4$ 364.5 *13492-01-8*

Action and use

Monoamine oxidase inhibitor; antidepressant.

Preparation

Tranylcypromine Tablets

DEFINITION

Tranylcypromine Sulfate is (1*RS*,2*SR*)-2-phenylcyclopropylamine sulfate. It contains not less than 98.0% and not more than 101.0% of $(C_9H_{11}N)_2,H_2\ SO_4$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Soluble in *water*; very slightly soluble in *ethanol (96%)* and in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of tranylcypromine sulfate *(RS 345)*.

B. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Hydrazine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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Solution A Suspend 0.25 g of *4-dimethylaminobenzaldehyde* in 50 mL of *water*, add 4 mL of *hydrochloric acid* and swirl until completely dissolved. Dilute to produce 100 mL with *water* (derivatisation solution).

(1) 0.100 g of the substance being examined in 10.0 mL of *water*.

(2) Dissolve 9.9 mg of *hydrazine sulfate* in 250 mL of *water* to produce a solution containing 0.001% w/v of hydrazine. Dilute 4.0 mL to 20.0 mL with *water*.

(3) *Water* (blank solution).

Derivatise the solutions prior to analysis by mixing 0.5 mL of each solution with 0.5 mL of solution A

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 460 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of the peak due to hydrazine.

MOBILE PHASE

30 volumes of *methanol* and 70 volumes of 0.02M *potassium dihydrogen orthophosphate*, previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to hydrazine is about 4 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *signal to noise ratio* is at least 10.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to hydrazine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (195 ppm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) Dissolve 0.5 g of the substance being examined in 30 mL and dilute to 50 mL.

(2) Dilute 1 volume of solution (1) to 10 volumes.

(3) Dilute 1 volume of solution (2) to 100 volumes. Dilute 8 volumes of this solution to 100 volumes.

(4) Dilute 1 volume of solution (3) to 10 volumes.

(5) 0.1% w/v of *tranylcypromine sulfate impurity BPCRS*.

(6) Dilute 1 volume of solution (3) to 2 volumes.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of tranylcypromine.

MOBILE PHASE

150 volumes of *acetonitrile* and 850 volumes of 0.79% w/v of *sodium perchlorate*, previously adjusted to pH 2.5 with *perchloric acid*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *signal to noise ratio* is at least 10;

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to tranylcypromine and impurity B is at least 2.8.

CALCULATION OF IMPURITIES

Use solution (1) as the test solution for impurities C and D.

Use solution (2) as the test solution for all other impurities.

For each impurity excluding impurities C and D, use the concentration of tranylcypromine sulfate in solution (3).

For impurities C and D, use the concentration of tranylcypromine sulfate in solution (4).

For the reporting threshold, use the concentration of tranylcypromine sulfate in solution (6).

For peak identification, use solution (5).

Tranylcypromine retention time: about 10 minutes.

Relative retention: impurity A, about 0.6; impurity C, about 0.9; impurity B, about 1.3 and impurity D, about 1.7.

LIMITS

— impurities A and B: for each impurity, not more than 0.15%;

— impurities C and D: for each impurity, not more than 8 ppm;

— unspecified impurities: for each impurity, not more than 0.10%;

— total impurities: not more than 0.50%;

— reporting threshold: 0.05%, excluding impurities C and D.

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Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

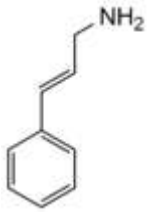
ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.3 g and determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 36.45 mg of $(C_9H_{11}N)_2,H_2SO_4$.

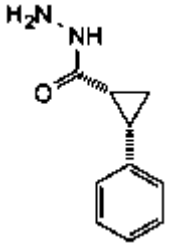
IMPURITIES

The impurities limited by the requirements of this monograph include:

A. (±)-*cis*-2-phenylcyclopropanamine (*cis*-cypromine)



B. 3-phenylallylamine (cinnamylamine)



C. (±)-*cis*-2-phenylcyclopropanecarbohydrazide (*cis*-tranylcypromine hydrazide)

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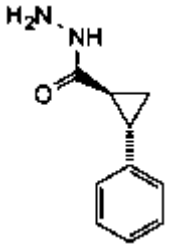
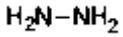


D. (±)-*trans*-2-phenylcyclopropanecarbohydrazide (*trans*-tranylcypromine hydrazide)



E. hydrazine

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Tranylcypromine Tablets

General Notices

Action and use

Monoamine oxidase inhibitor; antidepressant.

DEFINITION

Tranylcypromine Tablets contain Tranylcypromine Sulfate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of tranylcypromine, $C_9H_{11}N$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution obtained in the Assay exhibits three maxima, at 258, 264 and 271 nm. The *absorbances* at the maxima are about 1.2, about 1.3 and about 0.96, respectively.

B. Suspend a quantity of the powdered tablets containing the equivalent of 5 mg of tranylcypromine in 0.5 mL of *ethanol* (*96%*) and add 5 mg of *ninhydrin*. A purple colour is produced within 15 minutes.

C. The powdered tablets yield the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Related substances

Dissolve 10 mg of *4-chloroaniline* (internal standard) in sufficient 0.1M *hydrochloric acid* to produce 20 mL (solution A). Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) add 5 mL of 1M *sodium hydroxide* to 1 mL of solution A, extract with 10 mL of *dichloromethane*, add 1 mL of *trifluoroacetic anhydride* to the dichloromethane extract and allow to stand for 10 minutes. Evaporate the solution at a pressure of 2 kPa using a rotary evaporator and a water bath at 20° and dissolve the residue in 2 mL of *dichloromethane*. For solution (2) add 10 mL of 0.05M *sulfuric acid* to a quantity of the powdered tablets containing the equivalent of 75 mg of tranylcypromine, shake for 15 minutes, filter and wash the filter with two 5 mL quantities of 0.05M *sulfuric acid*. To the combined filtrate and washings add 1 mL of 5M *sodium hydroxide* and extract with 10 mL of *dichloromethane*. Dry the dichloromethane extract with *anhydrous sodium sulfate*, evaporate to about 5 mL without heating, add 1 mL of *trifluoroacetic anhydride* and allow to stand for 10 minutes. Evaporate the solvent at a pressure of 2 kPa using a rotary evaporator and a water bath at 20° and dissolve the residue in 2 mL of *dichloromethane*. For solution (3) add 10 mL of 0.05M *sulfuric acid* and 1 mL of solution A to a quantity of the powdered tablets containing the equivalent of 75 mg of tranylcypromine and complete the procedure described above, beginning at the words ‘shake for 15 minutes…’.

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The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 3% w/w of cyanopropylmethylphenyl methyl silicone fluid (OV-225 is suitable) and maintained at 170°.

In the chromatogram obtained with solution (3) the area of any *secondary peak* is not greater than that of the peak due to the trifluoroacetyl derivative of 4-chloroaniline (0.5%, calculated with reference to tranylcypromine sulfate).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 30 mg of tranylcypromine add 60 mL of 0.1M *sulfuric acid*, shake for 30 minutes, add sufficient 0.1M *sulfuric acid* to produce 100 mL and filter. Measure the *absorbance* of the resulting solution at the maximum at 271 nm and at 282 nm, Appendix II B. Calculate the content of $C_9H_{11}N$ from the difference between the absorbances taking 14.6 as the value of ΔA(1%, 1 cm).

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of tranylcypromine.

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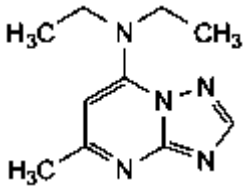
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Trapidil

General Notices

(Ph. Eur. monograph 1576)



$C_{10}H_{15}N_5$ 205.3 *15421-84-8*

Action and use

Antiplatelet agent; vasodilator.

Ph Eur

DEFINITION

N,*N*-Diethyl-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in anhydrous ethanol and in methylene chloride.

mp

About 102 °C.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison trapidil CRS.

TESTS

Solution S

Dissolve 2.0 g in carbon dioxide-free water R and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of methyl red solution R and 0.2 mL of 0.01 M hydrochloric acid. The solution is red. Add 0.4 mL of 0.01 M sodium hydroxide. The solution is yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of trapidil impurity A CRS in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of trapidil impurity B CRS in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (c) Mix equal volumes of reference solution (a) and reference solution (b).

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm,

— *stationary phase*: base-deactivated octadecylsilyl silica gel for chromatography R (5 µm),

Mobile phase 50 mL of methanol R, 75 mL of acetonitrile R and 800 mL of a 1.7 g/L solution of potassium dihydrogen phosphate R adjusted to pH 2.45 with phosphoric acid R; dilute to 1000 mL with water R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL.

Run time 3 times the retention time of trapidil.

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System suitability:

— *resolution*: minimum of 4.0 between the peaks due to impurity A and impurity B in the chromatogram obtained with reference solution (c).

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Chlorides (2.4.4)

Maximum 100 ppm.

Dissolve 0.25 g in 10 mL of *water R* and dilute to 15 mL with *water R*. Prepare the standard using 5 mL of *chloride standard solution (5 ppm Cl) R*.

Ammonium (2.4.1)

Maximum 20 ppm.

0.50 g complies with limit test A. Prepare the standard using 0.1 mL of *ammonium standard solution (100 ppm NH_4) R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 20.53 mg of $C_{10}H_{15}N_5$.

STORAGE

Protected from light.

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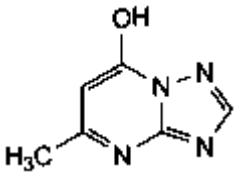
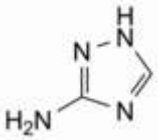
IMPURITIES



A. 5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol,



B. 1,2,4-triazol-3-amine.

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Trazodone Capsules

General Notices

Action and use

Monoamine reuptake inhibitor; antidepressant.

DEFINITION

Trazodone Capsules contain Trazodone Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

PRODUCTION

The manufacturing process of Trazodone Hydrochloride, used in the formulation of Trazodone Capsules, is validated to ensure that the content of impurity F, 1-(3-chloropropyl)-3-chlorophenylpiperazine, is not more than 2.5 ppm.

Content of trazodone hydrochloride, $C_{19}H_{22}ClN_5O,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.3 g of Trazodone Hydrochloride with 50 mL of *acetone*, filter and evaporate to dryness. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of trazodone hydrochloride *(RS 346)*. In the preparation of the disc, avoid excessive grinding when triturating the substance being examined with *potassium chloride*.

TESTS

Dissolution

Carry out the procedure protected from light. Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 311 nm, Appendix II B, using 0.01M *hydrochloric acid* in the reference cell.

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(2) Measure the *absorbance* of a suitable solution of *trazodone hydrochloride BPCRS* using 0.01M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of trazodone hydrochloride, $C_{19}H_{22}ClN_5O,HCl$, in the medium from the absorbances obtained and using the declared content of $C_{19}H_{22}ClN_5O,HCl$ in *trazodone hydrochloride BPCRS*.

LIMITS

The amount of trazodone hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the procedures protected from light. The combined nominal total content of impurities determined in tests A and B below is not more than 1.0%.

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the contents of the capsules containing 0.1 g of Trazodone Hydrochloride in 60 mL for 30 minutes, dilute to 100 mL and filter.

(2) Dilute 2 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 10 volumes.

(3) Dilute 5 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 100 volumes.

(4) 0.1% w/v of *trazodone hydrochloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (XTerra RP18 or Phenomenex Prodigy are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of the principal peak.

MOBILE PHASE

0.4 volumes of *diethylamine*, 350 volumes of *acetonitrile* and 650 volumes of *water*. If necessary, adjust the proportions of *acetonitrile* and *water* in the mobile phase to obtain a retention time of about 10 minutes for the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and trazodone is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity D is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any *secondary peak* with a retention time of up to and including that of impurity E, identified from reference chromatogram A supplied with *trazodone hydrochloride impurity standard BPCRS*, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the contents of the capsules containing 0.1 g of Trazodone Hydrochloride with 60 mL for 30 minutes, dilute to 100 mL and filter.

(2) Dilute 2 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 10 volumes.

(3) Dilute 5 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 100 volumes.

(4) 0.1% w/v of *trazodone hydrochloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (XTerra RP18 or Phenomenex Prodigy are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.7 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for at least 5 times the retention time of the principal peak.

MOBILE PHASE

0.4 volumes of *diethylamine*, 320 volumes of *water* and 680 volumes of *acetonitrile*. If necessary adjust the proportions of *acetonitrile* and *water* in the mobile phase to obtain a retention time of about 2.5 minutes for the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to trazodone and impurity E is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* with a retention time longer than that of impurity E identified from reference chromatogram B, supplied with *trazodone hydrochloride impurity standard BPCRS*, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

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Carry out the procedure protected from light.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Weigh the contents of 20 capsules. Shake a quantity of the contents containing 0.1 g of Trazodone Hydrochloride with 60 mL for 30 minutes in a volumetric flask and dilute to 100 mL and filter. Dilute 1 volume to 10 volumes.

(2) 0.01% w/v of *trazodone hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Spherisorb C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of a solution containing 0.115% w/v of *diammonium hydrogen orthophosphate*, previously adjusted to pH 6.0 with 10% v/v *orthophosphoric acid* or 1M *sodium hydroxide*, and 60 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{22}ClN_5O,HCl$ in the capsules using the declared content of $C_{19}H_{22}ClN_5O,HCl$ in *trazodone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Trazodone Hydrochloride.

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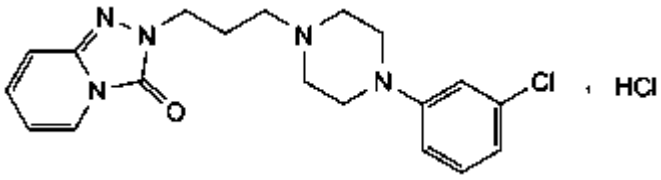
Trazodone Hydrochloride

General Notices

(Ph. Eur. monograph 2857)



$C_{19}H_{23}Cl_2N_5O$ 408.3 *25332-39-2*

Action and use

Monoamine reuptake inhibitor; antidepressant.

Preparations

Trazodone Capsules

Trazodone Tablets

Ph Eur

DEFINITION

2-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl][1,2,4]triazolo[4,3-*a*]pyridin-3(*2H*)-one hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine and 2-chloro-*N*-(2-chloroethyl)ethan-1-amine are genotoxic and are potential impurities in trazodone hydrochloride. These impurities are controlled by a suitable validated method.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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Solubility

Soluble in water, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *trazodone hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

pH (*2.2.3*)

3.9 to 4.5.

Dissolve 0.5 g in *water R* and dilute to 50 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase B, mobile phase A (20:80 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *trazodone for system suitability CRS* (containing impurity C) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of *trazodone hydrochloride CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm).

Mobile phase:

— *mobile phase A*: *triethylamine R*, *water for chromatography R* (0.01:100 *V/V*);

— *mobile phase B*: *triethylamine R*, *acetonitrile R* (0.01:100 *V/V*);

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	80 → 32	20 → 68

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *trazodone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to trazodone (retention time = about 6 min): impurity C = about 0.9.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to trazodone.

Calculation of percentage contents:

— for each impurity, use the concentration of trazodone hydrochloride in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.400 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{19}H_{23}Cl_2N_5O$ taking into account the assigned content of *trazodone hydrochloride CRS*.

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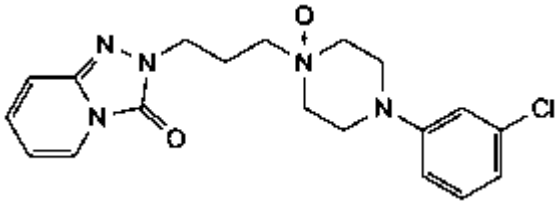
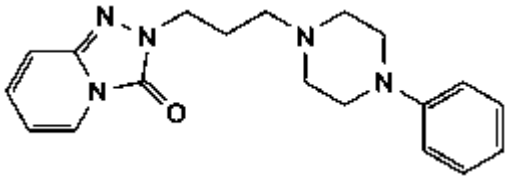
IMPURITIES

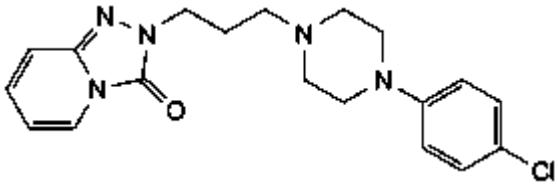
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, G, H, I, J, K, L, M.*



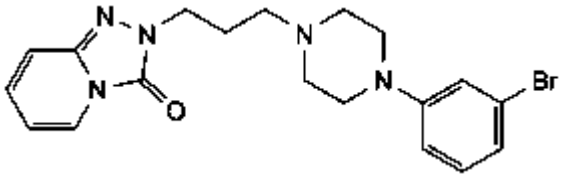
A. 4-(3-chlorophenyl)-1-[3-(3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-2-yl)propyl]piperazine 1-oxide,



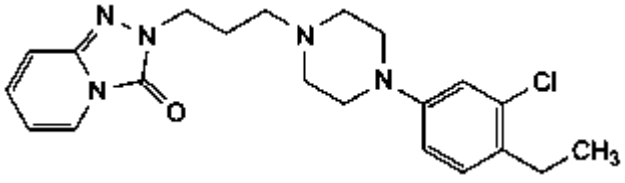
B. 2-[3-(4-phenylpiperazin-1-yl)propyl][1,2,4]triazolo[4,3-*a*]pyridin-3(*2H*)-one,



C. 2-[3-[4-(4-chlorophenyl)piperazin-1-yl]propyl][1,2,4]triazolo[4,3-*a*]pyridin-3(*2H*)-one,



D. 2-[3-[4-(3-bromophenyl)piperazin-1-yl]propyl][1,2,4]triazolo[4,3-*a*]pyridin-3(*2H*)-one,



E. 2-[3-[4-(3-chloro-4-ethylphenyl)piperazin-1-yl]propyl][1,2,4]triazolo[4,3-*a*]pyridin-3(*2H*)-one,

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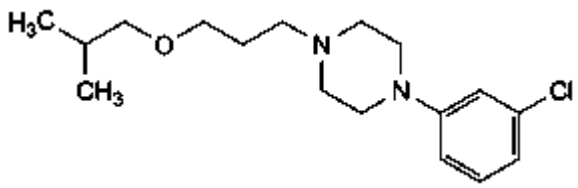
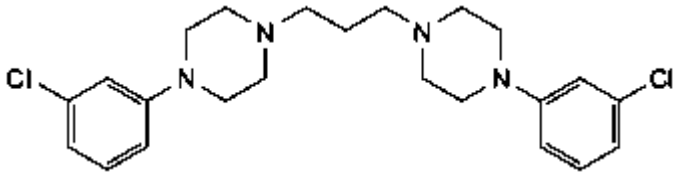
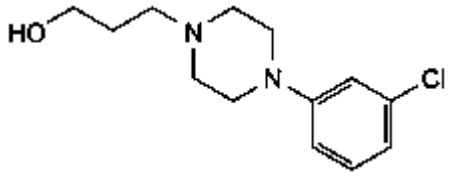


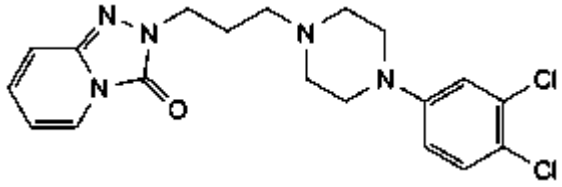
G. 1-(3-chlorophenyl)-4-[3-(2-methylpropoxy)propyl]piperazine,



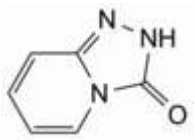
H. 1,1′-(propane-1,3-diyl)bis[4-(3-chlorophenyl)piperazine],



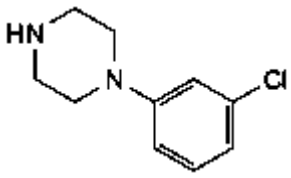
I. 3-[4-(3-chlorophenyl)piperazin-1-yl]propan-1-ol,



J. 2-[3-[4-(3,4-dichlorophenyl)piperazin-1-yl]propyl][1,2,4]triazolo[4,3-*a*]pyridin-3(*2H*)-one,



K. [1,2,4]triazolo[4,3-*a*]pyridin-3(*2H*)-one,



L. 1-(3-chlorophenyl)piperazine,

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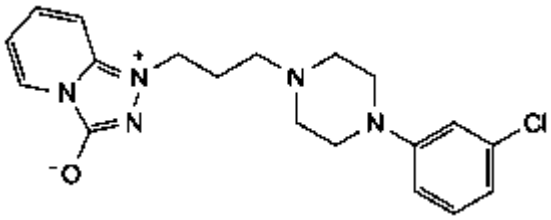

M. 1-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl][1,2,4]triazolo[4,3-*a*]pyridin-1-ium-3-olate.

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Trazodone Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; antidepressant.

DEFINITION

Trazodone Tablets contain Trazodone Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

The manufacturing process of Trazodone Hydrochloride, used in the formulation of Trazodone Tablets, is validated to ensure that the content of impurity F, 1-(3-chloropropyl)-3-chlorophenylpiperazine, is not more than 2.5 ppm.

Content of trazodone hydrochloride, $C_{19}H_{22}ClN_5O,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove any coating. Shake a quantity of the powdered tablet cores containing 0.3 g of Trazodone Hydrochloride with 50 mL of *acetone*, filter and evaporate to dryness. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of trazodone hydrochloride *(RS 346)*. In the preparation of the disc, avoid excessive grinding when triturating the substance being examined with *potassium chloride*.

TESTS

Dissolution

Carry out the procedure protected from light. Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 311 nm, Appendix II B, using 0.01M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *trazodone hydrochloride BPCRS* using 0.01M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of trazodone hydrochloride, $C_{19}H_{22}ClN_5O,HCl$, in the medium from the absorbances obtained and using the declared content of $C_{19}H_{22}ClN_5O,HCl$ in *trazodone hydrochloride BPCRS*.

LIMITS

The amount of trazodone hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the procedures protected from light. The combined nominal total content of impurities determined in tests A and B below is not more than 1.0%.

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of powdered tablets containing 0.1 g of Trazodone Hydrochloride in 60 mL for 30 minutes, dilute to 100 mL and filter.

(2) Dilute 2 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 10 volumes.

(3) Dilute 5 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 100 volumes.

(4) 0.1% w/v of *trazodone hydrochloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (XTerra RP18 or Phenomenex Prodigy are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of the principal peak.

MOBILE PHASE

0.4 volumes of *diethylamine*, 350 volumes of *acetonitrile* and 650 volumes of *water*. If necessary, adjust the proportions of *acetonitrile* and *water* in the mobile phase to obtain a retention time of about 10 minutes for the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and trazodone is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity D is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any *secondary peak* with a retention time of less than or equal to impurity E, identified from reference chromatogram A supplied with *trazodone hydrochloride impurity standard BPCRS*, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of powdered tablets containing 0.1 g of Trazodone Hydrochloride in 60 mL for 30 minutes, dilute to 100 mL and filter.

(2) Dilute 2 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 10 volumes.

(3) Dilute 5 volumes of solution (1) to 100 volumes and further dilute 1 volume of this solution to 100 volumes.

(4) 0.1% w/v of *trazodone hydrochloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (XTerra RP18 or Phenomenex Prodigy are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.7 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for at least 5 times the retention time of the principal peak.

MOBILE PHASE

0.4 volumes of *diethylamine*, 320 volumes of *water* and 680 volumes of *acetonitrile*. If necessary, adjust the proportions of *acetonitrile* and *water* in the mobile phase to obtain a retention time of about 2.5 minutes for the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to trazodone and impurity E is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* with a retention time longer than that of impurity E identified from reference chromatogram B, supplied with *trazodone hydrochloride impurity standard BPCRS*, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

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Carry out the procedure protected from light.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of Trazodone Hydrochloride in 60 mL for 30 minutes in a volumetric flask and dilute to 100 mL and filter. Dilute 1 volume to 10 volumes.

(2) 0.01% w/v of *trazodone hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Spherisorb C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of a solution containing 0.115% w/v of *diammonium hydrogen orthophosphate*, previously adjusted to pH 6.0 with 10% v/v *orthophosphoric acid* or 1M *sodium hydroxide*, and 60 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{22}ClN_5O$,HCl in the tablets using the declared content of $C_{19}H_{22}ClN_5O$,HCl in *trazodone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Trazodone Hydrochloride.

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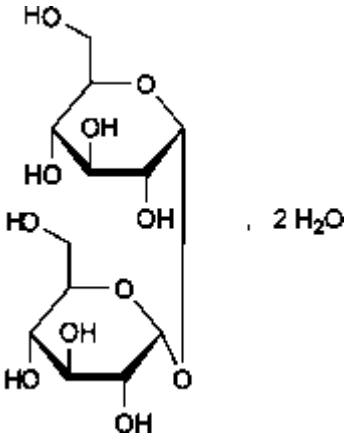
Trehalose Dihydrate

General Notices

(Ph. Eur. monograph 2297)



$C_{12}H_{22}O_{11},2H_2O$ 378.3 *6138-23-4*

Ph Eur

DEFINITION

α-D-Glucopyranosyl α-D-glucopyranoside dihydrate (α,α-trehalose dihydrate). It is obtained by enzymatic modification of starch.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in methanol, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *trehalose dihydrate CRS*.

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B. Dissolve 2 g in 5 mL of *water R*. To 1 mL of this solution add 0.4 mL of a 50 g/L solution of *α-naphthol R* in *ethanol (96 per cent) R* and mix thoroughly. Carefully add 2 mL of *sulfuric acid R*. A violet colour develops at the interface.

C. Dissolve 1 g in 25 mL of *water R*. To 2 mL of this solution add 1 mL of *dilute hydrochloric acid R* and mix. Keep the solution for 20 min at room temperature. Add 4 mL of a 40 g/L solution of *sodium hydroxide R* and 2 mL of a 40 g/L solution of *glycine R* and mix. Heat the solution in a water-bath for 10 min. No brown colour develops.

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.5 for solution S.

Specific optical rotation (*2.2.7*)

+ 197 to + 201 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.100 g of *trehalose dihydrate CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 25.0 mL with *water R*.

Reference solution (d) Dissolve 25 mg of *glucose R* (impurity A) and 25 mg of *maltotriose R* in *water R*, add 2.5 mL of reference solution (a) and dilute to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.3 m, Ø = 8 mm;

— *stationary phase*: *strong cation-exchange resin (sodium form) R* (6 µm);

— *temperature*: 80 °C.

Mobile phase *water R*.

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Flow rate 0.4 mL/min.

Detection Refractometer maintained at 40 °C.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time Twice the retention time of trehalose.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A and B; impurity B has the same retention time as maltotriose.

Relative retention With reference to trehalose (retention time = about 15 min): impurity B = about 0.9; impurity A = about 1.2.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to maltotriose and trehalose.

Limits:

— *impurities A, B*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Chlorides (2.4.4)

Maximum 125 ppm.

Dilute 4 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 200 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Soluble starch

Dissolve 1 g in 10 mL of *water R*. Add 0.1 mL of *iodine solution R1*. No blue colour develops.

Water (2.5.12)

9.0 per cent to 11.0 per cent, determined on 0.10 g.

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

If intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

If not intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^3 CFU/g (2.6.12);

— TYMC: acceptance criterion 10^2 CFU/g (2.6.12);

— absence of *Escherichia coli* (2.6.13);

— absence of *Salmonella* (2.6.13).

Bacterial endotoxins (2.6.14)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins:

— less than 4 IU/g for parenteral preparations having a concentration of 100 g/L or less of trehalose dihydrate;

— less than 2.5 IU/g for parenteral preparations having a concentration of more than 100 g/L of trehalose dihydrate.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of trehalose from the declared content of *trehalose dihydrate CRS*.

LABELLING

The label states:

— where applicable, the maximum concentration of bacterial endotoxins;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, B.*

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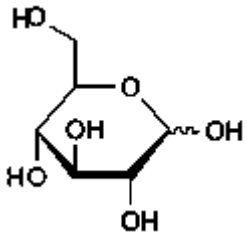
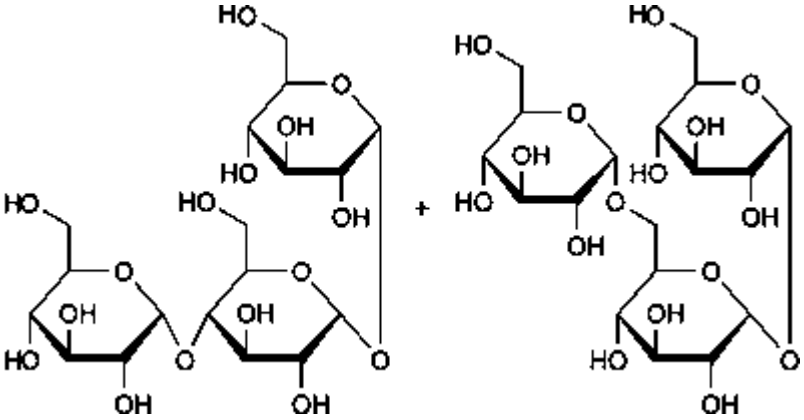


A. D-glucopyranose (glucose),



B. oligosaccharides, mainly glucosyltrehalose: mixture of α-D-glucopyranosyl α-D-glucopyranosyl-(1→4)-α-D-glucopyranoside (4-*O*-glucosyltrehalose or α-D-maltosyl α-D-glucoside) and α-D-glucopyranosyl-(1→6)-α-D-glucopyranosyl α-D-glucopyranoside (6-*O*-glucosyltrehalose or α-D-isomaltosyl α-D-glucoside).

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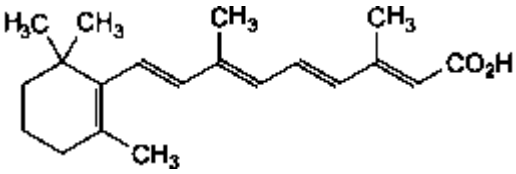
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Tretinoin

General Notices

(Ph. Eur. monograph 0693)



$C_{20}H_{28}O_2$ 300.4 *302-79-4*

Action and use

Vitamin A analogue (retinoid); treatment of acne.

Preparations

Tretinoin Gel

Tretinoin Solution

Tretinoin, Hydrocortisone and Hydroquinone Cream

Ph Eur

DEFINITION

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow or light orange, crystalline powder.

Solubility

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Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

mp

About 182 °C, with decomposition.

It is sensitive to air, heat and light, especially in solution.

Carry out all operations as rapidly as possible and avoid exposure to actinic light; use freshly prepared solutions.

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tretinoin CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 10 mg of *tretinoin CRS* in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *1,1-dimethylethyl methyl ether R*, *cyclohexane R* (2:4:40:54 *V/V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

Detection B Spray with a solution prepared as follows: dissolve 15 g of *antimony trichloride R* in 50 mL of *methylene chloride R*; examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

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Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *isotretinoin CRS* (impurity A) in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Mix 1.0 mL of reference solution (a) and 0.5 mL of the test solution and dilute to 25.0 mL with *methanol R*.

Reference solution (c) Dilute 0.5 mL of the test solution to 100.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *glacial acetic acid R*, *water for chromatography R*, *methanol R* (5:225:770 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 355 nm.

Injection 10 µL.

Run time 1.2 times the retention time of tretinoin.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to tretinoin (retention time = about 35 min): impurity A = about 0.75.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and tretinoin.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

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Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* for 16 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 70 mL of *acetone R*. Titrate with *0.1 M tetrabutylammonium hydroxide in 2-propanol*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 30.04 mg of $C_{20}H_{28}O_2$.

STORAGE

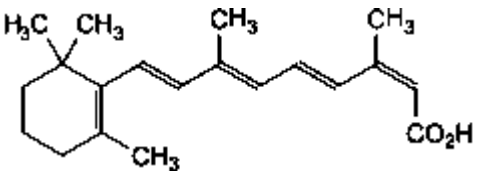
Under an inert gas, in an airtight container, protected from light.

It is recommended that the contents of an opened container be used as soon as possible and any unused part be protected by an atmosphere of inert gas.

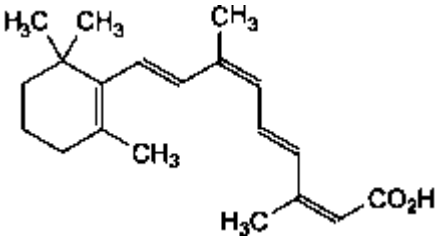
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, F, G.



A. (2*Z*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (isotretinoin),



B. (2*Z*,4*E*,6*Z*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (9,13-di-*cis*-retinoic acid),

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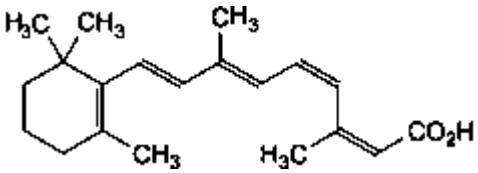
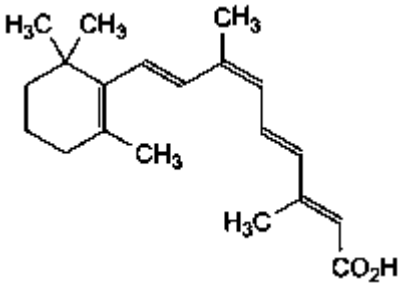
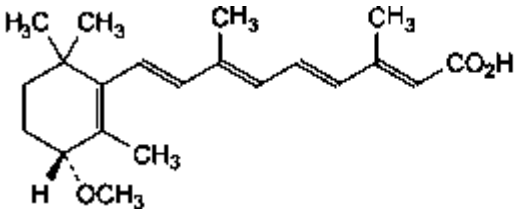


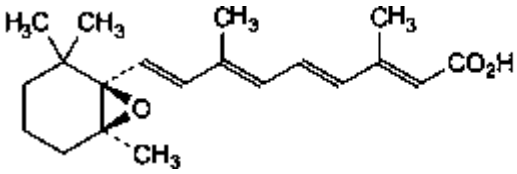
C. (2*Z*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (11,13-di-*cis*-retinoic acid),



D. (2*E*,4*E*,6*Z*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (9-*cis*-retinoic acid),



F. (2*E*,4*E*,6*E*,8*E*)-9-[(3*RS*)-3-methoxy-2,6,6-trimethylcyclohex-1-en-1-yl]-3,7-dimethylnona-2,4,6,8-tetraenoic acid (*rac*-4-methoxytretinoin),



G. (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl)nona-2,4,6,8-tetraenoic acid (*rac*-5,6-epoxytretinoin).

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Tretinoin Gel

General Notices

Action and use

Vitamin A analogue (retinoid); treatment of acne.

DEFINITION

Tretinoin Gel is a solution of Tretinoin in a suitable basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of tretinoin, $C_{20}H_{28}O_2$

90.0 to 120.0% of the stated amount.

IDENTIFICATION

Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 70 volumes of *cyclohexane* and 30 volumes of *propan-2-ol* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) disperse a quantity of the gel containing 1.25 mg of Tretinoin as completely as possible in 25 mL of warm *methanol*, allow to cool to room temperature and extract with three 50 mL quantities of *hexane*. Wash the combined extracts with 20 mL of *water*, filter through *anhydrous sodium sulfate* and evaporate the filtrate to dryness using a rotary evaporator at a temperature not exceeding 60°. Dissolve the residue in 5 mL of *methanol*. Solution (2) contains 0.025% w/v of *tretinoin EPCRS* in *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) use solution (1) from the test for Identification. For solution (2) dilute 3 volumes of solution (1) to 100 volumes with *methanol*.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) as the mobile phase with a flow rate of 1.4 mL per minute a solution containing 0.5% v/v of *glacial acetic acid* in a mixture of *methanol* and *water* the proportions being adjusted to give a retention time for tretinoin of about 15 minutes (a mixture of 77 volumes of *methanol* and 23 volumes of *water* is usually suitable) and (c) a detection wavelength of 353 nm. Adjust the sensitivity of the instrument so that the height of the principal peak in the chromatogram obtained with solution (2) is about 70% of full-scale deflection.

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In the chromatogram obtained with solution (1) the sum of the areas of any *secondary peaks* is not greater than the area of the peak in the chromatogram obtained with solution (2).

ASSAY

Dissolve a quantity of the gel containing 0.5 mg of Tretinoin in sufficient *chloroform* to produce 100 mL and measure the *absorbance* of the resulting solution at the maximum at 365 nm, Appendix II B. Calculate the content of $C_{20}H_{28}O_2$ taking 1430 as the value of A(1%, 1 cm) at the maximum at 365 nm.

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Tretinoin, Hydrocortisone and Hydroquinone Cream

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Vitamin A analogue (retinoid) + corticosteroid + depigmenting agent.

DEFINITION

Tretinoin, Hydrocortisone and Hydroquinone Cream contains Tretinoin, Hydrocortisone and Hydroquinone in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the cream also complies with the requirements stated under Unlicensed Medicines.

Content of tretinoin, $C_{20}H_{28}O_2$

90.0 to 110.0% of the stated amount.

Content of hydrocortisone, $C_{21}H_{30}O_5$

90.0 to 110.0% of the stated amount.

Content of hydroquinone, $C_6H_6O_2$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A bright yellow cream.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in amber glassware and protected from light.

(1) Add 5 mL of *methanol* to a quantity of the cream containing 25 mg of Hydrocortisone. Shake, mix with the aid of ultrasound for 15 minutes and add sufficient *methanol* to produce 10 mL.

(2) 0.25% w/v of *hydrocortisone BPCRS* in *methanol*.

(3) 0.01% w/v of *tretinoin BPCRS* in *methanol*.

(4) 0.5% w/v of *hydroquinone BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use as the coating *silica gel* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

The three principal spots in the chromatogram obtained with solution (1) correspond to those in the chromatograms obtained with solutions (2) to (4).

B. In the Assay for tretinoin, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

C. In the Assay for hydrocortisone, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

D. In the Assay for hydroquinone, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

ASSAY

For tretinoin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in amber glassware and protected from light.

(1) Shake a quantity of the cream containing 1 mg of Tretinoin with 100 mL of *methanol* until fully dispersed, add sufficient *methanol* to produce 250 mL and filter (a 0.45-µm nylon syringe filter is suitable).

(2) 0.0004% w/v of *tretinoin BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with the same material.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 350 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.1% w/v of *tetramethylammonium hydrogen sulfate* in a mixture of 1 volume of *water* and 9 volumes of *methanol*.

DETERMINATION OF CONTENT

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Calculate the content of $C_{20}H_{28}O_2$ in the cream using the declared content of $C_{20}H_{28}O_2$ in *tretinoin BPCRS*.

For hydrocortisone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

(1) Shake a quantity of the cream containing 25 mg of Hydrocortisone in 150 mL of *methanol*, add sufficient *methanol* to produce 250 mL and filter (a 0.45-µm nylon syringe filter is suitable).
(2) 0.01% w/v of *hydrocortisone BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with the same material.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 238 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

11 volumes of *methanol*, 35 volumes of *acetonitrile* and 54 volumes of a 0.1% w/v solution of *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{30}O_5$ in the cream using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

For hydroquinone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

(1) Shake a quantity of the cream containing 50 mg of Hydroquinone with 100 mL of *methanol* until fully dispersed, add sufficient *methanol* to produce 250 mL and filter (a 0.45-µm nylon syringe filter is suitable). Dilute 1 volume of the filtrate to 5 volumes with the mobile phase.
(2) 0.004% w/v of *hydroquinone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with the same material.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 295 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

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1 volume of *water* and 9 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_6O_2$ in the cream using the declared content of $C_6H_6O_2$ in *hydroquinone BPCRS*.

STORAGE

Tretinoin, Hydrocortisone and Hydroquinone Cream should be protected from light.

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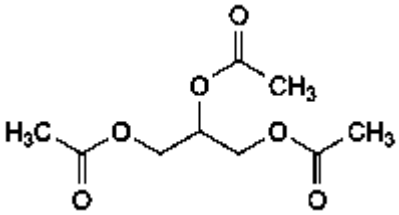
Triacetin

General Notices

(Ph. Eur. monograph 1106)



$C_9H_{14}O_6$ 218.2 *102-76-1*

Action and use

Antifungal.

Ph Eur

DEFINITION

Propane-1,2,3-triyl triacetate.

Content

97.0 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless, slightly viscous oily liquid.

Solubility

Soluble in water, miscible with ethanol (96 per cent) and toluene.

bp

About 260 °C.

IDENTIFICATION

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Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of triacetin*.

TESTS

Appearance

It is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity

Dissolve 5.00 g in 25 mL of *anhydrous ethanol R*, previously neutralised to 0.2 mL of *phenolphthalein solution R* and add 0.20 mL of *0.1 M sodium hydroxide*. The pink colour of the mixture persists for 15 s.

Relative density (*2.2.5*)

1.159 to 1.164.

Refractive index (*2.2.6*)

1.429 to 1.432.

Water (*2.5.12*)

Maximum 0.2 per cent, determined on 5.00 g.

ASSAY

Introduce 0.300 g into a 250 mL borosilicate glass flask fitted with a reflux condenser. Add 25.0 mL of 0.5 M alcoholic potassium hydroxide and a few glass beads. Attach the condenser and heat under reflux for 30 min. Add 1 mL of *phenolphthalein solution R1* and titrate immediately with *0.5 M hydrochloric acid*. Carry out a blank test under the same conditions. Calculate the content from the difference in consumption of alkali in the main and the blank procedure.

1 mL of 0.5 M alcoholic potassium hydroxide is equivalent to 36.37 mg of $C_9H_{14}O_6$.

STORAGE

In a well-filled container.

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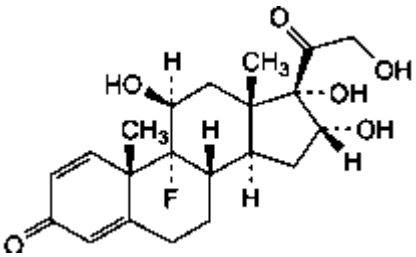
Triamcinolone

General Notices

(Ph. Eur. monograph 1376)



$C_{21}H_{27}FO_6$ 394.4 *124-94-7*

Action and use

Glucocorticoid.

Preparation

Triamcinolone Tablets

Ph Eur

DEFINITION

9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione.

Content

97.0 per cent to 103.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in methanol, practically insoluble in methylene chloride.

It shows polymorphism (*5.9*).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *triamcinolone CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness, dry the residues at 60 °C at a pressure not exceeding 0.7 kPa and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use and protect from light. Examine the plate under ultraviolet light immediately after development.*

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *triamcinolone CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *dexamethasone CRS* in reference solution (a) and dilute to 10 mL with the same solution.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Specific optical rotation (2.2.7)

+ 65 to + 72 (anhydrous substance).

Dissolve 0.100 g in *dimethylformamide R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 25.0 mg of the substance to be examined in a mixture of equal volumes of *methanol R* and *water R* and dilute to 10.0 mL with the same mixture of solvents.

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Reference solution (a) Dissolve 2 mg of *triamcinolone CRS* and 2 mg of *triamcinolone impurity C CRS* in a mixture of equal volumes of *methanol R* and *water R* and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Blank *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase A mixture prepared as follows: in a 1000 mL volumetric flask mix 525 mL of *methanol R* with 400 mL of *water R* and allow to equilibrate; adjust the volume to 1000 mL with *water R* and mix again.

Flow rate 1 mL/min.

Detection Spectrophotometer set at 238 nm.

Injection 20 µL.

Run time 4.5 times the retention time of triamcinolone.

Retention time Triamcinolone = about 11 min.

System suitability Reference solution (a):

— *resolution*: minimum of 1.8 between the peaks due to triamcinolone and to impurity C.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent) and not more than 2 such peaks have an area greater than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.500 g.

ASSAY

Prepare the solutions immediately before use and protect from light.

Dissolve 50.0 mg in *alcohol R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *alcohol R*. Measure the absorbance (*2.2.25*) at the maximum at 238 nm.

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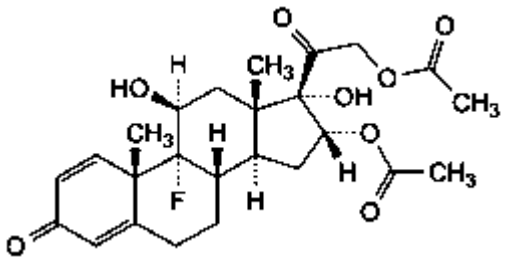
Calculate the content of $C_{21}H_{27}FO_6$ taking the specific absorbance to be 389.

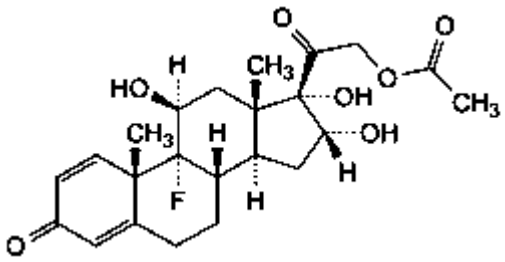
STORAGE

Protected from light.

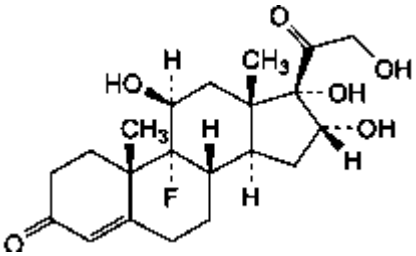
IMPURITIES



A. 9-fluoro-11β,17-dihydroxy-3,20-dioxopregna-1,4-diene-16α,21-diyl diacetate (triamcinolone 16,21-diacetate),



B. 9-fluoro-11β,16α,17-trihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate (triamcinolone 21-acetate),



C. 9-fluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione (pretriamcinolone).

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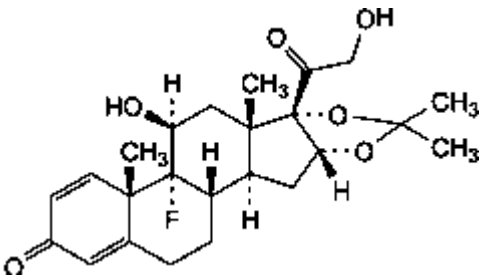
Triamcinolone Acetonide

General Notices

(Ph. Eur. monograph 0533)



$C_{24}H_{31}FO_6$ 434.5 *76-25-5*

Action and use

Glucocorticoid.

Preparations

Triamcinolone Cream

Triamcinolone Acetonide Injection

Triamcinolone Acetonide Nasal Spray

Triamcinolone Ointment

Triamcinolone Dental Paste

Ph Eur

DEFINITION

9-Fluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, C.

Second identification: B, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *triamcinolone acetonide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methanol R* and evaporate to dryness. Using the residues, prepare halogen salt discs or mulls in *liquid paraffin R* and record new spectra.

B. Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *triamcinolone acetonide CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *triamcinolone hexacetonide CRS* in reference solution (a) and dilute to 10 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm, immediately after development.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

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Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*, add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution to that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Specific optical rotation (*2.2.7*)

+ 110 to + 117 (anhydrous substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution Dissolve 25.0 mg of the substance to be examined in mobile phase B and dilute to 25.0 mL with mobile phase B.

Reference solution (a) Dissolve 5 mg of *triamcinolone acetonide for system suitability CRS* (containing impurities B and C) in mobile phase B and dilute to 5.0 mL with mobile phase B.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase B.

Reference solution (c) Dissolve 25.0 mg of *triamcinolone acetonide CRS* in mobile phase B and dilute to 25.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water for chromatography R* (32:68 *V/V*);

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— *mobile phase B*: *water for chromatography R*, *acetonitrile R* (35:65 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 40	100 → 0	0 → 100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *triamcinolone acetonide for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and C.

Relative retention With reference to triamcinolone acetonide (retention time = about 16 min): impurity C = about 0.7; impurity B = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurities C and B.

Limits:

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.500 g.

ASSAY

Carry out the assay protected from light.

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

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Mobile phase Mobile phase A.

Injection Test solution and reference solution (c).

Run time 1.5 times the retention time of triamcinolone acetonide.

Retention time Triamcinolone acetonide = about 16 min.

Calculate the percentage content of $C_{24}H_{31}FO_6$ taking into account the assigned content of *triamcinolone acetonide CRS*.

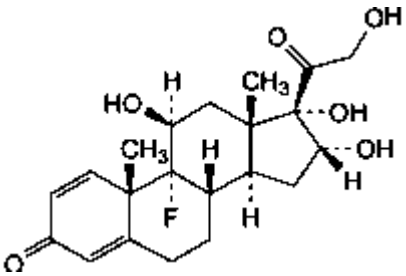
STORAGE

Protected from light.

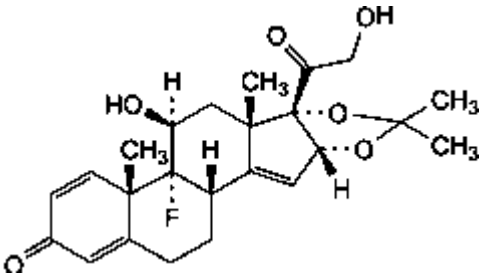
IMPURITIES

Specified impurities *B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, F.*



A. 9-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (triamcinolone),



B. 9-fluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4,14-triene-3,20-dione (Δ14-triamcinolone acetonide),

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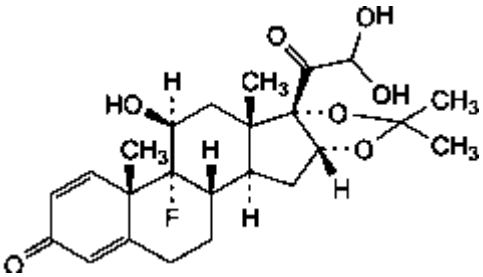
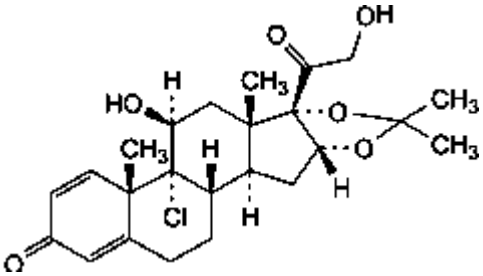
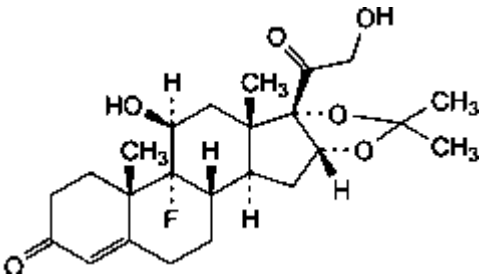


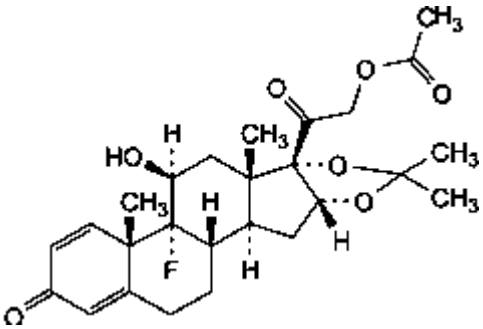
C. 9-fluoro-11β,21,21-trihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione (triamcinolone acetonide 21-aldehyde hydrate),



D. 9-chloro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione (9α-chloro triamcinolone acetonide),



E. 9-fluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-4-ene-3,20-dione (1,2-dihydrotriamcinolone acetonide),



F. 9-fluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregna-1,4-dien-21-yl acetate (21-acetate triamcinolone acetonide).

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Triamcinolone Acetonide Injection

General Notices

Action and use

Glucocorticoid.

DEFINITION

Triamcinolone Acetonide Injection is a sterile suspension of Triamcinolone Acetonide, in very fine particles, in Water for Injections containing suitable dispersing agents.

PRODUCTION

A suitable test is carried out to demonstrate the particle size of the injection is in accordance with the recommendations of the manufacturer.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of triamcinolone acetonide, $C_{24}H_{31}FO_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Extract a volume of the injection containing 50 mg of Triamcinolone Acetonide with two 10-mL quantities of *ether* and discard the ether extracts. Filter the aqueous layer through a sintered-glass filter, wash the residue with four 5-mL quantities of *water* and dry at 105° for 1 hour. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of triamcinolone acetonide (*RS 348*).
B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 5.0 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

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Solution A 40 volumes of *acetonitirile* and 60 volumes of 0.01% v/v of *formic acid* in *water*.

(1) Dilute a volume of the injection containing 40 mg of Triamcinolone Acetonide to 200 mL with solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A, further dilute 1 volume of this solution to 5 volumes with solution A.

(3) 0.0002% w/v of *triamcinolone acetonide for system suitability EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Inertsil ODS-3 is suitable).

(b) Use gradient elution and the mobile phase below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Maintain the autosampler at 4°.

(f) Use a detection wavelength of 240 nm.

(g) Inject 40 µL of each solution.

MOBILE PHASE

Mobile phase A 30 volumes of *acetonitrile* and 70 volumes of a 0.01% v/v of *formic acid* in *water*.

Mobile phase B 35 volumes of *water* and 65 volumes of 0.1% v/v of *formic acid* in *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-40	100→0	0→100	linear gradient
40-41	0	100	isocratic
41-42	0→100	100→0	linear gradient
42-45	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retentions relative to triamcinolone acetonide (retention time about 15 minutes) are; impurity A, about 0.2; impurity C, about 0.7; impurity B, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to impurity C and the peak due to impurity B is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

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the sum of the areas of all *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Solution A 40 volumes of *acetonitirile* and 60 volumes of 0.01% v/v of *formic acid* in *water*.

(1) Dilute a quantity of the injection containing 40 mg of Triamcinolone Acetonide to 200 mL with solution A.

(2) 0.02% w/v of *triamcinolone acetonide EPCRS* in solution A.

(3) 0.0002% w/v of *triamcinolone acetonide for system suitability EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to impurity C and the peak due to impurity B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{31}FO_6$ in the preparation being examined using peak heights and the declared content of $C_{24}H_{31}FO_6$ in *triamcinolone acetonide EPCRS*.

STORAGE

Triamcinolone Acetonide Injection should be protected from light. It should not be allowed to freeze.

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Triamcinolone Acetonide Nasal Spray

General Notices

Action and use

Glucocorticoid.

DEFINITION

Triamcinolone Acetonide Nasal Spray is a suspension of Triamcinolone Acetonide containing suitable buffering agents in a suitable container fitted with an appropriate nasal delivery system.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of triamcinolone acetonide, $C_{24}H_{31}FO_6$

80.0 to 120.0% of the amount stated to be delivered by actuation of the valve.

IDENTIFICATION

A. Carry out the method for *thin layer chromatography*, Appendix III A, using the following solutions protected from light.

(1) Shake a quantity of the nasal spray expected to contain 0.5 mg of Triamcinolone Acetonide with 3 mL of *methanol*, add sufficient *methanol* to produce 5 mL and filter.

(2) 0.01% w/v of *triamcinolone acetonide EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} *(Merck TLC silica gel 60* F_{254} *plates are suitable).*

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution, as 10-mm bands.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

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TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light, in *methanol (50%)*.

(1) To a quantity of the nasal spray containing 1 mg of Triamcinolone Acetonide add sufficient *methanol (50%)* to produce 5 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.0002% w/v each of *triamcinolone acetonide EPCRS* and *triamcinolone EPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 200 µL of each solution.

(g) Allow the chromatography to proceed for 3.5 times the retention time of triamcinolone acetonide.

MOBILE PHASE

Dilute 525 volumes of *methanol* to 1000 volumes with *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to triamcinolone and the peak due to triamcinolone acetonide is at least 15.

LIMITS

In the chromatogram obtained with solution (1):

— the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

— the area of not more than one *secondary peak* is greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

— the area of not more than two *secondary peaks* is greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

— the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) After priming the pump, discharge the container a sufficient number of times to obtain 1 mg of Triamcinolone Acetonide, add sufficient *methanol (50%)* to produce 5 mL and filter.

(2) 0.02% w/v of *triamcinolone acetonide EPCRS* in *methanol (50%)*.

(3) 0.02% w/v each of *triamcinolone acetonide EPCRS* and *triamcinolone EPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Related substances test may be used. Inject 20 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peak due to triamcinolone and the peak due to triamcinolone acetonide is at least 15.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{31}FO_6$ in the nasal spray using the declared content of $C_{24}H_{31}FO_6$ in *triamcinolone acetonide EPCRS*.

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Triamcinolone Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Triamcinolone Cream contains Triamcinolone Acetonide in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of triamcinolone acetonide, $C_{24}H_{31}FO_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and *ethyl acetate* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) add 25 mL of *methanol* and 5 g of *anhydrous sodium sulfate* to a quantity of the preparation being examined containing 5 mg of Triamcinolone Acetonide, shake for 10 minutes and filter through a sintered-glass crucible (ISO 4793, porosity grade 4, is suitable) containing a 2 cm layer of *washed, flux-calcined diatomaceous filter-aid*, rinsing the flask and crucible with 10 mL of *methanol*; evaporate the combined filtrate and washings to dryness on a water bath and dissolve the residue in 10 mL of *chloroform*. Solution (2) contains 0.05% w/v of *triamcinolone acetonide EPCRS* in *chloroform*. Solution (3) is a mixture of equal volumes of solutions (1) and (2). After removal of the plate, allow it to dry in air and spray with *alkaline tetrazolium blue solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to the spot in the chromatogram obtained with solution (2) and the chromatogram obtained with solution (3) shows a single, compact principal spot.

B. In the Assay, the chromatogram obtained with solution (3) shows a peak with the same retention time as the peak due to triamcinolone acetonide in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 1 mL of a 0.1% w/v solution of *fluoxymesterone BPCRS* (internal standard) in *methanol* to 1 mL of a 0.1% w/v solution of *triamcinolone acetonide EPCRS* in *methanol* and add sufficient *methanol* to produce 10 mL. For solution (2) add 10 mL of *methanol* to a quantity of the preparation being examined containing 1 mg of Triamcinolone Acetonide, heat on a water bath at 60° to 70° until the preparation has melted, shake vigorously for 2 minutes, cool in ice and centrifuge; filter the supernatant liquid, if necessary. Prepare solution (3) in the same manner as solution (2) but use 1 mL of the internal standard solution and 9 mL of *methanol* in place of the 10 mL of methanol.

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The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography*, (10 µm) (Spherisorb ODS 1 is suitable), (b) a mixture of 65 volumes of *methanol*, 35 volumes of *water* and 0.025 volume of *triethylamine* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm.

Calculate the content of $C_{24}H_{31}FO_6$ in the preparation being examined using the declared content of $C_{24}H_{31}FO_6$ in *triamcinolone acetonide EPCRS*.

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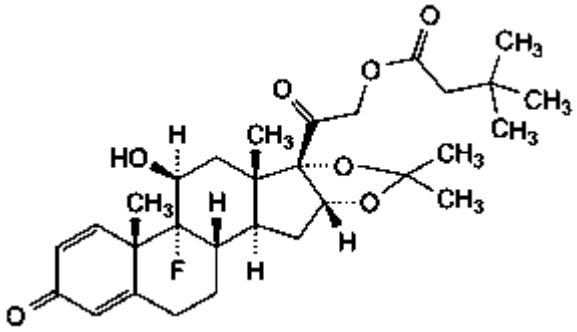
Triamcinolone Hexacetonide

General Notices

(Ph. Eur. monograph 0867)



$C_{30}H_{41}FO_7$ 532.6 *5611-51-8*

Action and use

Glucocorticoid.

Preparation

Triamcinolone Hexacetonide Injection

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DEFINITION

9-Fluoro-11β-hydroxy-2′,2′-dimethyl-3,20-dioxo-(16β*H*)-[1,3]dioxolo[4′,5′:16,17]pregna-1,4-dien-21-yl 3,3-dimethylbutanoate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in anhydrous ethanol and in methanol, practically insoluble in heptane.

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison triamcinolone hexacetonide CRS.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Specific optical rotation (2.2.7)

+ 95 to + 101 (anhydrous substance).

Dissolve 0.100 g in methylene chloride R and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution (a) Dissolve 25.0 mg of the substance to be examined in methanol R and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 5.0 mL with methanol R.

Reference solution (a) Dissolve 5 mg of triamcinolone hexacetonide for system suitability CRS (containing impurities B and C) in methanol R and dilute to 2.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 25.0 mg of triamcinolone hexacetonide CRS in methanol R and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 5.0 mL with methanol R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase water for chromatography R, methanol R (25:75 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

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Run time Twice the retention time of triamcinolone hexacetonide.

Identification of impurities Use the chromatogram supplied with *triamcinolone hexacetonide for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and C.

Relative retention With reference to triamcinolone hexacetonide (retention time = about 8 min): impurity B (epimer 1) = about 0.79; impurity B (epimer 2) = about 0.81; impurity C = about 1.3.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to triamcinolone hexacetonide and impurity C.

Calculation of percentage contents:

— for each impurity, use the concentration of triamcinolone hexacetonide in reference solution (b).

Limits:

— *impurity B*: for the sum of the areas of the 2 epimer peaks, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.50 g.

ASSAY

Carry out the test protected from light.

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 10 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{30}H_{41}FO_7$ taking into account the assigned content of *triamcinolone hexacetonide CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *B*.

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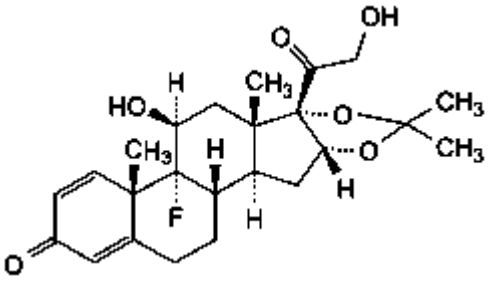
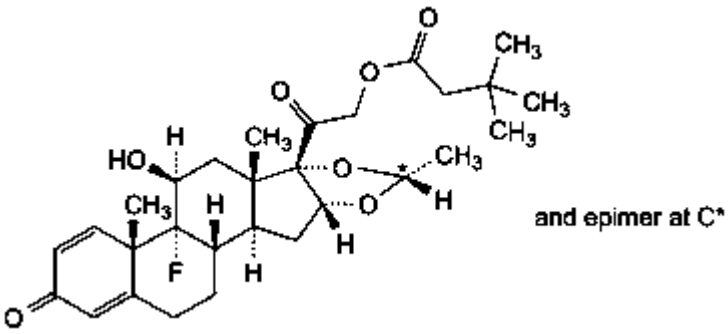
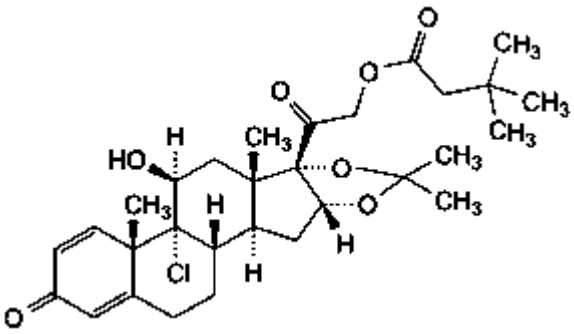
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*



A. 9-fluoro-11β,21-dihydroxy-2′,2′-dimethyl-(16β*H*)-[1,3]dioxolo[4′,5′:16,17]pregna-1,4-diene-3,20-dione (triamcinolone acetonide),



B. (2′*RS*)-9-fluoro-11β-hydroxy-2′-methyl-3,20-dioxo-(16β*H*)-[1,3]dioxolo[4′,5′:16,17]pregna-1,4-dien-21-yl 3,3-dimethylbutanoate,



C. 9-chloro-11β-hydroxy-2′,2′-dimethyl-3,20-dioxo-(16β*H*)-[1,3]dioxolo[4′,5′:16,17]pregna-1,4-dien-21-yl 3,3-dimethylbutanoate.

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Triamcinolone Hexacetonide Injection

General Notices

Action and use

Glucocorticoid.

DEFINITION

Triamcinolone Hexacetonide Injection is a suspension of Triamcinolone Hexacetonide, in *microfine powder*, in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of triamcinolone hexacetonide, $C_{30}H_{41}FO_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dilute an appropriate volume of the injection to a concentration of 25 mg of Triamcinolone Hexacetonide per 7 mL with *water*, filter under reduced pressure, wash the residue with two 5 -mL quantities of *water* and dry the filter and precipitate. Stir the dried filter and precipitate with 5 mL of *absolute ethanol* to dissolve the precipitate, decant the solution and evaporate to dryness with gentle heating and in a current of air. The *infrared absorption spectrum* of a dispersion of the residue in *potassium bromide*, Appendix II A, is concordant with the *reference spectrum* of triamcinolone hexacetonide (*RS 394*).

TESTS

Acidity or alkalinity

pH, 4.2 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a volume of the injection containing 20 mg of Triamcinolone Hexacetonide to 50 mL with *methanol*. For solution (2) dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Solution (3) contains 0.00040% w/v of *triamcinolone acetonide EPCRS* in the mobile phase. Solution (4) is a 0.0004% w/v solution of *triamcinolone hexacetonide BPCRS* in solution (3). Solution (5) contains 0.1% v/v of *benzyl alcohol* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable), (b) as the mobile phase with a flow rate of 1.4 mL per minute a mixture of 250 volumes of *water* and 750 volumes of *methanol* and (c) a detection wavelength of 254 nm.

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The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the two principal peaks is at least 10.

In the chromatogram obtained with solution (1) the area of any peak corresponding to triamcinolone acetonide is not greater than the area of the peak in the chromatogram obtained with solution (3) (1%) and the sum of the areas of any other *secondary peaks* is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%). Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%) and any peak corresponding to the peak in the chromatogram obtained with solution (5).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1), withdraw the nominal volume of a container and dilute with *methanol* to produce a solution containing 0.04% w/v of Triamcinolone Hexacetonide. Solution (2) contains 0.04% w/v of *triamcinolone hexacetonide BPCRS* in *methanol*. Solution (3) contains 0.04% w/v of *triamcinolone acetonide EPCRS* in solution (2).

The chromatographic conditions described under Related substances may be used.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 10.

Calculate the content of $C_{30}H_{41}FO_7$ from the chromatograms obtained using the declared content of $C_{30}H_{41}FO_7$ in *triamcinolone hexacetonide BPCRS*.

LABELLING

The label states the intended route of administration.

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Triamcinolone Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Triamcinolone Ointment contains Triamcinolone Acetonide in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of triamcinolone acetonide, $C_{24}H_{31}FO_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Complies with test A for Identification described under Triamcinolone Cream but preparing solution (1) in the following manner. To a quantity of the ointment containing 5 mg of Triamcinolone Acetonide add 10 mL of *chloroform* and shake for 10 minutes. Add 25 mL of *methanol* and shake for a further 10 minutes. Filter through a sintered-glass crucible (ISO 4793, porosity grade 4, is suitable) containing a 2 cm layer of *washed, flux-calcined diatomaceous filter-aid*, rinsing the flask and crucible with 10 mL of *methanol*. Evaporate the combined filtrate and washings to dryness on a water bath and dissolve the residue in 10 mL of *chloroform*.

B. In the Assay, the chromatogram obtained with solution (3) shows a peak with the same retention time as the peak due to triamcinolone acetonide in the chromatogram obtained with solution (1).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 4 mL of *dichloromethane* to a quantity of the preparation being examined containing 2 mg of Triamcinolone Acetonide, shake vigorously until it is completely dispersed, add 20 mL of *methanol* and shake vigorously for 1 minute. Cool in ice and centrifuge; evaporate the supernatant liquid or the liquid beneath the crust to dryness using a rotary evaporator, dissolve the residue as completely as possible in 1 mL of *methanol*, dilute to 2 mL with *water* and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *methanol (50%)*. Solution (3) contains 0.002% w/v each of *triamcinolone acetonide EPCRS* and *triamcinolone EPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a mixture of 475 volumes of *water* and 525 volumes of *methanol* and (c) a detection wavelength of 254 nm.

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Inject 20 µL of each solution. The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 15.

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%) and the sum of the areas of all such peaks is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 1 mL of a 0.1% w/v solution of *fluoxymesterone BPCRS* (internal standard) in *methanol*, 2 mL of *chloroform* and 8 mL of *methanol* to 1 mL of a 0.1% w/v solution of *triamcinolone acetonide EPCRS* in *methanol*. For solution (2) add 2 mL of *chloroform* to a quantity of the preparation being examined containing 1 mg of Triamcinolone Acetonide, shake vigorously until it is completely dispersed, add 10 mL of *methanol* and shake vigorously for 1 minute. Cool in ice and centrifuge; use the supernatant liquid or the liquid beneath the crust, filtered if necessary. Prepare solution (3) in the same manner as solution (2) but add 1 mL of the internal standard solution, 2 mL of *chloroform* and 9 mL of *methanol* in place of the 10 mL of methanol.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) a mixture of 65 volumes of *methanol*, 35 volumes of *water* and 0.025 volume of *triethylamine* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm.

Calculate the content of $C_{24}H_{31}FO_6$ in the preparation being examined using the declared content of $C_{24}H_{31}FO_6$ in *triamcinolone acetonide EPCRS*.

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Triamcinolone Oromucosal Paste

General Notices

Triamcinolone Dental Paste

Action and use

Glucocorticoid.

DEFINITION

Triamcinolone Oromucosal Paste contains Triamcinolone Acetonide in a suitable basis.

The oromucosal paste complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of triamcinolone acetonide, $C_{24}H_{31}FO_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin layer chromatography*, *Appendix III A*, using the following solutions protected from light.

(1) Shake a quantity of the paste containing 0.5 mg of Triamcinolone Acetonide with 3 mL of *methanol* add sufficient *methanol* to produce 5 mL and filter.

(2) 0.01% w/v of *triamcinolone acetonide EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254} (Merck TLC silica gel 60 F_{254} plates are suitable)*.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution, as 10-mm bands.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to triamcinolone acetonide in the chromatogram obtained with solution (2).

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TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Solution A 0.01% v/v of *formic acid* in *water*.

Solution B 0.1% v/v of *formic acid* in *acetonitrile*.

Solution C 30 volumes of *acetonitrile* and 60 volumes of solution A.

(1) Dilute a quantity of the oromucosal paste containing 1 mg of Triamcinolone Acetonide in 1 mL of *tetrahydrofuran* then add 9 mL of solution C and mix with the aid of ultrasound.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A, further dilute 1 volume of this solution to 5 volumes with solution A.

(3) 0.0002% w/v of *triamcinolone acetonide for system suitability EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Inertsil ODS-3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Maintain the autosampler at 4° .

(f) Use a detection wavelength of 254 nm.

(g) Inject 40 µL of each solution.

MOBILE PHASE

Mobile phase A 30 volumes of *acetonitrile* and 70 volumes of solution A.

Mobile phase B 35 volumes of *water* and 65 volumes of solution B.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-40	100→0	0→100	linear gradient
40-41	0	100	isocratic
41-42	0→100	100→0	linear gradient
42-45	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention relative to triamcinolone acetonide (retention time about 16 minutes) are: impurity C, about 0.7; impurity B, about 0.8.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to impurity C and the peak due to impurity B is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity C is not greater than ten times the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of *secondary peaks*, excluding impurity C, is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution C 30 volumes of *acetonitrile* and 60 volumes of solution A.
(1) Dilute a quantity of the oromucosal paste containing 1 mg of Triamcinolone Acetonide in 1 mL of *tetrahydrofuran* then add 9 mL of solution C and mix with the aid of ultrasound.
(2) 0.01% w/v of *triamcinolone acetonide EPCRS* in a mixture of 10 volumes of *tetrahydrofuran*, 30 volumes of solution A and 60 volumes of *acetonitirile*.
(3) 0.0002% w/v of *triamcinolone acetonide for system suitability EPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to impurity C and the peak due to impurity B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{31}FO_6$ in the preparation being examined using the declared content of $C_{24}H_{31}FO_6$ in *triamcinolone acetonide EPCRS*.

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Triamcinolone Tablets

General Notices

Action and use

Glucocorticoid.

DEFINITION

Triamcinolone Tablets contain Triamcinolone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of triamcinolone, $C_{21}H_{27}FO_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dissolve 1 mg of the residue obtained in the test for Related substances in 6 mL of *ethanol* (*96%*), add 5 mL of a 1% w/v solution of *butylated hydroxytoluene* in *ethanol* (*96%*) and 5 mL of 1M *sodium hydroxide* and heat on a water bath under a reflux condenser for 20 minutes. A pinkish lavender colour is produced.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to triamcinolone in the chromatogram obtained with solution (1).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Shake a quantity of the powdered tablets containing 15 mg of Triamcinolone with 15 mL of *absolute ethanol* for 15 minutes, filter under reduced pressure through fine filter paper (Whatman No. 42 is suitable) and evaporate to dryness using a rotary evaporator. Reserve 1 mg of the residue for test A for Identification. Dissolve the remainder of the residue in 15 mL of *methanol* (solution A). For solution (1) use solution (A). For solution (2) dilute 4 mL of solution A to 100 mL with *methanol*. For solution (3) dilute 5 mL of solution (A) to 50 mL with *methanol* and dilute 5 mL of the resulting solution to 50 mL with the same solvent.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable), (b) as the mobile phase a mixture of *methanol* and *water*, adjusted so that the retention time of triamcinolone is about 5 minutes (a mixture of equal volumes of *methanol* and *water* is usually suitable) with a flow rate of 2 mL per minute and (c) a detection wavelength of 238 nm. For solution (3) record the chromatogram for 4 times the retention time of the triamcinolone peak.

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The test is not valid unless the *column efficiency*, determined using the principal peak in the chromatogram obtained with solution (2), is at least 10,000 theoretical plates per metre.

The area of any *secondary peak* in the chromatogram obtained with solution (1) is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (2%) and not more than one such peak has an area greater than that of the principal peak in the chromatogram obtained with solution (3) (1%). The sum of the areas of any such peaks is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (4%).

ASSAY

Weigh and powder 20 tablets. Prepare a 0.06% w/v solution of *testosterone* (internal standard) in *methanol* (solution B) and carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 5 mL of solution B to 5 mL of a 0.08% w/v solution of *triamcinolone EPCRS* in *methanol* and add 15 mL of *methanol* (*50%*). For solution (2) shake a quantity of the powdered tablets containing 2.5 mg of Triamcinolone with 5 mL of *methanol* and 20 mL of a mixture of 5 volumes of *methanol* and 3 volumes of *water*. Shake for 15 minutes, mix with the aid of ultrasound for 10 minutes, centrifuge and use the supernatant liquid. Prepare solution (3) in the same manner as solution (2) but add 5 mL of solution B in place of the 5 mL of methanol.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) a mixture of 70 volumes of *methanol*, 30 volumes of *water* and 0.1 volume of *glacial acetic acid* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 238 nm.

Calculate the content of $C_{21}H_{27}FO_6$ using the declared content of $C_{21}H_{27}FO_6$ in *triamcinolone EPCRS*.

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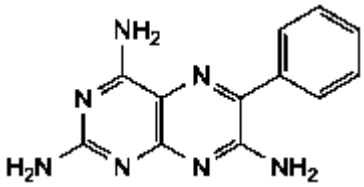
Triamterene

General Notices

(Ph. Eur. monograph 0058)



$C_{12}H_{11}N_7$ 253.3 *396-01-0*

Action and use

Sodium channel blocker; potassium-sparing diuretic.

Preparations

Co-triamterzide Tablets

Triamterene Capsules

Ph Eur

DEFINITION

6-Phenylpteridine-2,4,7-triamine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Very slightly soluble in water and in ethanol (96 per cent).

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison triamterene CRS.

TESTS

Acidity

Boil 1.0 g with 20 mL of water R for 5 min, cool, filter and wash the filter with 3 quantities, each of 10 mL, of water R. Combine the filtrate and washings and add 0.3 mL of phenolphthalein solution R. Not more than 1.5 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator.

Impurity D

Gas chromatography (2.2.28).

Internal standard solution Dilute 0.1 mL of nitrobenzene R to 100 mL with methanol R. Dilute 1 mL of this solution to 50 mL with methanol R.

Test solution Introduce 0.800 g of the substance to be examined into a suitable vial, add 5 mL of dimethyl sulfoxide R and heat until the sample is dissolved (do not heat to boiling). Allow to cool. Add 5 mL of cold methanol R to enhance the precipitation of triamterene. Filter and wash the filter with 5 mL of methanol R. Combine the filtrate and washing, add 2.0 mL of the internal standard solution and dilute to 20.0 mL with methanol R.

Reference solution Dissolve 20.0 mg of benzyl cyanide R (impurity D) in methanol R and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with methanol R. To 2.0 mL of this solution add 2.0 mL of the internal standard solution and 5 mL of dimethyl sulfoxide R and dilute to 20.0 mL with methanol R.

Blank solution Dilute 5 mL of dimethyl sulfoxide R to 20 mL with methanol R.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: macrogol 20 000 R (0.5 µm).

Carrier gas helium for chromatography R.

Flow rate 1.5 mL/min.

Split ratio 1:15.

Temperature:

— *column*: 170 °C;

— *injection port*: 210 °C;

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— *detector*: 230 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time Twice the retention time of the internal standard.

Relative retention With reference to the internal standard (retention time = about 6 min): impurity D = about 1.6.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peak due to impurity D and the nearest peak due to the solvent (blank solution);

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity D.

Limit:

— *impurity D*: calculate the ratio (*R*) of the area of the peak due to impurity D to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the area of the peak due to impurity D to the area of the peak due to the internal standard: this ratio is not greater than *R* (50 ppm).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *nitrosotriaminopyrimidine CRS* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *triamterene impurity B CRS* in 200 µL of *dimethyl sulfoxide R*. Add 5.0 mL of the test solution and dilute to 50.0 mL with the mobile phase. Filter the solution through a membrane filter (nominal pore size 0.45 µm) before injection.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *butylamine R*, *acetonitrile R*, *methanol R*, *water R* (2:200:200:600 *V/V/V/V*), adjusted to pH 5.3 with *acetic acid R*.

Flow rate 1 mL/min.

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Detection Spectrophotometer at 320 nm and at 355 nm.

Injection 50 µL.

Relative retention With reference to triamterene (retention time = about 5 min): impurity A = about 0.6; impurity B = about 0.8; impurity C = about 1.7.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity B and triamterene in the chromatogram obtained with reference solution (c) at 355 nm; if necessary, increase the quantity of *water R* in the mobile phase;

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (b) at 320 nm.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.8; impurity C = 1.5;

— *impurity A at 320 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (50 ppm);

— *impurities B, C at 355 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities at 355 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total at 355 nm*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit at 355 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 5 mL of *anhydrous formic acid R* and add 100 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.33 mg of $C_{12}H_{11}N_7$.

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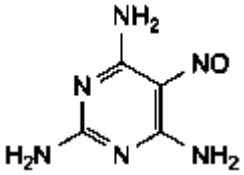
STORAGE

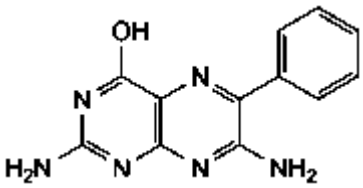
Protected from light.

IMPURITIES

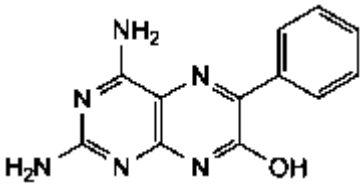
Specified impurities *A, B, C, D.*



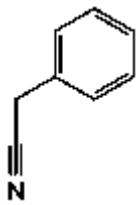
A. 5-nitrosopyrimidine-2,4,6-triamine (nitrosotriaminopyrimidine),



B. 2,7-diamino-6-phenylpteridin-4-ol,



C. 2,4-diamino-6-phenylpteridin-7-ol,



D. phenylacetonitrile (benzyl cyanide).

Ph Eur

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Triamterene Capsules

General Notices

Action and use

Sodium channel blocker; potassium-sparing diuretic.

DEFINITION

Triamterene Capsules contain Triamterene.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of triamterene, $C_{12}H_{11}N_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The final solution obtained in the Assay has a bluish fluorescence and the *light absorption*, Appendix II B, in the range 230 to 365 nm exhibits a maximum only at 360 nm.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 90 volumes of *ethyl acetate*, 10 volumes of *methanol* and 10 volumes of 18M *ammonia* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) dissolve a quantity of the contents of the capsules containing 0.10 g of Triamterene in sufficient *dimethyl sulfoxide* to produce 20 mL and dilute 2 mL to 50 mL with *methanol*. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *methanol*. After removal of the plate, allow it to dry in air until the solvent has evaporated and examine under *ultraviolet light* (*365 nm*). Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

Dissolve a quantity of the mixed contents of 20 capsules containing 0.1 g of Triamterene in 50 mL of a mixture of equal volumes of *glacial acetic acid* and *water* with the aid of gentle heat, cool and add sufficient *water* to produce 500 mL. Dilute 5 mL to 200 mL with 1M *acetic acid* and measure the *absorbance* of the resulting solution at the maximum at 360 nm, Appendix II B. Calculate the content of $C_{12}H_{11}N_7$ from a calibration curve prepared by treating suitable quantities of a solution of *triamterene BPCRS* in 1M *acetic acid* in the same manner and using the declared content of $C_{12}H_{11}N_7$ in *triamterene BPCRS*.

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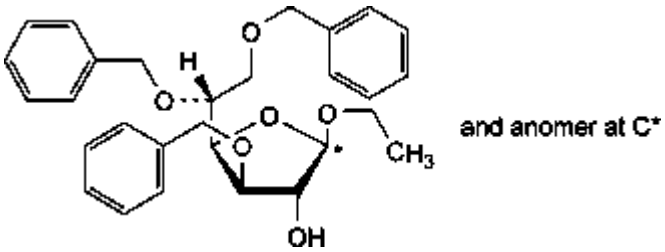
Tribenoside

General Notices

(Ph. Eur. monograph 1740)



$C_{29}H_{34}O_6$ 478.6 *10310-32-4*

Action and use

Sclerosing agent.

Ph Eur

DEFINITION

Mixture of α- and β-anomers of ethyl 3,5,6-tri-*O*-benzyl-D-glucofuranoside.

Content

96.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

Yellowish or pale yellow, clear, viscous liquid.

Solubility

Practically insoluble in water, very soluble in acetone, in methanol and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *tribenoside CRS*.

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TESTS

Solution S

Dissolve 4.00 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 420 nm has a maximum of 0.10.

Specific optical rotation (*2.2.7*)

-40.0 to -31.0.

Dilute 2.0 mL of solution S to 20.0 mL with *methanol R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 1.000 g of the substance to be examined in a mixture of 5 volumes of *water R* and 95 volumes of *acetonitrile R* and dilute to 25.0 mL with the same mixture of solvents.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in a mixture of 5 volumes of *water R* and 95 volumes of *acetonitrile R* and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 25.0 mg of *benzaldehyde CRS* (impurity C) and 30.0 mg of *tribenoside impurity A CRS* to 100.0 mL with *acetonitrile R*. Introduce 20.0 mL of this solution into a 50 mL volumetric flask, add 2.5 mL of *water R* and dilute to 50.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 50.0 mg of *tribenoside CRS* in a mixture of 5 volumes of *water R* and 95 volumes of *acetonitrile R* and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (c) Dissolve 12.0 mg of *tribenoside impurity D CRS* in a mixture of 5 volumes of *water R* and 95 volumes of *acetonitrile R* and dilute to 100.0 mL with the same mixture of solvents.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	55 → 10	45 → 90
40 - 55	10	90

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retentions With reference to the β-anomer of tribenoside (retention time = about 18 min): α-anomer = about 1.1; impurity C = about 0.2; impurity B = about 0.6; impurity D = about 0.8; impurity A = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to the α-anomer and to the β-anomer of tribenoside.

Limits:

— *impurity A*: not more than 1.7 times the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent); if the area of the peak due to impurity C in the chromatogram obtained with the test solution is greater than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.25 per cent), dilute the test solution to obtain an area equal to or smaller than the area of the peak in the chromatogram obtained with reference solution (a); calculate the content of impurity C taking into account the dilution factor;

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *any other impurity*: not more than the area of the peak due to impurity A in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *total*: maximum 2.0 per cent;

— *disregard limit*: 0.17 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (a) (0.05 per cent).

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

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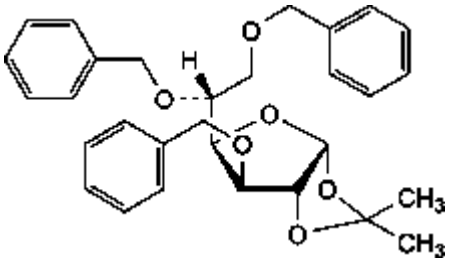
Injection Test solution (b) and reference solution (b).

Calculate the sum of the percentage contents of the α-anomer and the β-anomer of tribenoside taking into account the assigned content of *tribenoside CRS*.

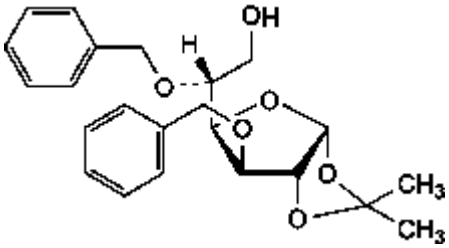
STORAGE

Under nitrogen, in an airtight container.

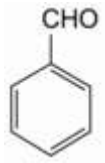
IMPURITIES



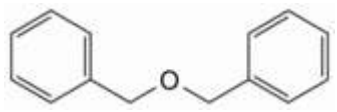
A. 3,5,6-tri-*O*-benzyl-1,2-*O*-(1-methylethylidene)-α-D-glucofuranose,



B. 3,5-di-*O*-benzyl-1,2-*O*-(1-methylethylidene)-α-D-glucofuranose,



C. benzaldehyde,



D. dibenzyl ether.

Ph Eur

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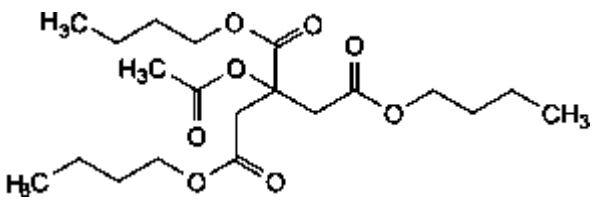
Tributyl Acetylcitrate

General Notices

(Ph. Eur. monograph 1770)



$C_{20}H_{34}O_8$ 402.5 *77-90-7*

Action and use

Excipient.

Ph Eur

DEFINITION

Tributyl 2-(acetyloxy)propane-1,2,3-tricarboxylate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, oily liquid.

Solubility

Not miscible with water, miscible with ethanol (96 per cent) and with methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation Thin films between 2 sodium chloride plates.

Comparison *tributyl acetylcitrate CRS*.

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TESTS

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Acidity

Dilute 10 g with 10 mL of previously neutralised *ethanol (96 per cent) R* and add 0.5 mL of *bromothymol blue solution R2*. Not more than 0.3 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Refractive index (2.2.6)

1.442 to 1.445.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 0.5 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of the substance to be examined and 50 mg of *tributyl citrate R* (impurity A) in *methylene chloride R* and dilute to 20 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 25.0 mL with *methylene chloride R*.

Reference solution (c) Dissolve the contents of a vial of *tributyl acetylcitrate for peak identification CRS* (containing impurities B and C) in 1 mL of *methylene chloride R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *cyanopropyl(25)phenyl(25)methyl(50)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 36 cm/s.

Split ratio 1:20.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 7	70 → 210
	7 - 50	210
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL; inject via an inert, glass-lined injection port using an automatic injection device.

Identification of impurities Use the chromatogram supplied with *tributyl acetylcitrate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B and C; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to tributyl acetylcitrate (retention time = about 24 min): impurity B = about 0.70; impurity C = about 0.83; impurity A = about 0.87.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity A and tributyl acetylcitrate in the chromatogram obtained with reference solution (a);

— *repeatability*: maximum relative standard deviation of 5.0 per cent after 6 injections of reference solution (b).

Limits:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.25 per cent, determined on 2.00 g.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

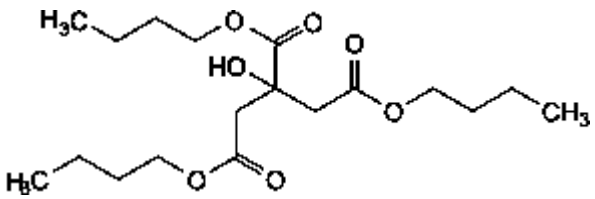
Introduce 1.500 g into a 250 mL borosilicate glass flask. Add 25 mL of *2-propanol R*, 50 mL of *water R*, 25.0 mL of *1 M sodium hydroxide* and a few glass beads. Heat under a reflux condenser for 3 h. Allow to cool. Add 1 mL of *phenolphthalein solution R1* and titrate with *1 M hydrochloric acid*. Carry out a blank titration.

1 mL of *1 M sodium hydroxide* is equivalent to 100.6 mg of $C_{20}H_{34}O_8$.

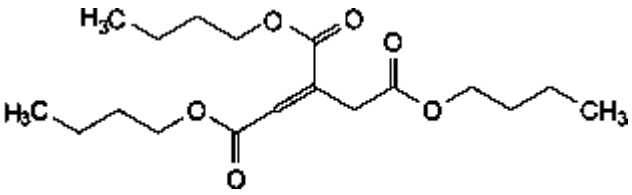
IMPURITIES

Specified impurities A, B, C.

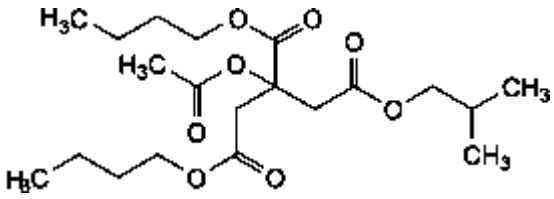
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, E.



A. tributyl 2-hydroxypropane-1,2,3-tricarboxylate (tributyl citrate),



B. tributyl propene-1,2,3-tricarboxylate (tributyl aconitate),



C. 1,2-dibutyl 3-(2-methylpropyl) 2-(acetyloxy)propane1,2,3-tricarboxylate,

D. butan-1-ol,

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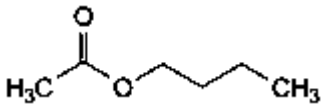

E. butyl acetate.

Ph Eur

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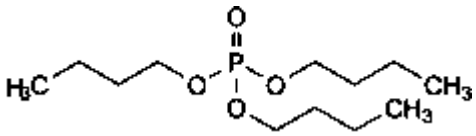
Tributyl Phosphate

General Notices

(Tri-n-butyl Phosphate, Ph. Eur. monograph 1682)



$C_{12}H_{27}O_4P$ 266.3 *126-73-8*

Action and use

Excipient.

Ph Eur

CHARACTERS

Appearance

Clear, colourless or pale yellow liquid.

Solubility

Slightly soluble in water, miscible with ethanol (96 per cent).

bp

About 289 °C, with decomposition.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *tri-n-butyl phosphate CRS*.

TESTS

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Acidity

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Dissolve 50 mL in 50 mL of *ethanol (96 per cent) R* previously adjusted with *0.02 M potassium hydroxide* or *0.02 M hydrochloric acid* to a bluish-green colour, using 0.5 mL of *bromothymol blue solution R1* as indicator. Titrate with *0.02 M potassium hydroxide* to the initial bluish-green coloration. Not more than 0.8 mL of *0.02 M potassium hydroxide* is required.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution The substance to be examined.

Reference solution Dissolve 10 mg of the substance to be examined and 10 mg of *methyl myristate R* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 32 cm/s.

Split ratio 65:1.

Temperature:

— *column*: 250 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time Twice the retention time of tri-*n*-butyl phosphate.

System suitability Reference solution:

— *resolution*: minimum 10 between the peaks due to tri-*n*-butyl phosphate and methyl myristate.

Limits:

— *any impurity*: for each impurity, maximum 0.3 per cent;

— *total*: maximum 0.5 per cent;

— *disregard limit*: 0.01 per cent.

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Chlorides (*2.4.4*)

Maximum 200 ppm.

Dissolve 0.25 g in 15 mL of *ethanol (70 per cent V/V) R*. The solution complies with the test. Prepare the reference solution using 10 mL of *chloride standard solution (5 ppm Cl) R* and 5 mL of *anhydrous ethanol R*.

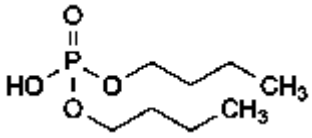
Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.0 g.

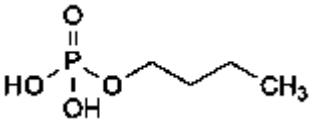
STORAGE

Protected from light.

IMPURITIES

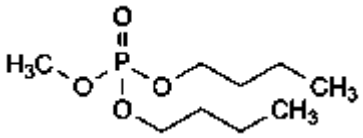


A. dibutyl hydrogen phosphate,

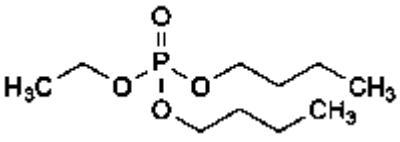


B. butyl dihydrogen phosphate,

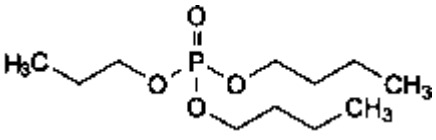
C. H_3C-$[CH_2]_3$-OH: butan-1-ol,



D. dibutyl methyl phosphate,



E. dibutyl ethyl phosphate,



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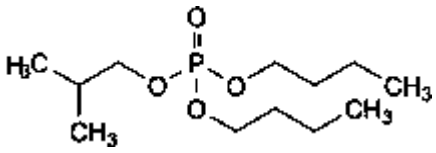
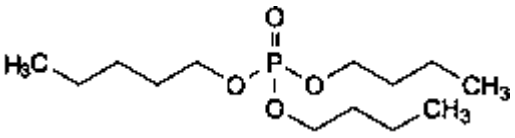
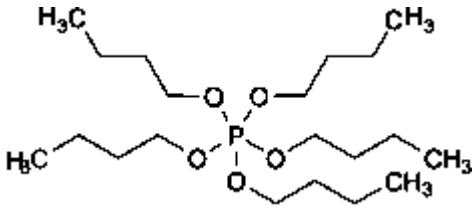
F. dibutyl propyl phosphate,



G. dibutyl 2-methylpropyl phosphate,



H. dibutyl pentyl phosphate,



I. pentabutyl phosphate.

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Triclofos Oral Solution

General Notices

Action and use

Hypnotic.

DEFINITION

Triclofos Oral Solution is a solution of Triclofos Sodium in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of triclofos sodium, $C_2H_3Cl_3NaO_4P$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the oral solution containing 0.25 g of Triclofos Sodium with 40 mL of *water*, add 5 mL of 1M *sulfuric acid* and extract with 25 mL of *isoamyl alcohol*. The extract complies with the following tests.

A. Evaporate 5 mL to dryness, heat the residue with 1 mL of a 50% v/v solution of *sulfuric acid* and 1 mL of a 5% w/v solution of *potassium permanganate* in a water bath for 5 minutes, add 7 mL of *water* and decolourise the solution with 1 mL of a 5% w/v solution of *oxalic acid*. To 1 mL add 1 mL of *pyridine* and 1 mL of 2M *sodium hydroxide*, heat in a water bath for 1 minute, stirring continuously. A pink colour is produced in the pyridine layer.

B. Evaporate 10 mL to dryness, heat the residue with 1 g of *anhydrous sodium carbonate* at a dull red heat for 10 minutes, cool, extract the residue with *water* and filter. The residue yields the reactions characteristic of *chlorides* and of *phosphates*, Appendix VI.

ASSAY

To a quantity containing 16 mg of Triclofos Sodium add 15 mL of *water*, 1 mL of 1M *sodium hydroxide* and 15 mL of *ether*, shake for 1 minute, allow to separate, wash the ether layer with 2 quantities each of 1 mL of *water* and discard the ether solution. Add 2.5 mL of 1M *sulfuric acid* to the combined aqueous layer and washings, extract with four 10-mL quantities of *isoamyl alcohol*, allowing each extract to stand until good separation is achieved, combine the isoamyl alcohol extracts, remove any further water that separates and dilute to 50 mL with *isoamyl alcohol*. Transfer 10 mL of this solution to a 20 mL glass ampoule, add 10 mL of *alcoholic potassium hydroxide solution*, seal the ampoule, mix well and heat in an autoclave at 120° for 2 hours. Allow the ampoule to cool, transfer the contents to a flask with the aid of 20 mL of 2M *nitric acid* and add 25 mL of *0.02M silver nitrate VS*. Titrate with *0.02M ammonium thiocyanate VS* using *ammonium iron(III) sulfate solution R2* as indicator. Repeat the titration using 10 mL of *alcoholic potassium hydroxide solution* in place of the contents of the ampoule. The difference between the titrations represents the amount of silver nitrate required. Each mL of *0.02M silver nitrate VS* is

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equivalent to 1.676 mg of $C_2H_3Cl_3NaO_4P$. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_2H_3Cl_3NaO_4P$, weight in volume.

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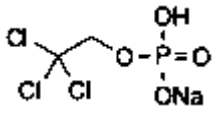
Triclofos Sodium

General Notices



$C_2H_3Cl_3NaO_4P$ 251.4 *7246-20-0*

Action and use

Hypnotic.

Preparation

Triclofos Oral Solution

DEFINITION

Triclofos Sodium is sodium 2,2,2-trichloroethyl hydrogen orthophosphate. It contains not less than 41.3% and not more than 43.2% of Cl and not less than 97.0% and not more than 102.0% of $C_2H_3Cl_3NaO_4P$, both calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder; hygroscopic.

Freely soluble in *water*; slightly soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of triclofos sodium *(RS 350)*.

B. Yields the reactions characteristic of *sodium salts*, Appendix VI.

C. Heat 0.1 g with 1 g of *anhydrous sodium carbonate* to a dull red heat and maintain for 10 minutes, cool, extract the residue with *water* and filter. The filtrate yields the reactions characteristic of *chlorides* and of *phosphates*, Appendix VI.

TESTS

Acidity

pH of a 2% w/v solution, 3.0 to 4.5, Appendix V L.

Clarity of solution

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A 2.0% w/v solution is *clear*, Appendix IV A.

Chloride

Dissolve 0.1 g in 50 mL of *water*. 15 mL of the solution complies with the *limit test for chlorides*, Appendix VII (0.17%).

Phosphate

Not more than 1.0%, calculated as PO_4, when determined by the following method. Dissolve 25 mg in 10 mL of *water*, add 4 mL of 1M *sulfuric acid*, 1 mL of *ammonium molybdate solution* and 2 mL of *methylaminophenol—sulfite reagent* and allow to stand for 15 minutes. Add sufficient *water* to produce 25 mL, allow to stand for a further 15 minutes and measure the *absorbance* of a 4 cm layer of the resulting solution at 730 nm, Appendix II B. Calculate the content of phosphate from a calibration curve prepared by treating suitable volumes of a 0.00143% w/v solution of *potassium dihydrogen orthophosphate* in the same manner.

Loss on drying

When dried at 100° at a pressure not exceeding 0.7 kPa for 3 hours, loses not more than 5.0% of its weight. Use 1 g.

ASSAY

For Cl

Mix 0.25 g with 1 g of *anhydrous sodium carbonate* in a nickel crucible about 3 cm in diameter, fill the crucible completely with *anhydrous sodium carbonate* and invert into a nickel crucible about 4 cm in diameter; cover the smaller crucible with *anhydrous sodium carbonate*, well pressed down, using about 25 g of *anhydrous sodium carbonate* in all. Heat for 30 minutes at a dull red heat, cool, transfer to a 400 mL beaker, add 150 mL of *water* and boil gently for 10 minutes. Filter through absorbent cotton into a 600 mL beaker, washing the residue thoroughly with hot *water*, until about 400 mL of filtrate has been collected. Cool, cautiously add *nitric acid* until the solution is neutral to *litmus paper* and add 3 mL of *nitric acid* in excess. Add 50 mL of *0.1M silver nitrate VS*, allow to stand until precipitation is complete, filter, wash the precipitate with *water* and titrate the combined filtrate and washings with *0.1M ammonium thiocyanate VS* using *ammonium iron(III) sulfate solution R2* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 3.545 mg of Cl.

For $C_2H_3Cl_3NaO_4P$

Heat 0.2 g in a Kjeldahl flask with 2 mL of *sulfuric acid* and 2.5 mL of *nitric acid* until brown fumes cease to be evolved, cool, add 1 mL of *nitric acid* and heat again. Continue adding *nitric acid* and heating until brown fumes are no longer evolved and the solution is colourless when cold. Heat until dense, white fumes are evolved, cool, transfer the solution to a flask with the aid of 150 mL of *water*, add 50 mL of *citric—molybdic acid solution* and heat slowly to boiling. Swirling the flask continuously, add 25 mL of *quinoline solution* at first drop wise and then in a steady stream, heat on a water bath for 5 minutes and cool. Filter, wash the precipitate with *water* until free from acid, transfer the precipitate to a flask with the aid of 100 mL of *water*, add 50 mL of *0.5M sodium hydroxide VS* and shake until dissolved. Titrate the excess of alkali with *0.5M hydrochloric acid VS* using *phenolphthalein—thymol blue solution* as indicator. Each mL of *0.5M sodium hydroxide VS* is equivalent to 4.835 mg of $C_2H_3Cl_3NaO_4P$. Correct the result for the content of phosphate, as determined by the test described above; each mg of PO_4 is equivalent to 2.65 mg of $C_2H_3Cl_3NaO_4P$.

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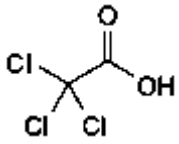
Trichloroacetic Acid

General Notices

(Ph. Eur. monograph 1967)



$C_2HCl_3O_2$ 163.4 *76-03-9*

Preparation

Trichloroacetic Acid Solution

Ph Eur

DEFINITION

2,2,2-Trichloroacetic acid.

Content

98.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline mass or colourless crystals, very deliquescent.

Solubility

Very soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *Ph. Eur. reference spectrum of trichloroacetic acid*.

B. To 0.5 mL of solution S (see Tests) add 2 mL of *pyridine R* and 5 mL of *strong sodium hydroxide solution R*. Shake vigorously and heat in a water-bath at 60-70 °C for 5 min. The upper layer shows an intense red colour.

C. Solution S is strongly acidic (*2.2.4*).

TESTS

Solution S

Dissolve 2.5 g in *water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 16.34 mg of $C_2HCl_3O_2$.

STORAGE

In an airtight container.

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Trichloroacetic Acid Solution

General Notices

Trichloroacetic Acid Cutaneous Solution

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in the treatment of warts.

DEFINITION

Trichloroacetic Acid Solution is a *cutaneous solution*. It contains Trichloroacetic Acid in Purified Water.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements. Where appropriate, the solution also complies with the requirements stated under Unlicensed Medicines.

Content of trichloroacetic acid, $C_2HCl_3O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The solution, diluted with *water* to contain 10% w/v of Trichloroacetic Acid, is strongly acidic, Appendix V K.

B. Dilute a quantity of the solution with sufficient *water* to produce a solution containing 10% w/v of Trichloroacetic Acid. To 0.5 mL of this solution add 2 mL of *pyridine* and 5 mL of *strong sodium hydroxide solution*. Shake vigorously and heat in a water-bath at 60° to 70° for 5 minutes; the upper layer shows an intense red colour.

TESTS

Chlorides

Dilute a quantity of the solution with sufficient *water* to produce a solution containing 10% w/v of Trichloroacetic Acid and dilute 5 mL of this solution to 15 mL with *water*. The resulting solution complies with the *limit test for chlorides*, Appendix VII (100 ppm).

ASSAY

Dilute a quantity of the solution with *water* to contain 0.18% w/v of Trichloroacetic Acid. Titrate with 0.1M *sodium hydroxide*, determining the end-point potentiometrically, Appendix VIII B.

Each mL of 0.1M *sodium hydroxide* is equivalent to 16.34 mg of $C_2HCl_3O_2$

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STORAGE

Trichloroacetic Acid Solution should be protected from light.

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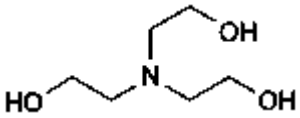
Triethanolamine

General Notices

(Trolamine, Ph. Eur. monograph 1577)



$C_6H_{15}NO_3$ 149.2 *102-71-6*

Action and use

Pharmaceutical aid.

Ph Eur

DEFINITION

2,2′,2″-Nitrilotriethanol.

Content

99.0 per cent *m/m* to 103.0 per cent *m/m* of total bases (anhydrous substance).

CHARACTERS

Appearance

Clear, viscous, colourless or slightly yellow liquid, very hygroscopic.

Solubility

Miscible with water and with ethanol (96 per cent), soluble in methylene chloride.

IDENTIFICATION

First identification: B, C.

Second identification: A, B, D.

A. Relative density (2.2.5): 1.120 to 1.130.

B. Refractive index (2.2.6): 1.482 to 1.485.

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C. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

D. To 1 mL add 0.3 mL of *copper sulfate solution R*. A blue colour develops. Add 2.5 mL of *dilute sodium hydroxide solution R* and heat to boiling. The blue colour remains unchanged.

TESTS

Solution S

Dissolve 12 g in *water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

Related substances

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 5.0 g of *3-aminopropanol R* in *water R* and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 10.0 g of the substance to be examined in *water R*. Add 1.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Reference solution (a) Dissolve 1.0 g of *trolamine CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dissolve 0.1 g of *trolamine impurity A CRS*, 0.5 g of *trolamine impurity B CRS* and 0.1 g of *trolamine CRS* in *water R* and dilute to 10.0 mL with the same solvent. To 1.0 mL of this solution add 1.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.50 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:35.

Temperature:

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	Time (min)	Temperature (°C)
Column	0	60
	0 - 8.5	60 → 230
	8.5 - 14	230
Injection port		260
Detector		280

Detection Flame ionisation.

Injection 2 µL; if necessary inject a blank solution.

Elution order Impurity A, 3-aminopropanol, impurity B, trolamine.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to 3-aminopropanol and impurity A.

Limits:

— *impurity A*: calculate the ratio (*R1*) of the area of the peak due to impurity A to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (b); from the chromatogram obtained with the test solution, calculate the ratio of the area of any peak due to impurity A to the area of the peak due to the internal standard: this ratio is not greater than *R1* (0.1 per cent);

— *impurity B*: calculate the ratio (*R2*) of the area of the peak due to impurity B to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (b); from the chromatogram obtained with the test solution, calculate the ratio of the area of any peak due to impurity B to the area of the peak due to the internal standard: this ratio is not greater than *R2* (0.5 per cent);

— *total*: calculate the ratio (*R4*) of the area of the peak due to trolamine to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (b); from the chromatogram obtained with the test solution, calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than 10 times *R4* (1.0 per cent);

— *disregard limit*: 0.5 times the ratio of the area of the peak due to trolamine to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity C

Gas chromatography (*2.2.28*).

Solvent mixture *acetone R*, *chloroform R* (10:50 *V/V*).

Preparation of solid phase extraction columns

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Column A Fill a glass chromatography column (*l* = 400 mm; Ø = 20 mm) fitted with a polytetrafluoroethylene stopcock and a sintered-glass filter (160) (2.1.2) with 3 g of anhydrous sodium sulfate R and cover with a mixture of 17 g of kieselguhr for chromatography R and 3 g of potassium carbonate R. Settle the column bed by gently tapping the column.

Column B Fill a glass chromatography column (*l* = 400 mm; Ø = 20 mm) fitted with a polytetrafluoroethylene stopcock and a sintered-glass filter (160) (2.1.2) with a slurry of 25 g of silica gel for chromatography R (0.063 to 0.200 mm) in the solvent mixture. Apply slight pressure to settle the column and cover the column bed with 5 g of anhydrous sodium sulfate R.

Standard solution (a) Dissolve 50 µL of N-nitrosodiethanolamine R (impurity C) in methanol R and dilute to 50.0 mL with the same solvent. Dilute 100 µL of this solution to 100.0 mL with methanol R.

Standard solution (b) Dilute 10.0 mL of standard solution (a) to 50.0 mL with methanol R.

Standard solution (c) Dissolve 50 mg of N-nitrosodiisopropanolamine R in methanol R and dilute to 50.0 mL with the same solvent. Dilute 100 µL of this solution to 100.0 mL with methanol R.

Test solution To 2.000 g of the substance to be examined add 200 µL of methanol R and 0.5 g of sulfamic acid R. Dissolve in 8 mL of water for chromatography R and apply the solution to column A. Rinse the vessel twice with 1.5 mL of water for chromatography R, applying the rinsings to the column as well. After 15 min of equilibration time elute the column with 100 mL of ethyl acetate R, collecting the eluate in a 250 mL distillation flask. Evaporate the eluate to dryness. Take up the residue in 1 mL of the solvent mixture, apply to column B and let it settle. Rinse the flask twice with 2 mL of the solvent mixture, apply the rinsings to the column and let it settle. Wash the column with 100 mL of the solvent mixture and discard. Elute the column with 120 mL of acetone R, collecting the eluate in a 250 mL distillation flask. Evaporate the eluate to dryness. Transfer the residue with the aid of a small volume of acetone R into a vial and evaporate again to dryness under a stream of nitrogen R. Dissolve the residue in 100 µL of trimethylpentane for chromatography R, add 100 µL of N-methyltrimethylsilyl-trifluoroacetamide R and heat at 70 °C for 1 h.

Reference solution (a) To 2.000 g of the substance to be examined add 200 µL of standard solution (b) and 0.5 g of sulfamic acid R. Dissolve in 8 mL of water for chromatography R, then proceed exactly as described for the test solution.

Reference solution (b) To 1.0 mL of standard solution (a) add 4.0 mL of standard solution (c) and mix. Transfer 500 µL of the solution to a vial and evaporate to dryness under a stream of nitrogen R. Dissolve the residue in 200 µL of trimethylpentane for chromatography R, add 200 µL of N-methyltrimethylsilyl-trifluoroacetamide R and heat at 70 °C for 1 h.

Reference solution (c) In a vial, evaporate 200 µL of standard solution (b) to dryness under a stream of nitrogen R. Dissolve the residue in 100 µL of trimethylpentane for chromatography R, add 100 µL of N-methyltrimethylsilyl-trifluoroacetamide R and heat at 70 °C for 1 h.

Blank solution In a gas chromatography vial, evaporate 200 µL of methanol R to dryness under a stream of nitrogen R. Dissolve the residue in 100 µL of trimethylpentane for chromatography R add 100 µL of N-methyltrimethylsilyl-trifluoroacetamide R and heat at 70 °C for 1 h.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m; Ø = 0.25 mm;

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— *stationary phase*: *base-deactivated phenyl(5)methyl(95)polysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	180 → 280
	5 - 10	280
Injection port		220

Detection Chemoluminescence:

— dual plasma burner in nitrosamine mode;

— burner temperature: 450 °C;

— oxygen flow rate: 4.4-5.0 mL/min.

Injection 4 µL.

System suitability:

— *resolution*: minimum 1.3 between the peaks due to impurity C and *N*-nitrosodiisopropanolamine in the chromatogram obtained with reference solution (b);

— *recovery*: minimum 50 per cent. The difference between the area of the peak due to impurity C in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution is not less than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c).

Limits:

— *impurity C*: not more than the difference between the area of the peak due to impurity C in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (24).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.000 g.

Open the titration vessel, introduce the substance to be examined directly into the previously titrated solvent. Stopper the flask immediately.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g. Do not carry out the initial heating on a water-bath.

ASSAY

Dissolve 1.200 g in 75 mL of *carbon dioxide-free water R*. Add 0.3 mL of *methyl red solution R*. Titrate with *1 M hydrochloric acid*.

1 mL of *1 M hydrochloric acid* is equivalent to 0.149 g of $C_6H_{15}NO_3$.

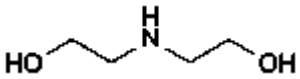
STORAGE

In an airtight container, protected from light.

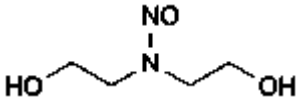
IMPURITIES

Specified impurities *A, B, C.*

A. 2-aminoethanol (ethanolamine),



B. 2,2′-iminodiethanol (diethanolamine),



C. 2,2′-(nitrosoimino)diethanol (*N*-nitrosodiethanolamine).

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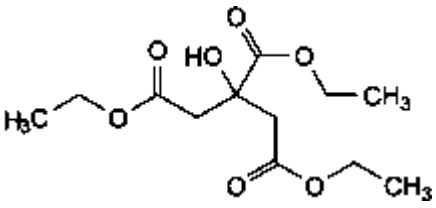
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Triethyl Citrate

General Notices

(Ph. Eur. monograph 1479)



$C_{12}H_{20}O_7$ 276.3 *77-93-0*

Action and use

Excipient.

Ph Eur

DEFINITION

Triethyl 2-hydroxypropane-1,2,3-tricarboxylate.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Clear, viscous, colourless or almost colourless, hygroscopic liquid.

Solubility

Soluble in water, miscible with ethanol (96 per cent), slightly soluble in fatty oils.

IDENTIFICATION

First identification: A, B.

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Second identification: A, C, D.

A. Refractive index (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of triethyl citrate*.

C. It gives the reaction of esters (2.3.1).

D. To 0.5 mL add 5 mL of *ethanol (96 per cent) R* and 4 mL of *dilute sodium hydroxide solution R*. Boil under reflux for about 10 min. 2 mL of the solution gives the reaction of citrates (2.3.1).

TESTS

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Acidity

Dilute 10 g with 10 mL of previously neutralised *ethanol (96 per cent) R*, add 0.5 mL of *bromothymol blue solution R2*. Not more than 0.3 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Refractive index (2.2.6)

1.440 to 1.446.

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution Dissolve 1.0 mL of the substance to be examined in *methylene chloride R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 1.0 mL of the substance to be examined and 0.5 mL of *methyl tridecanoate R* in *methylene chloride R*, then dilute to 50.0 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity About 26 cm/s.

Split ratio About 1:50.

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Temperature:

— *column*: 200 °C;

— *injection port and detector*: 220 °C.

Detection Flame ionisation.

Injection 1.0 µL.

Run time Twice the retention time of triethyl citrate.

Retention time Triethyl citrate = about 34 min.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to triethyl citrate and methyl tridecanoate.

Limits:

— *any impurity*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *disregard limit*: 0.04 per cent.

Water (*2.5.12*)

Maximum 0.25 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Introduce 1.500 g into a 250 mL borosilicate-glass flask fitted with a reflux condenser. Add 25 mL of *2-propanol R*, 50 mL of *water R*, 25.0 mL of *1 M sodium hydroxide* and a few glass beads. Heat under a reflux condenser for 1 h. Allow to cool. Add 1 mL of *phenolphthalein solution R1* and titrate with *1 M hydrochloric acid*. Carry out a blank titration.

1 mL of *1 M sodium hydroxide* is equivalent to 92.1 mg of $C_{12}H_{20}O_7$.

STORAGE

In an airtight container.

IMPURITIES

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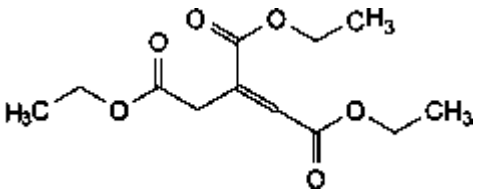

A. triethyl propene-1,2,3-tricarboxylate (triethyl aconitate).

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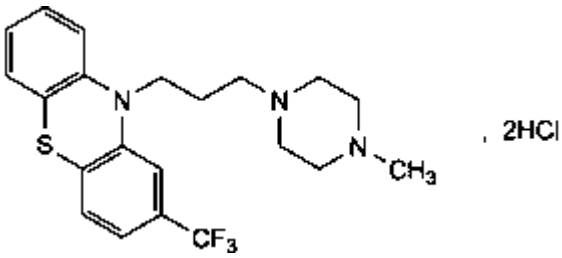
Trifluoperazine Hydrochloride

General Notices

(Ph. Eur. monograph 0059)



$C_{21}H_{26}Cl_2F_3N_3S$ 480.4 *440-17-5*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Trifluoperazine Tablets

Ph Eur

DEFINITION

Trifluoperazine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)-10*H*-phenothiazine dihydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white to pale yellow, crystalline powder, hygroscopic, freely soluble in water, soluble in ethanol (96 per cent).

It melts at about 242 °C, with decomposition.

IDENTIFICATION

A. *Protect the solutions from bright light and measure the absorbances immediately.* Dissolve 50 mg in *0.1 M hydrochloric acid* and dilute to 500 mL with the same acid. Examined between 280 nm and 350 nm, the solution shows an absorption maximum (2.2.25) at 305 nm.

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Dilute 5 mL of the solution to 100 mL with *0.1 M hydrochloric acid*. Examined between 230 nm and 280 nm, this solution shows an absorption maximum at 255 nm. The specific absorbance at this maximum is about 650.

B. It complies with the identification test for phenothiazines by thin-layer chromatography (*2.3.3*): use *trifluoperazine hydrochloride CRS* to prepare the reference solution.

C. Place 0.25 g in a 100 mL separating funnel, add 5 mL of *water R* and 2 mL of *dilute sodium hydroxide solution R*. Shake vigorously with 20 mL of *ether R*. Wash the ether layer with 5 mL of *water R*, add 0.15 g of *maleic acid R* and evaporate the ether. The residue, recrystallised from 30 mL of *alcohol R* and dried, melts (*2.2.14*) at about 192 °C.

D. Dissolve about 0.5 mg in 1 mL of *water R*, add 0.1 mL of *bromine water R* and shake for about 1 min. Add dropwise 1 mL of *sulfuric acid R* with constant, vigorous agitation. A red colour develops.

E. Dissolve about 50 mg in 5 mL of *water R* and add 2 mL of *nitric acid R*. A dark-red colour develops which turns to pale yellow. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

pH (*2.2.3*)

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent. The pH of the solution is 1.6 to 2.5.

Related substances

Carry out the test protected from bright light.

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel GF_{254} plate R*.

Test solution Dissolve 0.2 g of the substance to be examined in a mixture of 5 volumes of *diethylamine R* and 95 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents. Prepare immediately before use.

Reference solution Dilute 1 mL of the test solution to 200 mL with a mixture of 5 volumes of *diethylamine R* and 95 volumes of *methanol R*.

Apply to the plate 10 µL of each solution. Develop over a path of 12 cm using a mixture of 10 volumes of *acetone R*, 10 volumes of *diethylamine R* and 80 volumes of *cyclohexane R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Loss on drying (*2.2.32*)

Not more than 1.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.200 g in 50 mL of *alcohol R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 48.04 mg of $C_{21}H_{26}Cl_2F_3N_3S$.

STORAGE

Store in an airtight container, protected from light.

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Trifluoperazine Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Trifluoperazine Tablets contain Trifluoperazine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of trifluoperazine, $C_{21}H_{24}F_3N_3S$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 20 mg of trifluoperazine with 30 mL of 1M *hydrochloric acid* for 10 minutes, filter, make the filtrate alkaline to *litmus paper* with 5M *sodium hydroxide* and extract with two 20 mL quantities of *petroleum spirit* (*boiling range, 60° to 80°*). Combine the extracts, wash with 10 mL of *water*, shake with 5 g of *anhydrous sodium sulfate*, filter and evaporate the filtrate carefully to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of trifluoperazine (*RS 351*).

B. Extract a quantity of the powdered tablets containing the equivalent of 5 mg of trifluoperazine with 5 mL of *acetone*, filter and evaporate the filtrate to dryness. Add 2 mL of *sulfuric acid* to the residue and allow to stand for 5 minutes. An orange colour is produced.

C. Extract a quantity of the powdered tablets containing the equivalent of 7 mg of trifluoperazine with 5 mL of *acetone*, filter and evaporate the filtrate to dryness. Separately, heat 0.5 mL of *chromic-sulfuric acid mixture* in a small test tube in a water bath for 5 minutes; the solution readily wets the sides of the tube and there is no greasiness. Add the residue to the acid mixture and heat again on a water bath for 5 minutes; the solution does not wet the sides of the tube and does not pour easily from the tube.

TESTS

Uniformity of content

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of trifluoperazine comply with the requirements stated under Tablets using the following method of analysis. Carry out the following procedure protected from light. Place one tablet in a 100 mL graduated flask, add 50 mL of a mixture of 5 volumes of *hydrochloric acid* and 95 volumes of *water*, shake until the tablet has completely disintegrated, dilute to volume with the same solvent, mix and filter, discarding the first 10 mL of filtrate. Measure the *absorbance* of the filtrate at the maximum at 256 nm, Appendix II B. Calculate the content of $C_{21}H_{24}F_3N_3S$ taking 743 as the value of A(1%, 1 cm) at the maximum at 256 nm.

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ASSAY

Carry out the following procedure protected from light. Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 5 mg of trifluoperazine for 15 minutes with 400 mL of a mixture of 5 volumes of *hydrochloric acid* and 95 volumes of *water*, dilute to 500 mL with the same mixture, mix and filter. Measure the *absorbance* of the filtrate at the maximum at 256 nm, Appendix II B. Calculate the content of $C_{21}H_{24}F_3N_3S$ taking 743 as the value of A(1%, 1 cm) at the maximum at 256 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of trifluoperazine.

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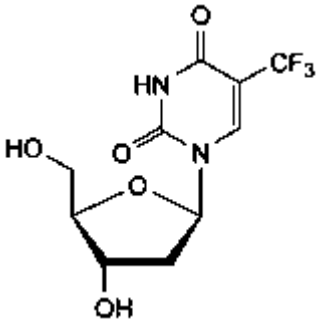
Trifluridine

General Notices

(Ph. Eur. monograph 2910)



$C_{10}H_{11}F_3N_2O_5$ 296.2 *70-00-8*

Action and use

Pyrimidine nucleoside analogue; antiviral (herpes viruses).

Preparation

Trifluridine Eye Drops

Ph Eur

DEFINITION

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble to slightly soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

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IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *trifluridine CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 47 to + 51 (dried substance).

Dissolve 0.300 g in *water R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light. Use the solutions within 12 h.*

Solvent mixture Mobile phase B, mobile phase A (5:95 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 20.0 mg of *trifluridine CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *5-carboxyuracil R* (impurity C) in 95 mL of mobile phase A and dilute to 100 mL with mobile phase B. Dilute 1 mL of the solution to 10 mL with the solvent mixture (solution A). Dissolve the contents of a vial of *trifluridine impurity A CRS* in 1 mL of solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 7.8 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 6.0 with *ammonia R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	95	5

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
3 - 10	95 → 85	5 → 15
10 - 15	85	15

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 263 nm.

Autosampler Set at 4 °C.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and C.

Relative retention With reference to trifluridine (retention time = about 13.8 min): impurity C = about 0.19; impurity A = about 0.21.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities C and A.

Calculation of percentage contents:

— for each impurity, use the concentration of trifluridine in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{10}H_{11}F_3N_2O_5$ taking into account the assigned content of *trifluridine CRS*.

IMPURITIES

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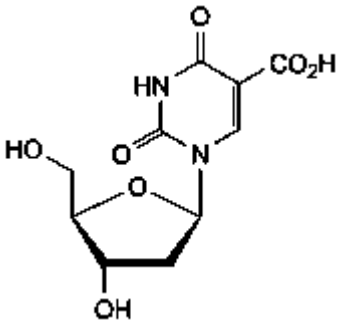
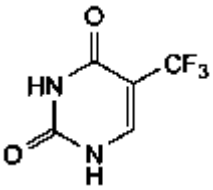
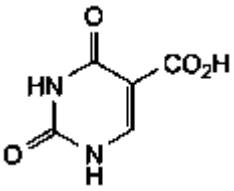
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E.*



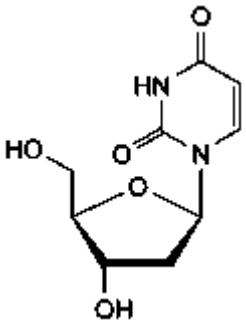
A. 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid,



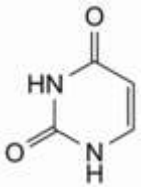
B. 5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione,



C. 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (5-carboxyuracil),



D. 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione,



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E. pyrimidine-2,4(1*H*,3*H*)-dione (uracil).

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Trifluridine Eye Drops

General Notices

Trifluorothymidine Eye Drops

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Pyrimidine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Trifluridine Eye Drops are a sterile solution of Trifluridine in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of trifluridine, $C_{10}H_{11}F_3N_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Evaporate a volume of the eye drops containing 0.1 g of Trifluridine to dryness using a rotary evaporator and dry at 60° under reduced pressure. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of trifluridine (*RS 469*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 5 volumes of *acetonitrile* and 95 volumes of a 0.05M solution of *sodium dihydrogen orthophosphate* which has been adjusted to pH 6.0 with *ammonia*.

(1) Dilute a volume of the eye drops, if necessary, to produce a solution containing 0.02% w/v of Trifluridine.

(2) Dilute 1 volume of solution (1) to 100 volumes.

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(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.02% w/v of *trifluridine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05M *sodium dihydrogen orthophosphate*, adjusted to pH 6.0 with *ammonia*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	95	5	isocratic
3-10	95→85	5→15	linear gradient
10-15	85	15	isocratic
15-16	85→95	15→5	linear gradient
16-25	95	5	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (4) closely resembles the chromatogram supplied with *trifluridine impurity standard BPCRS*;

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to 5-carboxy-2'-deoxyuridine (impurity A) and 5-carboxyuracil (impurity C) is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities C, D and E using solution (4) and multiply the areas of these peaks by the corresponding correction factors: impurity C, 0.6; impurity D, 0.7; impurity E, 0.4.

In the chromatogram obtained with solution (1):

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the areas of any peaks corresponding to 5-carboxy-2'-deoxyuridine (impurity A) or 5-(trifluoromethyl)uracil (impurity B) are not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than half the area of the peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 5 volumes of *acetonitrile* and 95 volumes of a 0.05M solution of *sodium dihydrogen orthophosphate* which has been adjusted to pH 6.0 with *ammonia*.

(1) Dilute a volume of the eye drops, if necessary, to produce a solution containing 0.02% w/v of Trifluridine.
(2) 0.02% w/v of *trifluridine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{11}F_3N_2O_5$ in the eye drops using the declared content of $C_{10}H_{11}F_3N_2O_5$ in *trifluridine BPCRS*.

STORAGE

Trifluridine Eye Drops should be protected from light and stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Trifluridine.

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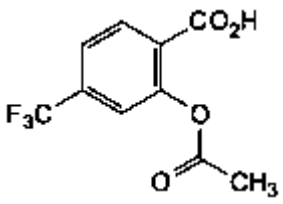
Triflusal

General Notices

(Ph. Eur. monograph 1377)



$C_{10}H_7F_3O_4$ 248.2 *322-79-2*

Action and use

Thromboxane synthesis inhibitor; antiplatelet drug.

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DEFINITION

2-(Acetyloxy)-4-(trifluoromethyl)benzoic acid.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in anhydrous ethanol, freely soluble in methylene chloride.

mp

About 118 °C, with decomposition.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *triflusal CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in *acetonitrile R* and dilute to 20.0 mL with the same solvent. *Prepare the solution immediately before use.*

Reference solution (a) Dissolve 5.0 mg of *triflusal impurity B CRS* in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 25.0 mL with *acetonitrile R*.

Reference solution (c) Dissolve 2.5 mg of the substance to be examined in *acetonitrile R*, add 5 mL of reference solution (a) and dilute to 10.0 mL with *acetonitrile R*. *Prepare the solution immediately before use.*

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4-5 µm).

Mobile phase:

— *mobile phase A*: 0.5 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	80 → 30	20 → 70
20 - 25	30	70

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 237 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to triflusal (retention time = about 11 min): impurity B = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to triflusal and impurity B.

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Limits:

— *impurity B*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *sum of impurities other than B*: not more than 0.5 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *disregard limit*: 0.25 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.200 g in 50 mL of *anhydrous ethanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M sodium hydroxide* is equivalent to 24.82 mg of $C_{10}H_7F_3O_4$.

STORAGE

In an airtight container, at a temperature not exceeding 25 °C.

IMPURITIES

Specified impurities B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D.

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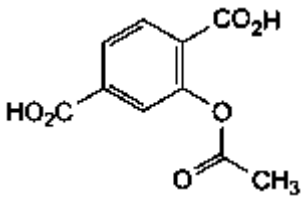
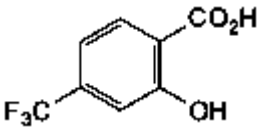
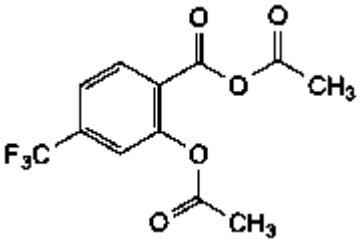


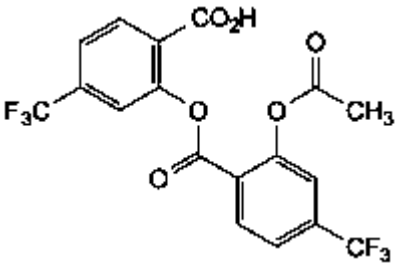
A. 2-(acetyloxy)benzene-1,4-dicarboxylic acid (2-acetoxyterephthalic acid),



B. 2-hydroxy-4-(trifluoromethyl)benzoic acid (4-(trifluoromethyl)salicylic acid),



C. acetic 2-(acetyloxy)-4-(trifluoromethyl)benzoic anhydride,



D. 2-[[2-(acetyloxy)-4-(trifluoromethyl)benzoyl]oxy]-4-(trifluoromethyl)benzoic acid.

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Triglycerol Diisostearate

General Notices

(Ph. Eur. monograph 2032)

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DEFINITION

Mixture of polyglycerol diesters of mainly isostearic acid, obtained by esterification of polyglycerol and isostearic acid. The polyglycerol consists mainly of triglycerol.

CHARACTERS

Appearance

Clear, yellowish, viscous liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent) and with fatty oils.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Film between 2 plates of *sodium chloride R*.

Comparison *triglycerol diisostearate CRS*.

B. Composition of fatty acids (see Tests).

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_3 (*2.2.2, Method I*).

Mix 10 mL with 10 mL of *ethanol (96 per cent) R*.

Acid value (*2.5.1*)

Maximum 3.0, determined on 1.0 g.

Hydroxyl value (*2.5.3, Method A*)

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180 to 230, determined on 0.25 g.

Iodine value (*2.5.4, Method B*)

Maximum 5.0.

Peroxide value (*2.5.5, Method B*)

Maximum 6.0.

Saponification value (*2.5.6*)

128 to 160.

Composition of fatty acids (*2.4.22, Method B*)

Use the mixture of calibrating substances in Table 2.4.22.-1.

Composition of the fatty-acid fraction of the substance:

— *sum of the contents of the fatty acids eluting between palmitic acid and stearic acid*: minimum 60.0 per cent;

— *sum of the contents of myristic acid, palmitic acid and stearic acid*: maximum 11.0 per cent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash

Maximum 0.5 per cent, determined on 1.0 g.

Heat a silica crucible to redness for 30 min, allow to cool in a desiccator and weigh. Evenly distribute 1.00 g of the substance to be examined in the crucible and weigh. Dry at 100-105 °C for 1 h and ignite in a muffle furnace at 600 °C ± 25 °C until the substance is thoroughly charred. Carry out the test for sulfated ash (*2.4.14*) on the residue obtained, starting with “Moisten the substance to be examined...”.

STORAGE

In an airtight container, protected from light.

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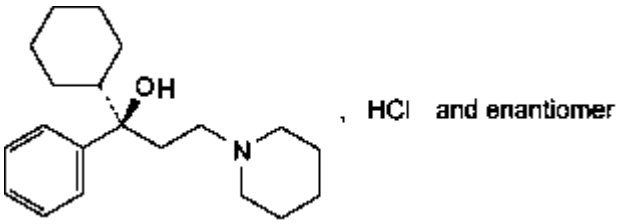
Trihexyphenidyl Hydrochloride

General Notices

(Ph. Eur. monograph 1626)



$C_{20}H_{32}ClNO$ 337.9 *52-49-3*

Action and use

Anticholinergic.

Preparation

Trihexyphenidyl Tablets

Ph Eur

DEFINITION

(1*RS*)-1-Cyclohexyl-1-phenyl-3-(piperidin-1-yl)propan-1-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in ethanol (96 per cent) and in methylene chloride.

mp

About 250 °C, with decomposition.

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IDENTIFICATION

First identification A, D.

Second identification B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison trihexyphenidyl hydrochloride CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in a mixture of 20 volumes of methanol R and 80 volumes of methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 25 mg of trihexyphenidyl hydrochloride CRS in a mixture of 20 volumes of methanol R and 80 volumes of methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Plate TLC silica gel G plate R.

Mobile phase diethylamine R, hexane R (5:95 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 0.1 g/L solution of chloroplatinic acid R in hydrochloric acid R containing 0.4 per cent *V/V* of hydriodic acid R.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 0.5 g in 5 mL of warm methanol R and make just alkaline to red litmus paper R with sodium hydroxide solution R. A precipitate is formed which, after recrystallisation from methanol R, melts (2.2.14) at about 113°C to 115 °C.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

5.2 to 6.2.

Dissolve 0.5 g with heating in 25 mL of carbon dioxide-free water R. Cool to room temperature and dilute to 50 mL with carbon dioxide-free water R.

Optical rotation (2.2.7)

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-0.10° to + 0.10°.

Dissolve 1.25 g in a mixture of 20 volumes of *methanol R* and 80 volumes of *methylene chloride R* and dilute to 25.0 mL with the same mixture of solvents.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase. Dilute 10.0 mL to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 10.0 mg of *trihexyphenidyl impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 100.0 mL with the mobile phase.

Reference solution (d) To 1 mL of reference solution (b), add 1 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 200 mL of *water R* with 0.2 mL of *triethylamine R*. Adjust to pH 4.0 with *phosphoric acid R* and add 800 mL of *acetonitrile R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time 3 times the retention time of trihexyphenidyl.

System suitability Reference solution (d):

— *resolution*: minimum 4.0 between the peaks due to trihexyphenidyl and to impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 0.5 per cent;

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— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

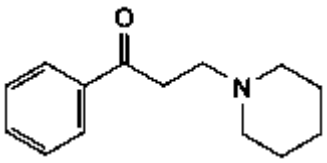
Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mLof *0.1 M sodium hydroxide* is equivalent to 33.79 mg of $C_{20}H_{32}ClNO$.

IMPURITIES



A. 1-phenyl-3-(piperidin-1-yl)propan-1-one.

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Trihexyphenidyl Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Trihexyphenidyl Tablets contain Trihexyphenidyl Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of trihexyphenidyl hydrochloride, $C_{20}H_{31}NO,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Trihexyphenidyl Hydrochloride with 20 mL of *water* and filter. The filtrate yields a yellow precipitate with *picric acid solution R1* and a white precipitate with 5M *sodium hydroxide*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets with sufficient *chloroform* to produce a solution containing 0.2% w/v of Trihexyphenidyl Hydrochloride and filter.

(2) 0.2% w/v of *trihexyphenidyl hydrochloride BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 50 mg of Trihexyphenidyl Hydrochloride with 10 mL of *water*, add 10 mL of *methanol*, disperse with the aid of ultrasound for 5 minutes, shake for 15 minutes, add sufficient *methanol* to produce 25 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol* (*60%*).
(3) 0.2% w/v of *trihexyphenidyl hydrochloride BPCRS* and 0.01% w/v of *3-piperidylpropiophenone hydrochloride BPCRS* in *methanol* (*60%*).
(4) Dilute 1 volume of solution (2) to 10 volumes with *methanol* (*60%*).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Trihexyphenidyl Hydrochloride comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of *water* to one tablet and mix with the aid of ultrasound for 5 minutes or until the tablet is dispersed. Add 10 mL of *methanol*, shake for 15 minutes, dilute to 25 mL with *methanol*, mix and filter through a filter with a maximum pore size of 0.2 µm.
(2) 0.008% w/v of *trihexyphenidyl hydrochloride BPCRS* and 0.004% w/v of *3-piperidylpropiophenone hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Resolve C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 210 nm.

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(f) Inject 20 µL of each solution.

MOBILE PHASE

0.2 volumes of *triethylamine*, 200 volumes of *water* and 800 volumes of *acetonitrile*, adjust the pH of the mixture to 4.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{31}NO,HCl$ in each tablet using the declared content of $C_{20}H_{31}NO,HCl$ in *trihexyphenidyl hydrochloride BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of trihexyphenidyl hydrochloride

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of trihexyphenidyl hydrochloride

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of *water* to a quantity of the powdered tablets containing 5 mg of Trihexyphenidyl Hydrochloride and mix with the aid of ultrasound for 5 minutes. Add 10 mL of *methanol*, shake for 15 minutes, dilute to 25 mL with *methanol* and filter through a filter with a maximum pore size of 0.2 µm.
(2) 0.02% w/v of *trihexyphenidyl hydrochloride BPCRS* and 0.01% w/v of *3-piperidylpropiophenone hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{31}NO,HCl$ in the tablets using the declared content of $C_{20}H_{31}NO,HCl$ in *trihexyphenidyl hydrochloride BPCRS*.

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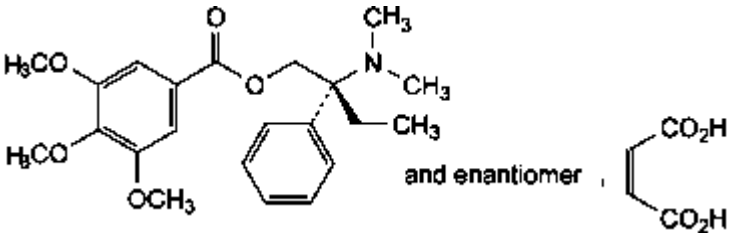
Trimebutine Maleate

General Notices

(Ph. Eur. monograph 2182)



$C_{26}H_{33}NO_9$ 503.5 *34140-59-5*

Action and use

Treatment of irritable bowel syndrome.

Ph Eur

DEFINITION

(2*RS*)-2-(Dimethylamino)-2-phenylbutyl 3,4,5-trimethoxybenzoate (*Z*)-butenedioate.

Content

99.0 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, soluble in acetonitrile, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent).

mp

About 133 °C.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison: *trimebutine maleate CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.5 g in *acetone R*, sonicate and dilute to 100 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Dissolve 0.24 g of *anhydrous sodium dihydrogen phosphate R* in 180 mL of *water R* and adjust to pH 2.5 with *dilute phosphoric acid R*; dilute to 200 mL with *water R*. Add 50 mL of *acetonitrile R* and mix.

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *methyl 3,4,5-trimethoxybenzoate R* (impurity C) in 10 mL of the solvent mixture. Dilute 1 mL of the solution to 20 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *trimebutine for system suitability CRS* (containing impurities D and E) in 1 mL of reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.6 g of *anhydrous sodium dihydrogen phosphate R* in 990 mL of *water for chromatography R* and adjust to pH 3.0 with *phosphoric acid R*; dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	78	22

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
3 - 6.5	78 → 65	22 → 35
6.5 - 15	65 → 60	35 → 40
15 - 35	60	40

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram supplied with *trimebutine for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D and E.

Relative retention With reference to trimebutine (retention time = about 12 min): maleic acid = about 0.17; impurity E = about 0.9; impurity D = about 1.3; impurity C = about 1.4.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities D and C;

— *peak-to-valley ratio*: minimum 10, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to trimebutine.

Limits:

— *impurity E*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to maleic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

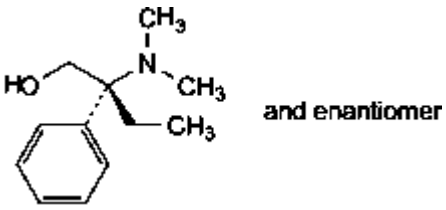
Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 50.35 mg of $C_{26}H_{33}NO_9$.

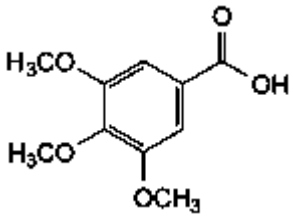
IMPURITIES

Specified impurities E.

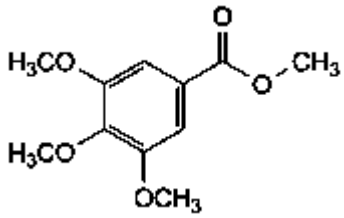
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



A. (2*RS*)-2-(dimethylamino)-2-phenylbutanol,



B. 3,4,5-trimethoxybenzoic acid,



C. methyl 3,4,5-trimethoxybenzoate,

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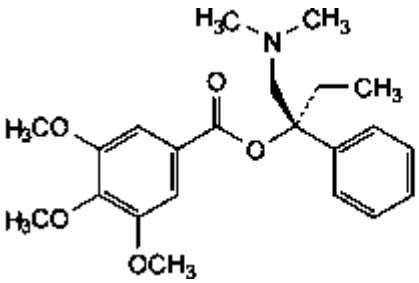
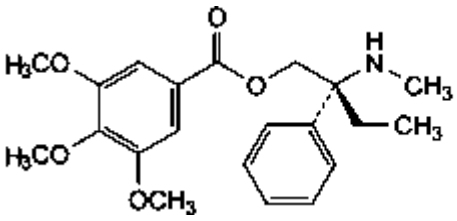


and enantiomer

D. (1*RS*)-1-[(dimethylamino)methyl]-1-phenylpropyl 3,4,5-trimethoxybenzoate,



and enantiomer

E. (2*RS*)-2-(methylamino)-2-phenylbutyl 3,4,5-trimethoxybenzoate.

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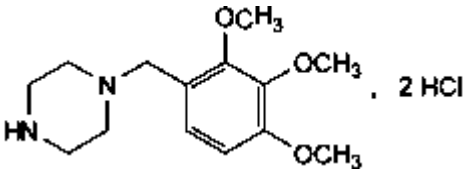
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Trimetazidine Hydrochloride

General Notices

(Trimetazidine Dihydrochloride, Ph. Eur. monograph 1741)



$C_{14}H_{24}Cl_2N_2O_3$ 339.3 *13171-25-0*

Action and use

Vasodilator.

Ph Eur

DEFINITION

1-(2,3,4-Trimethoxybenzyl)piperazine dihydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, slightly hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of trimetazidine dihydrochloride*.

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B. Dissolve 25 mg in 5 mL of *water R*. 2 mL of the solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 1.0 g in *water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 20.0 mg of *trimetazidine for system suitability CRS* in *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with *water R*. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (c) Dilute 25.0 mL of reference solution (b) to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 357 volumes of *methanol R* and 643 volumes of a 2.87 g/L solution of *sodium heptanesulfonate R* adjusted to pH 3.0 with *dilute phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	95 → 75	5 → 25
50 - 52	75 → 95	25 → 5

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

Equilibration For at least 1 h with the mobile phase at the initial composition.

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Injection 10 µL.

Relative retention With reference to trimetazidine (retention time = about 25 min): impurity D = about 0.2; impurity C = about 0.4; impurity H = about 0.6; impurities A and I = about 0.9; impurity E = about 0.95; impurity F = about 1.4; impurity B = about 1.8.

System suitability:

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the principal peak in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (c).

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.55; impurity C = 0.37; impurity F = 0.71;

— *impurities A, B, C, D, E, F, H, I*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Impurity G

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 22.6 mg of *piperazine hydrate R* in *methanol R* and dilute to 100 mL with the same solvent. Dilute 10 mL of the solution to 100 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *alcohol R* (20:80 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying At 100-105 °C for 30 min.

Detection Spray with *iodoplatinate reagent R*.

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Limit:

— *impurity G*: any spot due to impurity G is not more intense than the spot in the chromatogram obtained with the reference solution (0.1 per cent, expressed as anhydrous piperazine).

Loss on drying (2.2.32)

Maximum 2.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C at a pressure not exceeding 15 kPa.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.120 g in 50.0 mL of *water R*. Add 1 mL of *nitric acid R* and titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (2.2.20).

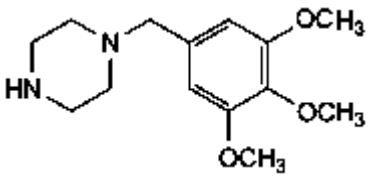
1 mL of *0.1 M silver nitrate* is equivalent to 16.96 mg of $C_{14}H_{24}Cl_2N_2O_3$.

STORAGE

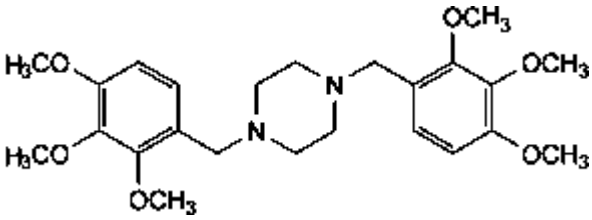
In an airtight container.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I.*



A. 1-(3,4,5-trimethoxybenzyl)piperazine,



B. 1,4-bis(2,3,4-trimethoxybenzyl)piperazine,

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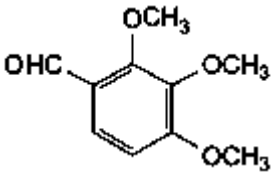
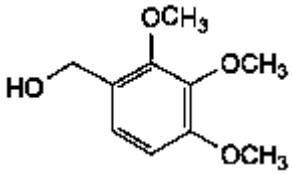
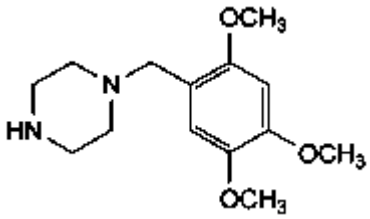


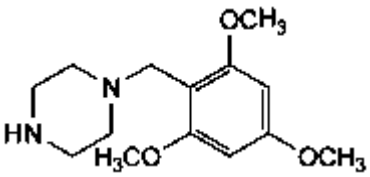
C. 2,3,4-trimethoxybenzaldehyde,



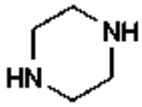
D. (2,3,4-trimethoxyphenyl)methanol,



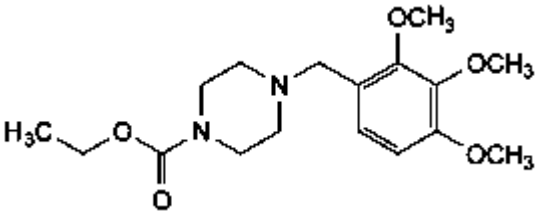
E. 1-(2,4,5-trimethoxybenzyl)piperazine,



F. 1-(2,4,6-trimethoxybenzyl)piperazine,



G. piperazine,



H. ethyl 4-(2,3,4-trimethoxybenzyl)piperazine-1-carboxylate,

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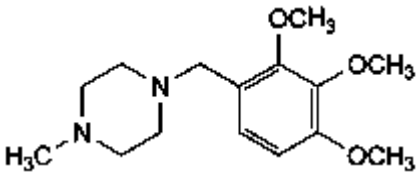

I. 1-methyl-4-(2,3,4-trimethoxybenzyl)piperazine (*N*-methyltrimetazidine).

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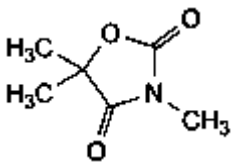
Trimethadione

General Notices

(Ph. Eur. monograph 0440)



$C_6H_9NO_3$ 143.1 *127-48-0*

Action and use

Antiepileptic.

Ph Eur

DEFINITION

3,5,5-Trimethyloxazolidine-2,4-dione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Colourless or almost colourless crystals.

Solubility

Soluble in water, very soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 45 °C to 47 °C, determined without previous drying.

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B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs prepared using 3 mg of substance per 0.4 g of *potassium bromide R*.

Comparison *trimethadione CRS*.

C. To 2 mL of solution S (see Tests) add 1 mL of *barium hydroxide solution R*. A white precipitate is formed, which dissolves on addition of 1 mL of *dilute hydrochloric acid R*.

D. Dissolve 0.3 g in a mixture of 5 mL of *alcoholic potassium hydroxide solution R* and 5 mL of *ethanol (96 per cent) R*. Allow to stand for 10 min. Add 0.05 mL of *phenolphthalein solution R1* and neutralise exactly with *hydrochloric acid R*. Evaporate to dryness on a water-bath and take up the residue with 4 quantities, each of 5 mL, of *ether R*. Filter the combined ether layers and evaporate to dryness. The residue, recrystallised from 5 mL of *toluene R* and dried, melts (2.2.14) at about 80 °C.

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 40 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R*. Not more than 0.1 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.00 g by drying in a desiccator over *anhydrous silica gel R* for 6 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (2.2.28).

Internal standard solution Dissolve 0.125 g of *decanol R* in *anhydrous ethanol R* and dilute to 25 mL with the same solvent.

Test solution Dissolve 0.100 g of the substance to be examined in the internal standard solution and dilute to 10.0 mL with the same solution.

Reference solution Dissolve 0.100 g of *trimethadione CRS* in the internal standard solution and dilute to 10.0 mL with the same solution.

Column:

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— *material*: stainless steel,

— *size*: *l* = 0.75 m, Ø = 3 mm,

— *stationary phase*: *styrene-divinylbenzene copolymer R* (125-150 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 20 mL/min.

Temperature:

— *column*: 210 °C,

— *injection port*: 240 °C,

— *detector*: 270 °C.

Detection Flame ionisation.

Injection 1 µL.

Calculate the content of $C_6H_9NO_3$ from the declared content of *trimethadione CRS*.

STORAGE

Protected from light.

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Trimethoprim

General Notices

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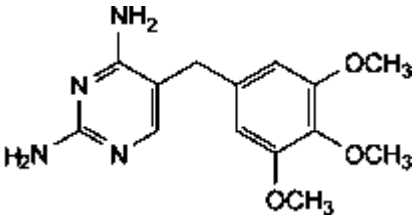

$C_{14}H_{18}N_4O_3$ 290.3 *738-70-5*

Action and use

Dihydrofolate reductase inhibitor; antibacterial.

Preparations

Co-trimoxazole Infusion

Co-trimoxazole Oral Suspension

Paediatric Co-trimoxazole Oral Suspension

Co-trimoxazole Tablets

Co-trimoxazole Dispersible Tablets

Paediatric Co-trimoxazole Tablets

Trimethoprim Oral Suspension

Trimethoprim Tablets

Ph Eur

DEFINITION

5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine.

Content

98.5 per cent to 101.0 per cent (dried substance).

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CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 199 °C to 203 °C.

B. Dissolve about 20 mg in *0.1 M sodium hydroxide* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *0.1 M sodium hydroxide*. Examined between 230 nm and 350 nm (2.2.25), the solution shows an absorption maximum at 287 nm. The specific absorbance at the absorption maximum is 240 to 250.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *trimethoprim CRS*.

D. Dissolve about 25 mg, heating if necessary, in 5 mL of *0.005 M sulfuric acid* and add 2 mL of a 16 g/L solution of *potassium permanganate R* in *0.1 M sodium hydroxide*. Heat to boiling and add to the hot solution 0.4 mL of *formaldehyde R*. Mix, add 1 mL of *0.5 M sulfuric acid*, mix and heat again to boiling. Cool and filter. To the filtrate, add 2 mL of *methylene chloride R* and shake vigorously. The organic layer, examined in ultraviolet light at 365 nm, shows green fluorescence.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Dissolve 0.5 g in 10 mL of a mixture of 1 volume of *water R*, 4.5 volumes of *methanol R* and 5 volumes of *methylene chloride R*.

Related substances

A. Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

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Reference solution (b) Dissolve the contents of a vial of *trimethoprim for system suitability CRS* (containing impurity E) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.250 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 30 volumes of *methanol R* and 70 volumes of a 1.4 g/L solution of *sodium perchlorate R* adjusted to pH 3.6 with *phosphoric acid R*.

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL loop injector.

Run time 11 times the retention time of trimethoprim.

Relative retention With reference to trimethoprim (retention time = about 5 min): impurity C = about 0.8; impurity E = about 0.9; impurity A = about 1.5; impurity D = about 2.0; impurity G = about 2.1; impurity B = about 2.3; impurity J = about 2.7; impurity F = about 4.0.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity E and trimethoprim.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.43; impurity E = 0.53; impurity J = 0.66;

— *any impurity*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.04 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent); disregard any peak corresponding to impurity H (relative retention = about 10.3).

B. Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *trimethoprim CRS* and 5.0 mg of *trimethoprim impurity B CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *nitrile silica gel for chromatography R* (5 µm) with a specific surface area of 350 m^2/g and a pore diameter of 10 nm.

Mobile phase Dissolve 1.14 g of *sodium hexanesulfonate R* in 600 mL of a 13.6 g/L solution of *potassium dihydrogen phosphate R*; adjust to pH 3.1 with *phosphoric acid R* and mix with 400 mL of *methanol R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL loop injector.

Run time 6 times the retention time of trimethoprim.

Relative retention With reference to trimethoprim (retention time = about 4 min): impurity H = about 1.8; impurity I = about 4.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to trimethoprim and impurity B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity H = 0.50; impurity I = 0.28;

— *any impurity*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.04 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent); disregard any peak due to impurity B (relative retention = about 1.3).

Impurity K

Gas chromatography (*2.2.28*).

Test solution Dissolve 0.500 g of the substance to be examined in 35.0 mL of *citrate buffer solution pH 5.0 R*, add 10.0 mL of *1,1-dimethylethyl methyl ether R*, shake thoroughly and centrifuge for 10 min. Use the upper layer.

Reference solution Dilute 5.0 mL of *hydrochloric acid R* to 50.0 mL with *water R*, add 12.5 mg of *aniline R* and shake thoroughly. Add 10.0 µL of this solution and 10.0 mL of *1,1-dimethylethyl methyl ether R* to 35.0 mL of *citrate buffer solution pH 5.0 R*, shake thoroughly and centrifuge for 10 min. Use the upper layer.

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Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 12 mL/min.

Temperature:

— *column*: 80 °C;

— *injection port*: 230 °C;

— *detector*: 270 °C.

Detection Nitrogen-phosphorus detector.

Injection 3 µL.

Run time 15 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 5.0 per cent after 6 injections.

Limit:

— *impurity K*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (5 ppm).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 29.03 mg of $C_{14}H_{18}N_4O_3$.

IMPURITIES

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Test A for related substances

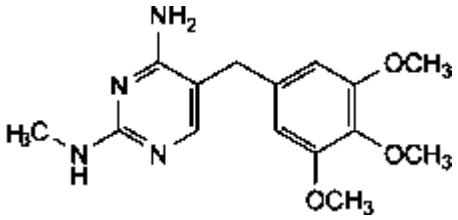
A, B, C, D, E, F, G, H, J.

Test B for related substances

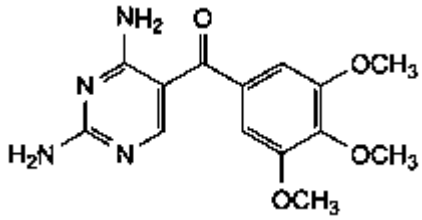
B, H, I.

Test for impurity K

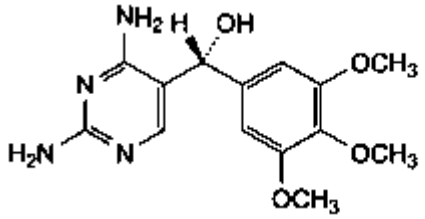
K.



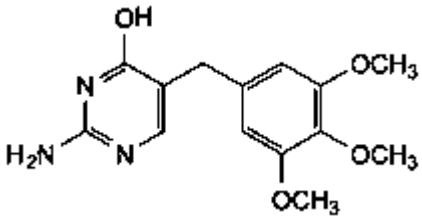
A. N^2-methyl-5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine,



B. (2,4-diaminopyrimidin-5-yl)(3,4,5-trimethoxyphenyl)methanone,



C. (*RS*)-(2,4-diaminopyrimidin-5-yl)(3,4,5-trimethoxyphenyl)methanol,



D. 2-amino-5-(3,4,5-trimethoxybenzyl)pyrimidin-4-ol,

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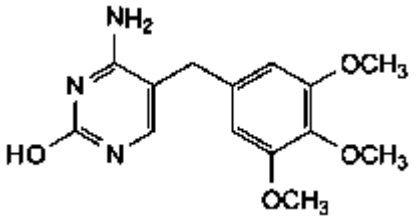
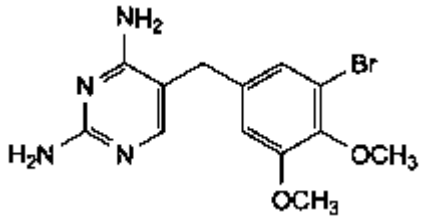
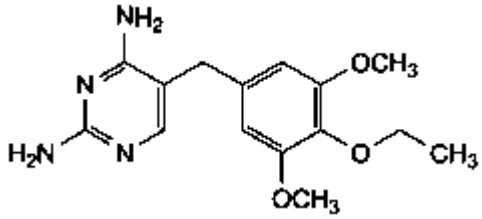


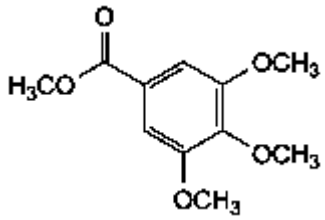
E. 4-amino-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-ol,



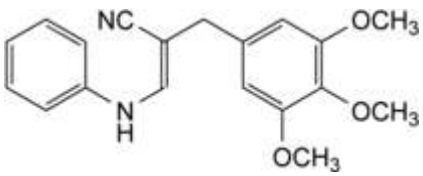
F. 5-(3-bromo-4,5-dimethoxybenzyl)pyrimidine-2,4-diamine,



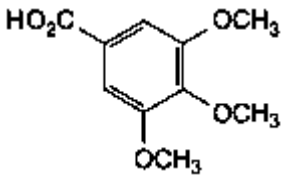
G. 5-(4-ethoxy-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine,



H. methyl 3,4,5-trimethoxybenzoate,



I. 3-(phenylamino)-2-(3,4,5-trimethoxybenzyl)prop-2-enenitrile,



J. 3,4,5-trimethoxybenzoic acid,

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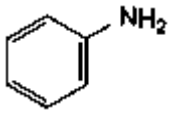

K. aniline.

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Trimethoprim Oral Suspension

General Notices

Action and use

Dihydrofolate reductase inhibitor; antibacterial.

DEFINITION

Trimethoprim Oral Suspension is a suspension of Trimethoprim in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of trimethoprim, $C_{14}H_{18}N_4O_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 15 mL of 0.1M *sodium hydroxide* to a quantity of the oral suspension containing 10 mg of Trimethoprim, extract with 50 mL of *dichloromethane* and wash the dichloromethane extract with two 10-mL quantities of 0.01M *sodium hydroxide*. Retain the sodium hydroxide solutions and repeat the extraction procedure with a further three 50-mL quantities of *dichloromethane*, washing the extracts each time with the same two 10-mL quantities of 0.01M *sodium hydroxide*. Evaporate the combined dichloromethane extracts until about 2 mL remains, transfer the residue to a 10-mL graduated flask with the aid of *dichloromethane*, add sufficient *dichloromethane* to produce 10 mL and mix well.

(2) 0.1% w/v of *trimethoprim BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of 13.5M *ammonia*, 8 volumes of *methanol* and 90 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

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B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 10 mL of *methanol* and 10 mL of the mobile phase to a weighed quantity of the oral suspension containing 10 mg of Trimethoprim, mix with the aid of ultrasound for 5 minutes and add sufficient of the mobile phase to produce 50 mL, mix and filter.

(2) 0.02% w/v of *trimethoprim BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Lichrosorb RP 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 260 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

225 volumes of 0.003M *tetrabutylammonium bromide* in *water*, 225 volumes of a buffer solution prepared as described below and 550 volumes of *methanol*.

For the buffer solution dissolve 1.36 g of *sodium acetate* and 23.4 g of *sodium dihydrogen orthophosphate* in 450 mL of *water*, adjust the pH of the mixture, if necessary, to 5.0 with 0.1M *glacial acetic acid* or 0.1M *sodium hydroxide* and add sufficient *water* to produce 500 mL.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{14}H_{18}N_4O_3$, weight in volume, using the declared content of $C_{14}H_{18}N_4O_3$ in *trimethoprim BPCRS*.

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Trimethoprim Tablets

General Notices

Action and use

Dihydrofolate reductase inhibitor; antibacterial.

DEFINITION

Trimethoprim Tablets contain Trimethoprim.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of trimethoprim, $C_{14}H_{18}N_4O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Trimethoprim with 10 mL of *chloroform*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of trimethoprim (*RS 354*).

B. Shake a quantity of the powdered tablets containing 0.1 g of Trimethoprim with 60 mL of 0.1M *hydrochloric acid* for 20 minutes, add sufficient 0.1M *hydrochloric acid* to produce 100 mL, filter and dilute 5 mL of the filtrate to 250 mL with 0.1M *sodium hydroxide*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum only at 287 nm.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.2 g of Trimethoprim with 50 mL of the mobile phase, filter and use the filtrate. For solution (2) dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable), (b) as the mobile phase with a flow rate of 1.3 mL per minute a 0.14% w/v solution of *sodium perchlorate* in *methanol* (*60%*) adjusted to pH 3.1 with 0.1M *hydrochloric acid* and (c) a detection wavelength of 280 nm.

The *column efficiency*, determined using the peak due to trimethoprim in the chromatogram obtained with solution (2), should be at least 8,000 theoretical plates per metre.

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In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%) and the sum of the areas of any such peaks is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.1 g of Trimethoprim add 100 mL of *glacial acetic acid*, shake for 20 minutes, dilute to 200 mL with *glacial acetic acid* and filter. To 5 mL of the filtrate add 15 mL of *glacial acetic acid* and dilute to 100 mL with *water*. Measure the *absorbance* of the resulting solution at the maximum at 271 nm, Appendix II B. Calculate the content of $C_{14}H_{18}N_4O_3$ taking 204 as the value of A(1%, 1 cm) at the maximum at 271 nm.

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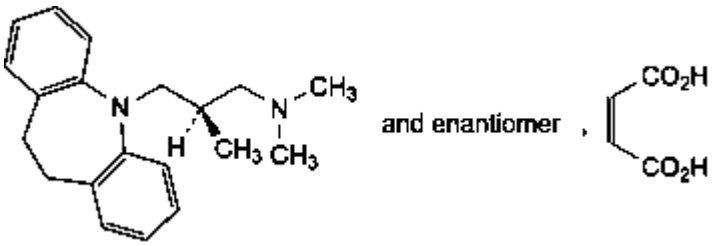
Trimipramine Maleate

General Notices

(Ph. Eur. monograph 0534)



$C_{24}H_{30}N_2O_4$ 410.5 *521-78-8*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparation

Trimipramine Tablets

Ph Eur

DEFINITION

(2*RS*)-3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*,2-trimethylpropan-1-amine hydrogen (2*Z*)-but-2-enedioate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water and in ethanol (96 per cent).

IDENTIFICATION

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A. Melting point (2.2.14): 140 °C to 144 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *trimipramine maleate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Buffer solution pH 7.7 2.64 g/L solution of *ammonium phosphate R* in *water for chromatography R*; adjust to pH 7.7 with *phosphoric acid R*.

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 100 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of the substance to be examined and 5 mg of *iminodibenzyl R* (impurity F) in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *trimipramine for peak identification CRS* (containing impurities A, B, C, D and E) in 1 mL of *acetonitrile R1*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R1*, buffer solution pH 7.7 (38:62 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time 3 times the retention time of trimipramine.

Identification of impurities Use the chromatogram supplied with *trimipramine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D and E; doubling of the peak due to impurity E may be observed.

Relative retention With reference to trimipramine (retention time = about 27 min): impurity A = about 0.1; impurity B = about 0.3; impurity C = about 0.4; impurity D = about 0.5; impurity F = about 1.4; impurity E = about 1.5.

System suitability:

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— *resolution*: minimum 3.5 between the peaks due to trimipramine and impurity F in the chromatogram obtained with reference solution (a);

— the chromatogram obtained with reference solution (c) is similar to the chromatogram supplied with *trimipramine for peak identification CRS*.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 0.5;

— *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity F*: not more than 2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities A, B, C, D*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 41.05 mg of $C_{24}H_{30}N_2O_4$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*

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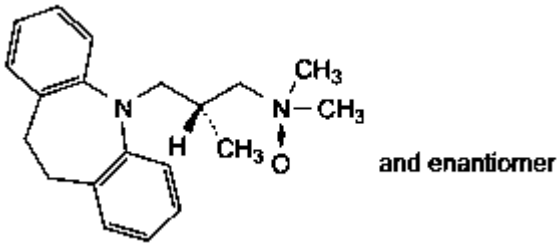
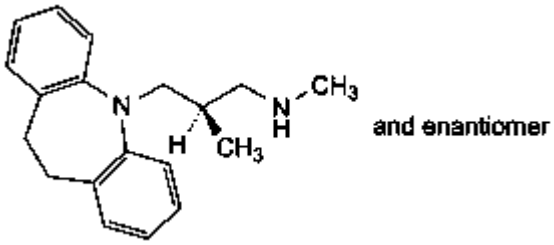
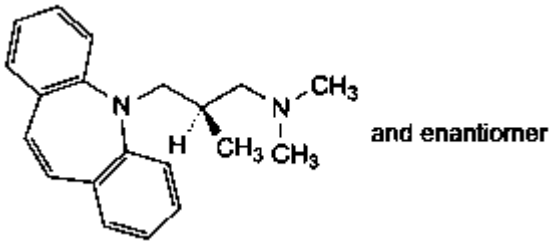
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*



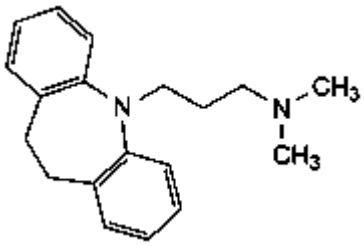
A. (2*RS*)-3-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*,2-trimethylpropan-1-amine *N*-oxide,



B. (2*RS*)-3-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,2-dimethylpropan-1-amine,



C. (2*RS*)-3-(5*H*-dibenzo[b,f]azepin-5-yl)-*N*,*N*,2-trimethylpropan-1-amine,



D. imipramine,

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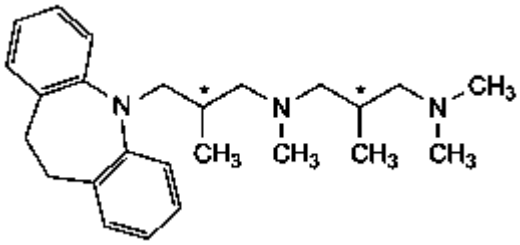
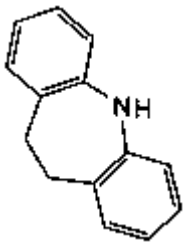
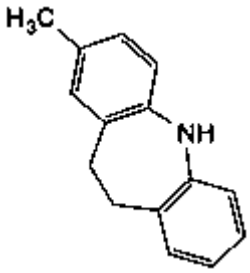


E. mixture of the stereoisomers of *N*-[3-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-2-methylpropyl]-*N*,*N*′,*N*′,2-tetramethylpropane-1,3-diamine,



F. 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine,



G. 2-methyl-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine.

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Trimipramine Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Trimipramine Tablets contain Trimipramine Maleate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of trimipramine, $C_{20}H_{26}N_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Triturate a quantity of the powdered tablets containing the equivalent of 0.25 g of trimipramine with 10 mL of *chloroform*, filter and evaporate the filtrate to low volume. Add *ether* until a turbidity is produced and allow to stand. The *infrared absorption spectrum*, Appendix II A, of the precipitate, after recrystallisation from *acetone*, is concordant with the *reference spectrum* of trimipramine maleate (*RS 355*).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 0.7 volume of 13.5M *ammonia*, 10 volumes of *ethanol* (*96%*) and 90 volumes of *toluene* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions prepared immediately before use. For solution (1) shake a quantity of the powdered tablets containing the equivalent of 0.18 g of trimipramine with three 10 mL quantities of *chloroform* and filter. Evaporate the combined filtrates to dryness and dissolve the residue in 10 mL of *methanol*. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *methanol*. For solution (3) dilute 2 volumes of solution (2) to 5 volumes with *methanol*. Solution (4) contains 0.0125% w/v of *iminodibenzyl* in *methanol*. After removal of the plate, allow it to dry in air for 15 minutes and spray with a 0.5% w/v solution of *potassium dichromate* in *sulfuric acid* (*20% v/v*). Examine the plate immediately. Any spot corresponding to iminodibenzyl in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4) (0.7%, with reference to trimipramine). Any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%) and not more than three such spots are more intense than the spot in the chromatogram obtained with solution (3) (0.2%). Disregard any spot remaining on the line of application.

ASSAY

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Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 50 mg of trimipramine with 190 mL of a mixture of equal volumes of *acetonitrile* and *water* for 1 minute, mix with the aid of ultrasound for 5 minutes, shake for 1 minute and mix again with the aid of ultrasound for 5 minutes. Add sufficient of a mixture of equal volumes of *acetonitrile* and *water* to produce 200 mL, filter and dilute 10 mL of the filtrate to 100 mL with the same solvent. Measure the *absorbance* of the resulting solution at the maximum at 250 nm, Appendix II B. Calculate the content of $C_{20}H_{26}N_2$ taking 320 as the value of A(1%, 1 cm) at the maximum at 250 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of trimipramine.

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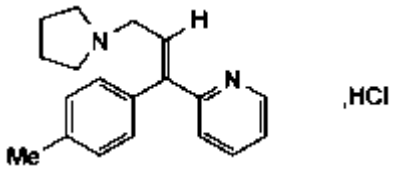
Triprolidine Hydrochloride

General Notices



$C_{19}H_{22}N_2$,HCl,H_2O 332.9 *6138-79-0*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparation

Triprolidine Tablets

DEFINITION

Triprolidine Hydrochloride is (*E*)-2-(3-pyrrolidin-1-yl-1-*p*-tolylprop1-enyl)pyridine hydrochloride monohydrate. It contains not less than 98.5% and not more than 101.0% of $C_{19}H_{22}N_2$,HCl, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white, crystalline powder.

Freely soluble in *water*; freely soluble in *ethanol (96%)* and practically insoluble in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of triprolidine hydrochloride *(RS 356)*.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) 1.0% w/v of the substance being examined.

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(2) 0.020% w/v of Z-*triprolidine hydrochloride BPCRS*.

(3) 0.010% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

Equal volumes of *butan-2-one* and *dimethylformamide*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to *Z*-triprolidine is not more intense than the spot in the chromatogram obtained with solution (2);

and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3).

Sulfated ash

Not more than 0.1%, Appendix IX A.

Water

4.5 to 6.0% w/w, Appendix IX C. Use 0.4 g.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.25 g dissolved in a mixture of 50 mL of *anhydrous acetic acid* and 0.5 mL of *acetic anhydride* and *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 15.74 mg of $C_{19}H_{22}N_2,HCl$.

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Triprolidine Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Triprolidine Tablets contain Triprolidine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of triprolidine hydrochloride, $C_{19}H_{22}N_2,HCl,H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 10 mg of Triprolidine Hydrochloride with *ether*, filter, discard the ether and dry the residue. Extract the residue with *chloroform* and evaporate to dryness. Add 0.1 mL of *ether*, stir and allow to evaporate. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of triprolidine hydrochloride (*RS 356*).

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (4).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of equal volumes of *butan-2-one* and *dimethylformamide* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 10 mg of Triprolidine Hydrochloride with *methanol*, filter, evaporate to dryness and dissolve the residue in 1 mL of *methanol*. Solution (2) contains 0.020% w/v of *Z-triprolidine hydrochloride BPCRS* in *methanol*. Solutions (3) and (4) contain 0.010% w/v and 1.0% w/v respectively of *triprolidine hydrochloride BPCRS* in *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to *Z*-triprolidine is not more intense than the spot in the chromatogram obtained with solution (2) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3).

ASSAY

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Weigh and powder 20 tablets. To a quantity of the powder containing 7.5 mg of Triprolidine Hydrochloride, add 15 mL of *water* and 1 g of *sodium chloride*, shake for 2 to 3 minutes and make alkaline with 5M *sodium hydroxide*. Extract with four 20 mL quantities of *ether* and wash the combined extracts with two 5 mL quantities of a mixture of equal volumes of a saturated solution of *sodium chloride* and *water*. Extract the ether solution with 20 mL of 0.1M *hydrochloric acid*, wash the ether with two 5 mL quantities of *water* and add the washings to the acid extract. Heat on a water bath for 30 minutes, cool and add sufficient *water* to produce 50 mL. Dilute 10 mL to 100 mL with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at 290 nm, Appendix II B. Calculate the content of $C_{19}H_{22}N_2$,HCl,H_2O taking 290 as the value of A(1%, 1 cm) at the maximum at 290 nm.

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Trisodium Edetate Infusion

General Notices

Trisodium Edetate Injection; Trisodium Edetate Intravenous Infusion

DEFINITION

Trisodium Edetate Infusion is a sterile solution conatining trisodium edetate. It is prepared immediately by diluting Trisodium Edetate Sterile Concentrate with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

LABELLING

The strength is stated as the amount of trisodium edetate in a suitable dose-volume.

TRISODIUM EDETATE STERILE CONCENTRATE

DEFINITION

Trisodium Edetate Sterile Concentrate is a sterile solution in Water for Injections containing 20% w/v of trisodium edetate prepared by the interaction of Disodium Edetate and Sodium Hydroxide.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of trisodium edetate, $C_{10}H_{13}N_2Na_3O_8$

19.0 to 21.0% w/v.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Dilute 2.5 mL with 7.5 mL of *water* and add 0.5 mL of a 10% w/v solution of *calcium chloride*; make alkaline to *litmus paper* with 5M *ammonia* and add 5 mL of a 2.5% w/v solution of *ammonium oxalate*. No precipitate is produced.

B. Dilute 10 mL with 15 mL of *water*, add 2 mL of a 10% w/v solution of *lead(II) nitrate*, shake and add 5 mL of *dilute potassium iodide solution*; no yellow precipitate is produced. Make alkaline to *litmus paper* with 5M *ammonia* and add 5 mL of a 2.5% w/v solution of *ammonium oxalate*; no precipitate is produced.

C. Evaporate to dryness and ignite. The residue yields the reactions characteristic of *sodium salts*, Appendix VI.

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TESTS

Acidity or alkalinity

pH, 7.0 to 8.0, Appendix V L.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. If necessary dilute the infusion with *water BET* to give a solution containing 10 mg per mL (solution A). The endotoxin limit concentration of solution A is less than 1.4 IU per mL.

ASSAY

Dilute 10 mL to 100 mL with *water* and use this solution to titrate a mixture of 25 mL of *0.05M magnesium sulfate VS* and 10 mL of *ammonia buffer pH 10.9* using *mordant black 11 mixed triturate* as indicator. Each mL of *0.05M magnesium sulfate VS* is equivalent to 17.91 mg of trisodium edetate, $C_{10}H_{13}N_2Na_3O_8$.

STORAGE

Trisodium Edetate Sterile Concentrate should be kept in containers made from lead-free glass.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of trisodium edetate.

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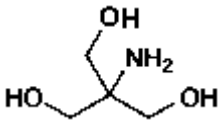
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Trometamol

General Notices

(Ph. Eur. monograph 1053)



$C_4H_{11}NO_3$ 121.1 *77-86-1*

Action and use

Organic amine proton acceptor; alkalinizing agent.

Ph Eur

DEFINITION

Trometamol contains not less than 99.0 per cent and not more than the equivalent of 100.5 per cent of aminomethylidynetri(methanol), calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, or colourless crystals, freely soluble in water, sparingly soluble in ethanol (96 per cent), very slightly soluble in ethyl acetate.

IDENTIFICATION

First identification: B, C.

Second identification: A, B, D.

A. Solution S (see Tests) is strongly alkaline (*2.2.4*).

B. Melting point (*2.2.14*): 168 °C to 174 °C.

C. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *trometamol CRS*.

D. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

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TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of freshly prepared solution S is 10.0 to 11.5.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance. Wash the plate with *methanol R* before applying the solutions.

Test solution (a) Dissolve 0.20 g in 1 mL of *water R*, with heating, and dilute to 10 mL with *methanol R*.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 20 mg of *trometamol CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1 mL of test solution (a) to 100 mL with *methanol R*.

Apply to the plate 10 µL of each solution. Develop over a path of 10 cm using a mixture of 10 volumes of *dilute ammonia R1* and 90 volumes of *2-propanol R*. Dry the plate at 100 °C to 105 °C. Spray with a 5 g/L solution of *potassium permanganate R* in a 10 g/L solution of *sodium carbonate R*. After about 10 min examine in daylight. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (1.0 per cent).

Chlorides (*2.4.4*)

To 10 mL of solution S add 2.5 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*. The solution complies with the limit test for chlorides (100 ppm).

Iron (*2.4.9*)

Dissolve 1.0 g in *water R* and dilute to 10 mL with the same solvent. The solution complies with the limit test for iron (10 ppm).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

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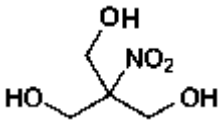
Less than 0.03 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.100 g in 20 mL of *water R*. Add 0.2 mL of *methyl red solution R*. Titrate with *0.1 M hydrochloric acid* until the colour changes from yellow to red.

1 mL of *0.1 M hydrochloric acid* is equivalent to 12.11 mg of $C_4H_{11}NO_3$.

IMPURITIES



A. nitromethylidynetri(methanol).

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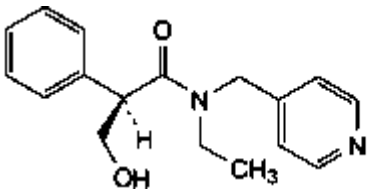
Tropicamide

General Notices

(Ph. Eur. monograph 1159)



and enantiomer

$C_{17}H_{20}N_2O_2$ 284.4 *1508-75-4*

Action and use

Anticholinergic.

Preparation

Tropicamide Eye Drops

Ph Eur

DEFINITION

(2*RS*)-*N*-Ethyl-3-hydroxy-2-phenyl-*N*-(pyridin-4-ylmethyl)propanamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: C.

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Second identification: A, B, D, E.

A. Melting point (2.2.14): 95 °C to 98 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in *0.1 M hydrochloric acid* and dilute to 50.0 mL with the same acid. Dilute 2.0 mL of this solution to 20.0 mL with *0.1 M hydrochloric acid*.

Spectral range 230-350 nm.

Absorption maximum At 254 nm.

Specific absorbance at the absorption maximum 170 to 190.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *tropicamide CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *tropicamide CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (0.5:5:95 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the spot in the chromatogram obtained with the reference solution.

E. Dissolve about 5 mg in 3 mL of a mixture of 9 mL of *acetic anhydride R*, 1 mL of *acetic acid R* and 0.1 g of *citric acid monohydrate R*. Heat on a water-bath for 5-10 min. A reddish-yellow colour is produced.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.1 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

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Optical rotation (*2.2.7*)

-0.1° to + 0.1°.

Dissolve 2.5 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in 3 mL of *acetonitrile R1* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water for chromatography R*. Dilute 1.0 mL of this solution to 10.0 mL with *water for chromatography R*.

Reference solution (b) Dissolve 5 mg of *4-[(ethylamino)methyl]pyridine R* (impurity A), 5.0 mg of *tropicamide impurity C CRS* and 5.0 mg of *tropicamide impurity D CRS* in 2 mL of *acetonitrile R1* and dilute to 50.0 mL with *water for chromatography R*. Dilute 1.0 mL of this solution to 10.0 mL with *water for chromatography R*.

Reference solution (c) Dissolve 5 mg of *tropicamide for peak identification CRS* (containing impurity B) in 1.0 mL of *acetonitrile R1* and dilute to 10.0 mL with *water for chromatography R*.

Reference solution (d) To 1 mL of reference solution (b) add 1 mL of reference solution (c).

Reference solution (e) Dilute 1.5 mL of reference solution (b) to 10.0 mL with *water for chromatography R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase Dissolve 0.135 g of *sodium dodecyl sulfate R* and 3.4 mL of *phosphoric acid R* in 950 mL of *water for chromatography R*. Adjust to pH 3.0 with *strong sodium hydroxide solution R* and dilute to 1000 mL with *water for chromatography R*. Mix 73 volumes of this solution with 27 volumes of *acetonitrile R1*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 210 nm and at 254 nm.

Injection 15 µL.

Run time 3 times the retention time of tropicamide.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C and D.

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Relative retention With reference to tropicamide (retention time = about 11 min): impurity C = about 0.4; impurity A = about 0.5; impurity D = about 0.8; impurity B = about 2.3.

System suitability Reference solution (d):

— *resolution at 210 nm*: minimum 2.0 between the peaks due to impurities C and A;

— *resolution at 210 nm*: minimum 2.0 between the peaks due to impurities A and D.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.8; impurity B = 0.6;

— *impurity B at 254 nm*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity A at 254 nm*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *impurity C at 210 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.15 per cent);

— *impurity D at 210 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.15 per cent);

— *unspecified impurities at 254 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than C and D at 254 nm*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit at 254 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dissolve 1.0 g with heating in 8 mL of *acetic acid R*, cool and dilute to 10 mL with the same acid. Dilute 5 mL of this solution to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 80 °C at a pressure not exceeding 0.7 kPa for 4 h.

Sulfated ash (*2.4.14*)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *anhydrous acetic acid R*. Add 0.2 mL of *naphtholbenzein solution R* and titrate with *0.1 M perchloric acid* until the colour changes from orange to green.

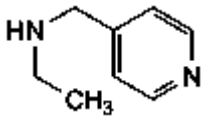
1 mL of *0.1 M perchloric acid* is equivalent to 28.44 mg of $C_{17}H_{20}N_2O_2$.

STORAGE

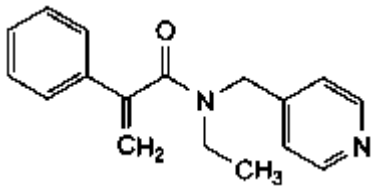
Protected from light.

IMPURITIES

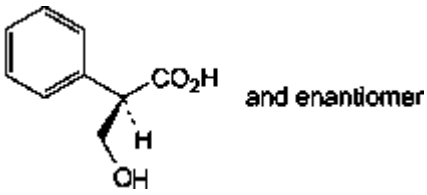
Specified impurities *A, B, C, D.*



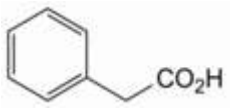
A. *N*-(pyridin-4-ylmethyl)ethanamine,



B. *N*-ethyl-2-phenyl-*N*-(pyridin-4-ylmethyl)propenamide,



C. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (tropic acid),



D. phenylacetic acid.

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Tropicamide Eye Drops

General Notices

Action and use

Anticholinergic.

DEFINITION

Tropicamide Eye Drops are a sterile solution of Tropicamide in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of tropicamide, $C_{17}H_{20}N_2O_2$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a volume of the eye drops containing 20 mg of Tropicamide with 10 mL of *chloroform*, dry the chloroform layer over *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. Dissolve the residue in the minimum quantity of *chloroform*, add drop wise to finely powdered *potassium bromide*, mix and dry at 60°. The *infrared absorption spectrum*, Appendix II A, of the dispersion examined as a disc is concordant with the *reference spectrum* of tropicamide (*RS 357*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits a maximum only at 254 nm.

TESTS

Acidity

pH, 4.0 to 5.8, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 1 volume of 13.5M *ammonia*, 10 volumes of *methanol* and 190 volumes of *chloroform* as the mobile phase. Apply separately to the plate (1) a volume of the eye drops containing 0.2 mg of Tropicamide, (2) the same volume of a solution prepared by diluting 1 volume of the eye drops to 200 volumes and (3) the same volume of a solution prepared by diluting 1 volume of the eye drops to 500 volumes. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

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ASSAY

To a quantity containing 30 mg of Tropicamide add sufficient *water* to produce 100 mL and mix. To 10 mL of the resulting solution add 2 mL of a 10% w/v solution of *anhydrous sodium carbonate* and extract with four 20 mL quantities of *chloroform*. Wash the combined chloroform extracts with 25 mL of a solution containing 0.0176% w/v of *disodium hydrogen orthophosphate* and 0.243% w/v of *sodium dihydrogen orthophosphate*. Wash the aqueous layer with 10 mL of *chloroform*, combine the chloroform extracts and shake with four 20 mL quantities of 0.5M *sulfuric acid*. Combine the acid extracts and add sufficient 0.5M *sulfuric acid* to produce 100 mL. Measure the *absorbance* of the resulting solution at the maximum at 254 nm, Appendix II B. Calculate the content of $C_{17}H_{20}N_2O_2$ in the eye drops taking 172 as the value of A(1%, 1 cm) at the maximum at 254 nm.

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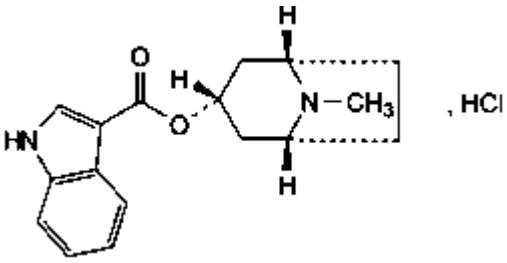
Tropisetron Hydrochloride

General Notices

(Ph. Eur. monograph 2102)



$C_{17}H_{21}ClN_2O_2$ 320.8 *105826-92-4*

Action and use

Serotonin $5HT_3$ receptor antagonist; antiemetic.

Ph Eur

DEFINITION

Hydrochloride of (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 1*H*-indole-3-carboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble or soluble in water, sparingly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

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A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in methanol R and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with methanol R.

Spectral range 220-360 nm.

Absorption maxima At 228 nm and 282 nm.

Absorbance ratio A_{228}/A_{282} = 1.3 to 1.4.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison tropisetron hydrochloride CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 5 mL with the same mixture of solvents.

Reference solution Dissolve 5 mg of tropisetron hydrochloride CRS in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 5 mL with the same mixture of solvents.

Plate TLC silica gel F_{254} plate R.

Mobile phase *anhydrous formic acid R*, water R, methanol R, methylene chloride R (2:2:30:70 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In cold air.

Detection A Examine in ultraviolet light at 254 nm.

Detection B Spray first with a solution prepared as follows: dissolve 0.85 g of bismuth subnitrate R in a mixture of 10 mL of acetic acid R and 40 mL of water R; to 5 mL of this solution add 5 mL of a 400 g/L solution of potassium iodide R and dilute to 100 mL with water R. Then spray with strong hydrogen peroxide solution R.

Results For both detection methods, the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

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The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, Method II).

Dissolve 1.00 g in *water R* and dilute to 20 mL with the same solvent.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.200 g of the substance to be examined in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 5.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 5.0 mg of *tropine CRS* (impurity A) in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 25.0 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with a mixture of equal volumes of *methanol R* and *methylene chloride R*. To 0.1 mL of this solution add 1.0 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ammonia R*, *methanol R*, *methylene chloride R* (5:40:60 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of cold air.

Detection Dip the plate in *potassium iodobismuthate solution R1*.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5.0 mg of *tropisetron impurity B CRS* and 5 mg of *ethyl indole-3-carboxylate CRS* in mobile phase A and dilute to 20.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 50.0 mL with mobile phase A.

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Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *triethylamine R*, *acetonitrile R*, *water R*, *methanol R* (0.3:35:400:565 *V/V/V/V*);

— *mobile phase B*: *triethylamine R*, *acetonitrile R*, *water R*, *methanol R* (0.3:100:100:800 *V/V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	100	0
14 - 32	100 → 0	0 → 100
32 - 36	0	100
36 - 37	0 → 100	100 → 0
37 - 52	100	0

Flow rate 2 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Relative retention With reference to tropisetron (retention time = about 22 min): impurity B = about 0.05; ethyl indole-3-carboxylate = about 0.2.

System suitability Reference solution (b):

— *resolution*: minimum 4 between the peaks due to impurity B and ethyl indole-3-carboxylate.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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***N*,*N*-Dimethylaniline**

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 250 mg of the substance to be examined in mobile phase A and dilute to 5.0 mL with mobile phase A.

Reference solution Dissolve 10.0 mg of *N,N-dimethylaniline R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *triethylamine R*, *acetonitrile R*, *water R*, *methanol R* (0.3:35:400:565 *V/V/V/V*);

— *mobile phase B*: *triethylamine R*, *acetonitrile R*, *water R*; *methanol R* (0.3:100:100:800 *V/V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 11	100 → 0	0 → 100
11 - 30	0	100
30 - 31	0 → 100	100 → 0
31 - 50	100	0

Flow rate 1 mL/min.

Detection Spectrophotometer at 248 nm.

Injection 20 µL.

Limit:

— *N,N-dimethylaniline*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (20 ppm).

Loss on drying (2.2.32)

Maximum 0.3 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

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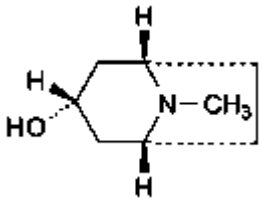
ASSAY

Dissolve 0.250 g in 10 mL of *anhydrous acetic acid R* and add 70 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

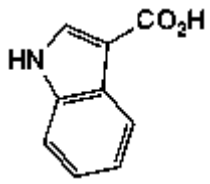
1 mL of *0.1 M perchloric acid* is equivalent to 32.08 mg of $C_{17}H_{21}ClN_2O_2$.

IMPURITIES

Specified impurities *A, B.*



A. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (tropine),



B. 1*H*-indole-3-carboxylic acid.

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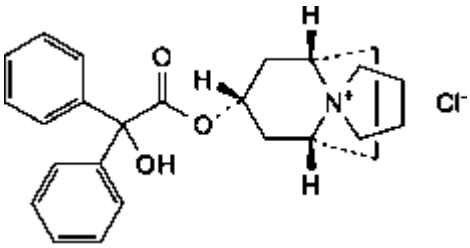
Trospium Chloride

General Notices

(Ph. Eur. monograph 1798)



$C_{25}H_{30}ClNO_3$ 428.0 *10405-02-4*

Action and use

Anticholinergic.

Preparations

Trospium Chloride Prolonged-release Capsules

Trospium Chloride Tablets

Ph Eur

DEFINITION

(1*R*,3*r*,5*S*)-3-[(Hydroxydiphenylacetyl)oxy]spiro[8-azoniabicyclo[3.2.1]octane-8,1′-pyrrolidinium] chloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *trospium chloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 3.0 g in *carbon dioxide-free water R* and dilute to 30 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, *Method II*).

pH (2.2.3)

5.0 to 7.0.

Dilute 5 mL of solution S to 50 mL with *carbon dioxide-free water R*.

Impurity C

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in 2.0 mL of *methanol R*.

Reference solution (a) Dissolve 1.0 mg of *trospium impurity C CRS* in 2.0 mL of *methanol R*.

Reference solution (b) Dilute 1.0 mL of test solution to 10.0 mL with *methanol R*. To 50 µL of this solution add 1 mL of reference solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *hydrochloric acid R*, *acetonitrile R* (1:3.5:45 *V/V/V*).

Application 10 µL as bands.

Development Over 2/3 of the plate.

Drying In a current of warm air until the odour of acetic acid is no longer perceptible.

Detection Spray with *potassium iodobismuthate solution R* and subsequently with a 5 g/L solution of *sodium nitrite R*.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly visible and separated zones.

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Limit:

— *impurity C*: any zone due to impurity C is not more intense than the zone in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 6.0 mg of *trospium impurity A CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 7.5 mg of *trospium impurity B CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (c) Dilute a mixture of 0.3 mL of the test solution, 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 1 volume of *triethylamine R* and 3 volumes of *phosphoric acid R* with 700 volumes of *water R* and add 300 volumes of *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 3 times the retention time of trospium.

Relative retention With reference to trospium (retention time = about 10 min): impurity B = about 0.7; impurity A = about 1.9.

System suitability Reference solution (c):

— *resolution*: minimum 3 between the peaks due to impurity B and trospium.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity A*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

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— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than twice the area of the peak due to impurity B in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (2.2.20).

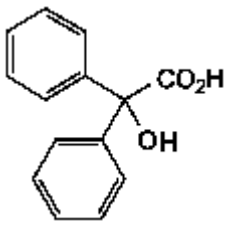
1 mL of *0.1 M silver nitrate* is equivalent to 42.80 mg of $C_{25}H_{30}ClNO_3$.

STORAGE

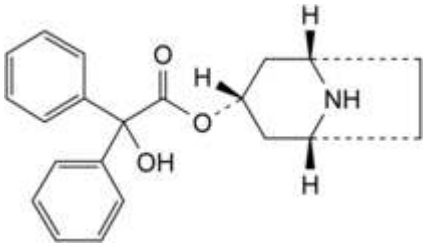
Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. hydroxydiphenylacetic acid (benzilic acid),



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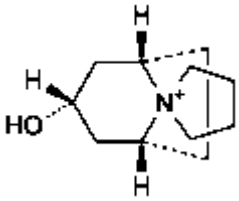
B. (1*R*,3*r*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl hydroxydiphenylacetate,



C. (1*R*,3*r*,5*S*)-3-hydroxyspiro[8-azoniabicyclo[3.2.1]octane8,1′-pyrrolidinium].

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Trospium Chloride Prolonged-release Capsules

General Notices

Prolonged-release Trospium Chloride Capsules

Trospium Chloride Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Anticholinergic.

DEFINITION

Trospium Chloride Prolonged-release Capsules contain Trospium Chloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Trospium Chloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of trospium chloride, $C_{25}H_{30}ClNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the contents of the capsules containing 20 mg of Trospium Chloride, add 20 mL of *methanol*. Mix with the aid of ultrasound for 10 minutes and filter through a glass-fibre filter paper (Whatman GF/C is suitable).

(2) 0.1% w/v of *trospium chloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *potassium iodobismuthate solution* followed by 0.5% w/v *sodium nitrate*. Examine in white light.

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MOBILE PHASE

1 volume of *hydrochloric acid*, 4 volumes of *glacial acetic acid* and 9 volumes of *acetonitrile*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered capsules content containing 60 mg of Trospium Chloride with 80 mL of the mobile phase. Dilute to 100 mL, filter through a 0.45-µm PTFE filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.01% w/v of *trospium chloride impurity standard BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP8-select B is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 215 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for twice the retention time of trospium chloride.

MOBILE PHASE

1 volume of *triethylamine*, 3 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile R1* and 700 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to trospium chloride (retention time, about 12.0 minutes) are: impurity B, about 0.8 and impurity A, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and trospium chloride is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

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Identify any peak corresponding to impurity A using solution (3) and multiply the area of this peak by a correction factor of 0.6.

the area of any peak corresponding to impurity A is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To a quantity of the powdered mixed contents of 20 capsules containing 50 mg of Trospium Chloride, add 80 mL of the mobile phase. Mix with the aid of ultrasound for 15 minutes. Dilute to 100 mL and filter through a 0.45-µm PTFE filter. Dilute 1 volume to 5 volumes.
(2) 0.01% w/v of *trospium chloride BPCRS*.
(3) 0.01% w/v of *trospium chloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a flow rate of 1.5 mL per minute.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and trospium chloride is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{30}ClNO_3$ in the capsules using the declared content of $C_{25}H_{30}ClNO_3$ in *trospium chloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed in the monograph for Trospium Chloride.

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Trospium Chloride Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Trospium Chloride Tablets contain Trospium Chloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of trospium chloride, $C_{25}H_{30}ClNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the powdered tablets containing 20 mg of Trospium Chloride add 20 mL of *methanol*. Mix with the aid of ultrasound and filter through a glass-fibre filter (Whatman GF/C is suitable).

(2) 0.1% w/v of *trospium chloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *potassium iodobismuthate solution* followed by 0.5% w/v *sodium nitrate*. Examine in white light.

MOBILE PHASE

1 volume of *hydrochloric acid*, 4 volumes of *glacial acetic acid* and 9 volumes of *acetonitrile*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the dissolution medium.

(1) After 45 minutes withdraw a sample of the medium, filter and dilute the filtrate with sufficient dissolution medium, if necessary, to give a solution expected to contain 0.002% w/v of Trospium Chloride.

(2) 0.002% w/v of *trospium chloride BPCRS*.

(3) 0.01% w/v of *trospium chloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP8-Select B is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *triethylamine*, 3 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile R1* and 700 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and trospium chloride is at least 3.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{25}H_{30}ClNO_3$, in the medium from the chromatograms obtained and using the declared content of $C_{25}H_{30}ClNO_3$ in *trospium chloride BPCRS*.

LIMITS

The amount of Trospium Chloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

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(1) Shake a quantity of the powdered tablets containing 60 mg of Trospium Chloride with 80 mL of the mobile phase. Dilute to 100 mL, filter through a 0.45-µm PTFE filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.01% w/v of *trospium chloride impurity standard BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with a flow rate of 1.0 mL per minute.

When the chromatograms are recorded under the prescribed conditions the retention times relative to trospium chloride (retention time, about 12.0 minutes) are: impurity B, about 0.8 and impurity A, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) and the chromatagram supplied with *trospium chloride impurity standard BPCRS*, the *resolution* between the peaks due to impurity B and trospium chloride is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify any peak corresponding to impurity A using solution (3) and multiply the area of this peak by a correction factor of 0.6.

the area of any peak corresponding to impurity A is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

(1) To a quantity of the powdered tablets containing 50 mg of Trospium Chloride, add 80 mL of the mobile phase. Mix with the aid of ultrasound for 15 minutes. Dilute to 100 mL and filter through a 0.45-µm PTFE filter. Dilute 1 volume to 5 volumes.

(2) 0.01% w/v of *trospium chloride BPCRS*.

(3) 0.01% w/v of *trospium chloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and trospium chloride is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{30}ClNO_3$ in the tablets using the declared content of $C_{25}H_{30}ClNO_3$ in *trospium chloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed in the monograph for Trospium Chloride.

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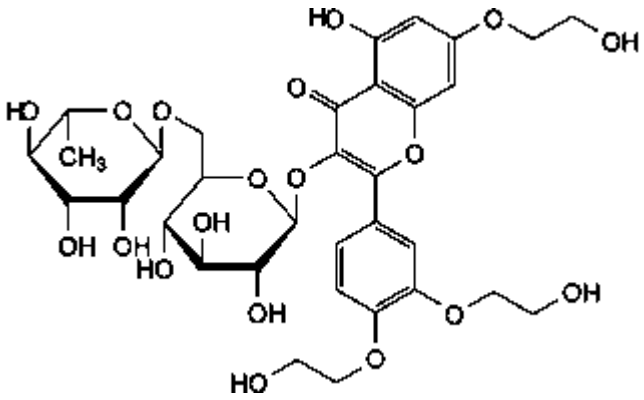
Troxerutin

General Notices

(Ph. Eur. monograph 2133)



$C_{33}H_{42}O_{19}$ 743 *7085-55-4*

Action and use

Bioflavonoid.

Ph Eur

DEFINITION

Mixture of *O*-hydroxyethylated derivatives of rutoside containing minimum 80 per cent of 2-[3,4-bis(2-hydroxyethoxy)phenyl]-3-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-7-(2-hydroxyethoxy)-4*H*-1-benzopyran-4-one (tris(hydroxyethyl)rutin).

Content

95.0 per cent to 105.0 per cent (dried substance).

CHARACTERS

Appearance

Yellowish-green, crystalline powder, hygroscopic.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent) and practically insoluble in methylene chloride.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison troxerutin CRS.

B. Examine the chromatograms obtained in the test for composition.

Results The principal peak in the chromatogram obtained with the test solution is similar in position and size to the principal peak in the chromatogram obtained with the reference solution (a).

TESTS

Composition

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase, if necessary using an ultrasonic bath and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 10.0 mg of troxerutin CRS in the mobile phase, if necessary using an ultrasonic bath and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1 mL of reference solution (a) to 10 mL with the mobile phase. Dilute 1 mL of this solution to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 20 volumes of acetonitrile R and 80 volumes of a 15.6 g/L solution of sodium dihydrogen phosphate R adjusted to pH 4.4 with dilute phosphoric acid R or dilute sodium hydroxide solution R.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 350 nm.

Injection 10 µL.

Run time Twice the retention time of the main compound of troxerutin (tris(hydroxyethyl)rutin).

Relative retention With reference to tris(hydroxyethyl)rutin (retention time = about 25 min): tetrakis(hydroxyethyl)rutin = about 0.5; mono(hydroxyethyl)rutin = about 0.8; bis(hydroxyethyl)rutin = about 1.1.

System suitability Reference solution (a):

— peak-to-valley ratio: minimum 2.0, where H_p = height above the baseline of the peak due to bis(hydroxyethyl)rutin and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to tris(hydroxyethyl)rutin;

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— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *principal peak*: minimum 80 per cent,

— *any other peak*: for each peak, maximum 5 per cent, except for 1 peak which can be maximum 10 per cent.

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (b).

Ethylene oxide

Head-space gas chromatography (*2.2.28*).

Test solution To 1.00 g of the substance to be examined in a vial, add 1.0 mL of *water R*. Mix to obtain a homogeneous solution. Heat at 70 °C for 45 min.

Reference solution To 1.00 g of the substance to be examined in a vial, add 50 µL of *ethylene oxide solution R4* and 950 µL of *water R* and close tightly. Mix to obtain a homogeneous solution. Heat at 70 °C for 45 min.

Column:

— *material*: fused silica,

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.1 mL/min.

Static head-space conditions which may be used:

— *equilibration temperature*: 70 °C,

— *equilibration time*: 45 min,

— *transfer line temperature*: 110 °C,

— *pressurisation time*: 2 min,

— *injection time*: 12 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	40

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	Time (min)	Temperature (°C)
	5 - 18	40 → 200
Injection port		150
Detector		250

Detection Flame ionisation.

Injection 1.0 mL.

The peak due to ethylene oxide is identified by injecting solutions of ethylene oxide of increasing concentration.

Determine the content of ethylene oxide (ppm) in the substance to be examined using the following expression:

$$\frac{A_1 \times m_1}{(A_2 \times m_2) - (A_1 \times m_3)}$$

A_1 = area of the peak due to ethylene oxide in the chromatogram obtained with the test solution,

A_2 = area of the peak due to ethylene oxide in the chromatogram obtained with the reference solution,

m_1 = mass of ethylene oxide in the reference solution, in micrograms,

m_2 = mass of the substance to be examined in the test solution, in grams,

m_3 = mass of the substance to be examined in the reference solution, in grams.

Limit:

— *ethylene oxide*: maximum 1 ppm.

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.4 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 100.0 mL of *water R*. Dilute 10.0 mL of this solution to 100.0 mL with *water R*. Dilute 10.0 mL to 100.0 mL with *water R*. Measure the absorbance (2.2.25) at the absorption maximum at 350 nm.

Calculate the percentage content of $C_{33}H_{42}O_{19}$ taking the specific absorbance to be 250.

STORAGE

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In an airtight container, protected from light.

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Trypsin

General Notices

(Ph. Eur. monograph 0694)

9002-07-7

Action and use

Proteolytic enzyme.

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DEFINITION

Trypsin is a proteolytic enzyme obtained by the activation of trypsinogen extracted from the pancreas of mammals. It has an activity of not less than 0.5 microkatal per milligram, calculated with reference to the dried substance. In solution, it has maximum enzymic activity at pH 8; the activity is reversibly inhibited at pH 3, the pH at which it is most stable.

PRODUCTION

The animals from which trypsin is derived must fulfil the requirements for the health of animals suitable for human consumption.

The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

Histamine (*2.6.10*)

Not more than 1 µg of histamine base per 0.2 microkatal of trypsin activity. Use a 10 g/L solution of the substance to be examined in *0.0015 M borate buffer solution pH 8.0 R* inactivated by heating on a water-bath for 30 min. Carry out dilutions with a 9 g/L solution of *sodium chloride R*.

CHARACTERS

Appearance

White or almost white, crystalline or amorphous powder, hygroscopic if amorphous.

Solubility

Sparingly soluble in water.

IDENTIFICATION

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A. Dilute 1 mL of solution S (see Tests) to 100 mL with *water R*. In a depression in a white spot-plate, mix 0.1 mL of this solution with 0.2 mL of *tosylarginine methyl ester hydrochloride solution R*. A reddish-violet colour develops within 3 min.

B. Dilute 0.5 mL of solution S to 5 mL with *water R*. Add 0.1 mL of a 20 g/L solution of *tosyl-lysyl-chloromethane hydrochloride R*. Adjust to pH 7.0, shake for 2 h and dilute to 50 mL with *water R*. In one of the depressions of a white spot-plate, mix 0.1 mL of this solution with 0.2 mL of *tosylarginine methyl ester hydrochloride solution R*. No reddish-violet colour develops within 3 min.

TESTS

Solution S

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*).

pH (*2.2.3*)

3.0 to 6.0 for solution S.

Specific absorbance (*2.2.25*)

13.5 to 16.5, determined at the absorption maximum at 280 nm; maximum 7.0, determined at the absorption minimum at 250 nm.

Dissolve 30.0 mg in *0.001 M hydrochloric acid* and dilute to 100.0 mL with the same acid.

Chymotrypsin

Test solution To 1.8 mL of *buffer solution pH 8.0 R* add 7.4 mL of *water R* and 0.5 mL of *0.2 M acetyltyrosine ethyl ester R*. While shaking the solution, add 0.3 mL of solution S and start a timer. After exactly 5 min, measure the pH (*2.2.3*).

Reference solution Prepare in the same manner as the test solution, replacing solution S by 0.3 mL of a 0.5 g/L solution of *chymotrypsin BRP*, and measure the pH (*2.2.3*) exactly 5 min after adding the chymotrypsin.

The pH of the test solution is higher than that of the reference solution.

Loss on drying (*2.2.32*)

Not more than 5.0 per cent, determined on 0.500 g by drying at 60 °C at a pressure not exceeding 0.67 kPa for 2 h.

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

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Absence of *Salmonella* (2.6.13).

ASSAY

The activity of trypsin is determined by comparing the rate at which it hydrolyses *benzoylarginine ethyl ester hydrochloride R* with the rate at which *trypsin BRP* hydrolyses the same substrate in the same conditions.

Apparatus Use a reaction vessel of about 30 mL capacity provided with:

— a device that will maintain a temperature of 25.0 ± 0.1 °C;

— a stirring device (for example, a magnetic stirrer);

— a lid with holes for the insertion of electrodes, the tip of the burette, a tube for the admission of nitrogen and the introduction of reagents.

An automatic or manual titration device may be used. For the latter, the burette is graduated in 0.005 mL and the pH meter is provided with a wide-range scale and glass-silver-silver chloride or other suitable electrodes.

Test solution Dissolve a suitable quantity of the substance to be examined in *0.001 M hydrochloric acid* and dilute to 25.0 mL with the same acid in order to obtain a solution containing approximately 700 nanokatals per millilitre.

Reference solution Dissolve a suitable quantity of *trypsin BRP* in *0.001 M hydrochloric acid* and dilute to 25.0 mL with the same acid in order to obtain a solution containing approximately 700 nanokatals per millilitre.

Store the solutions at 0-5 °C. Warm 1 mL of each solution to about 25 °C over 15 min and use 50 µL of each solution for each titration. Carry out the titration in an atmosphere of nitrogen. Transfer 10.0 mL of *0.0015 M borate buffer solution pH 8.0 R* to the reaction vessel and, while stirring, add 1.0 mL of a freshly prepared 6.86 g/L solution of *benzoylarginine ethyl ester hydrochloride R*. When the temperature is steady at 25.0 ± 0.1 °C (after about 5 min) adjust to pH 8.0 exactly with *0.1 M sodium hydroxide*. Add 50 µL of the test solution and start a timer. Maintain at pH 8.0 by the addition of *0.1 M sodium hydroxide*, the tip of the microburette being immersed in the solution; note the volume added every 30 s. Follow the reaction for 8 min. Calculate the volume of *0.1 M sodium hydroxide* used per second. Carry out a titration in the same manner using the reference solution and calculate the volume of *0.1 M sodium hydroxide* used per second.

Calculate the activity in microkatals per milligram using the following expression:

$$\frac{m' \times V}{m \times V'} \times A$$

m	=	mass of the substance to be examined, in milligrams;
m'	=	mass of *trypsin BRP*, in milligrams;
V	=	volume of *0.1 M sodium hydroxide* used per second by the test solution;
V'	=	volume of *0.1 M sodium hydroxide* used per second by the reference solution;
A	=	activity of *trypsin BRP*, in microkatals per milligram.

STORAGE

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In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

LABELLING

The label states:

— the activity in microkatals per milligram;

— for the amorphous substance, that it is hygroscopic.

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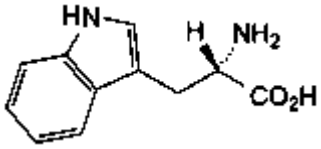
Tryptophan

General Notices

(Ph. Eur. monograph 1272)



$C_{11}H_{12}N_2O_2$ 204.2 *73-22-3*

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or amorphous powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of mineral acids and alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *tryptophan CRS*.

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C. Thin-layer chromatography (2.2.27).

Solvent mixture glacial acetic acid R, water R (50:50 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution Dissolve 10 mg of tryptophan CRS in the solvent mixture and dilute to 50 mL with the solvent mixture.

Plate TLC silica gel plate R.

Mobile phase glacial acetic acid R, water R, butanol R (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with ninhydrin solution R and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 20 mg in 10 mL of water R. Add 5 mL of dimethylaminobenzaldehyde solution R6 and 2 mL of hydrochloric acid R1. Heat on a water-bath. A purple-blue colour develops.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Dissolve 0.1 g in 1 M hydrochloric acid and dilute to 10 mL with the same acid.

Specific optical rotation (2.2.7)

-33.0 to -30.0 (dried substance).

Dissolve 0.25 g in water R, heating on a water-bath if necessary, and dilute to 25.0 mL with the same solvent.

Ninhydrin-positive substances

Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A dilute hydrochloric acid R1 or a sample preparation buffer suitable for the apparatus used.

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Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* and 30 mg of *leucine R* in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of tryptophan in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Impurity A and other related substances

Liquid chromatography (*2.2.29*). *Prepare the standard, test and reference solutions immediately before use.*

Buffer solution pH 2.3 Dissolve 3.90 g of *sodium dihydrogen phosphate R* in 1000 mL of *water R*. Add about 700 mL of a 2.9 g/L solution of *phosphoric acid R* and adjust to pH 2.3 with the same acid solution.

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Solvent mixture acetonitrile R, water R (10:90 *V/V*).

Standard solution Dissolve 10.0 mg of N-acetyltryptophan R in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 100.0 mL with the solvent mixture.

Test solution (a) Dissolve 0.10 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 0.10 g of the substance to be examined in the standard solution and dilute to 10.0 mL with the standard solution.

Reference solution (a) Dissolve the contents of a vial of 1,1'-ethylidenebistryptophan CRS (impurity A) in 1.0 mL of the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of 1,1'-ethylidenebistryptophan CRS (impurity A) in 1.0 mL of the standard solution.

Reference solution (c) Dilute 0.5 mL of reference solution (a) to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, buffer solution pH 2.3 (115:885 *V/V*);

— *mobile phase B*: acetonitrile R, buffer solution pH 2.3 (350:650 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 45	100 → 0	0 → 100
45 - 65	0	100

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solutions (a) and (b) and reference solutions (b) and (c).

Retention time Tryptophan = about 8 min; *N*-acetyltryptophan = about 29 min; impurity A = about 34 min.

System suitability:

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— *resolution*: minimum 8.0 between the peaks due to *N*-acetyltryptophan and impurity A in the chromatogram obtained with reference solution (b); if necessary, adjust the time programme for the elution gradient (an increase in the duration of elution with mobile phase A produces longer retention times and a better resolution);

— *signal-to-noise ratio*: minimum 15 for the principal peak in the chromatogram obtained with reference solution (c);

— *symmetry factor*: maximum 3.5 for the peak due to impurity A in the chromatogram obtained with reference solution (b);

— in the chromatogram obtained with test solution (a) there is no peak with the same retention time as *N*-acetyltryptophan (in such case correct the area of the *N*-acetyltryptophan peak).

Limits Test solution (b):

— *impurity A*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (10 ppm);

— *sum of impurities with a retention time less than that of tryptophan*: not more than 0.6 times the area of the peak due to *N*-acetyltryptophan in the chromatogram obtained with reference solution (b) (100 ppm);

— *sum of impurities with a retention time greater than that of tryptophan and up to 1.8 times the retention time of N-acetyltryptophan*: not more than 1.9 times the area of the peak due to *N*-acetyltryptophan in the chromatogram obtained with reference solution (b) (300 ppm);

— *disregard limit*: 0.02 times the area of the peak due to *N*-acetyltryptophan in the chromatogram obtained with reference solution (b); disregard the peak due to *N*-acetyltryptophan.

Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.25 g in 3 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*. The solution, without any further addition of nitric acid, complies with the test.

Sulfates (2.4.13)

Maximum 300 ppm.

Dissolve 0.5 g in a mixture of 5 volumes of *dilute hydrochloric acid R* and 25 volumes of *distilled water R*, and dilute to 15 mL with the same mixture of solvents.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

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— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 20 ppm.

In a separating funnel, dissolve 0.50 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Examine the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 3 mL of *anhydrous formic acid R*. Add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 20.42 mg of $C_{11}H_{12}N_2O_2$.

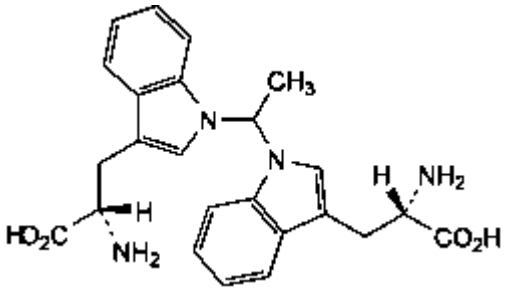
STORAGE

Protected from light.

IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, G, H, I, J, K, L.



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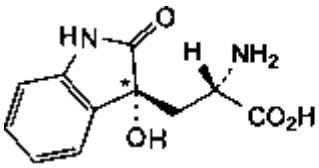
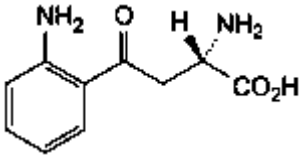
A. 3,3′-[ethane-1,1-diylbis(1*H*-indol-1,3-diyl)]bis[(2*S*)-2-aminopropanoic acid] (ethane-1,1-diylbistryptophan),

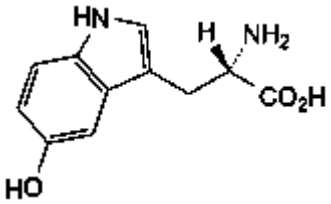


and epimer at C*

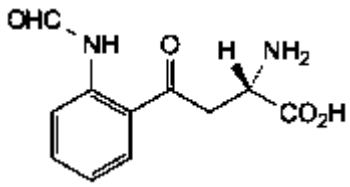
B. (2*S*)-2-amino-3-[(3*RS*)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl]propanoic acid (dioxyindolylalanine),



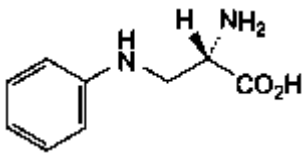
C. (2*S*)-2-amino-4-(2-aminophenyl)-4-oxobutanoic acid (kynurenine),



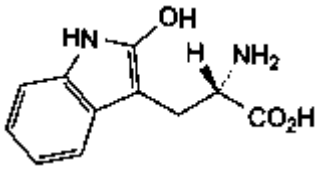
D. (2*S*)-2-amino-3-(5-hydroxy-1*H*-indol-3-yl)propanoic acid (5-hydroxytryptophan),



E. (2*S*)-2-amino-4-[2-(formylamino)phenyl]-4-oxobutanoic acid (*N*-formylkynurenine),



F. (2*S*)-2-amino-3-(phenylamino)propanoic acid (3-phenylaminoalanine),



G. (2*S*)-2-amino-3-(2-hydroxy-1*H*-indol-3-yl)propanoic acid (2-hydroxytryptophan),

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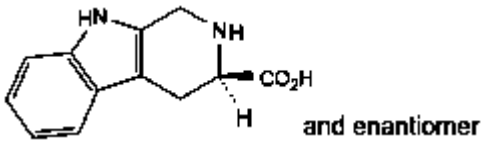
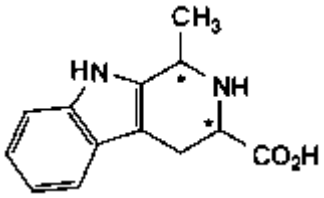
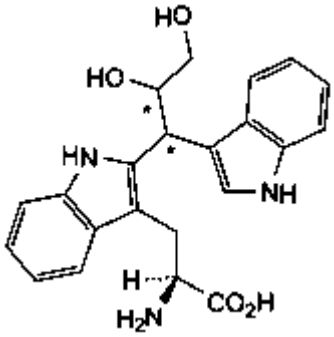


and enantiomer

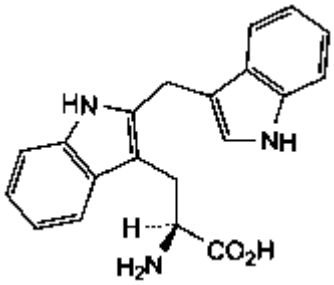
H. (3*RS*)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid,



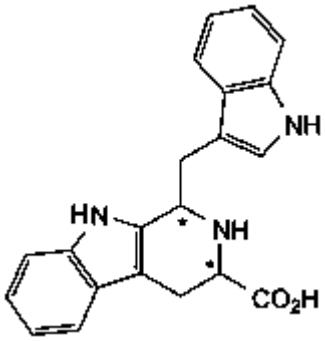
I. 1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid,



J. (2*S*)-2-amino-3-[2-[2,3-dihydroxy-1-(1*H*-indol-3-yl)propyl]-1*H*-indol-3-yl]propanoic acid,



K. (2*S*)-2-amino-3-[2-(1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]propanoic acid,



L. 1-(1*H*-indol-3-ylmethyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid.

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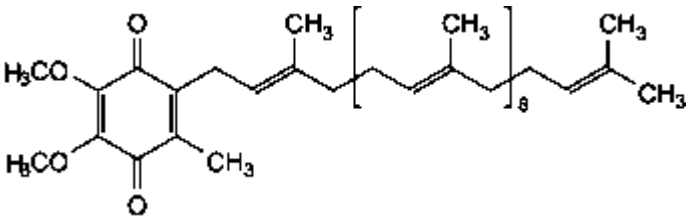
Ubidecarenone

General Notices

(Ph. Eur. monograph 1578)



$C_{59}H_{90}O_4$ 863 *303-98-0*

Action and use

Co-enzyme in mitochondrial electron transport.

Ph Eur

DEFINITION

2-[(*all-E*)-3,7,11,15,19,23,27,31,35,39-Decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-5,6-dimethoxy-3-methylbenzene-1,4-dione.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow or orange, hygroscopic, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone, very slightly soluble in anhydrous ethanol.

It gradually decomposes and darkens on exposure to light.

mp

About 48 °C.

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Carry out all operations protected from light.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ubidecarenone CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 25.0 mg of the substance to be examined in 25.0 mL of *anhydrous ethanol R* by heating at about 50 °C for 2 min. Allow to cool.

Reference solution (a) Dissolve 25.0 mg of *ubidecarenone CRS* in 25.0 mL of *anhydrous ethanol R* by heating at about 50 °C for 2 min. Allow to cool.

Reference solution (b) Dissolve 2 mg of *ubidecarenone impurity D CRS* in 2.0 mL of the test solution by heating at about 50 °C for 2 min. Allow to cool. Dilute 1.0 mL of this solution to 50.0 mL with *anhydrous ethanol R*.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with *anhydrous ethanol R*. Dilute 5.0 mL of this solution to 10.0 mL with *anhydrous ethanol R*.

Column:

— *size*: *l* = 0.2 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *anhydrous ethanol R*, *methanol R2* (20:80 *V/V*).

Flow rate 1.7 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of ubidecarenone.

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Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to ubidecarenone (retention time = about 14 min): impurity D = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 6.5 between the peaks due to impurity D and ubidecarenone.

Calculation of percentage contents:

— for each impurity, use the concentration of ubidecarenone in reference solution (c).

Limits:

— *impurity D*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent,

— *reporting threshold*: 0.05 per cent.

Impurity F

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 25.0 mg of the substance to be examined in 25.0 mL of *hexane R*.

Reference solution (a) Dissolve the contents of a vial of *ubidecarenone for system suitability CRS* (containing impurity F) in 1.0 mL of *hexane R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *hexane R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *silica gel for chromatography R* (7 µm).

Mobile phase *ethyl acetate R*, *hexane R* (3:97 *V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 20 µL.

Run time 1.2 times the retention time of ubidecarenone.

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Identification of impurities Use the chromatogram supplied with *ubidecarenone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity F.

Relative retention With reference to ubidecarenone (retention time = about 10 min): impurity F = about 0.85.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity F and ubidecarenone.

Limit:

— *impurity F*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent).

Water (2.5.12)

Maximum 0.2 per cent, determined on 3.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{59}H_{90}O_4$ taking into account the assigned content of *ubidecarenone CRS*.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *D, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, G.*

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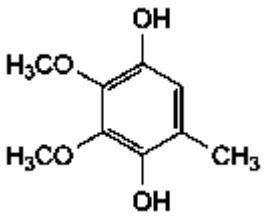
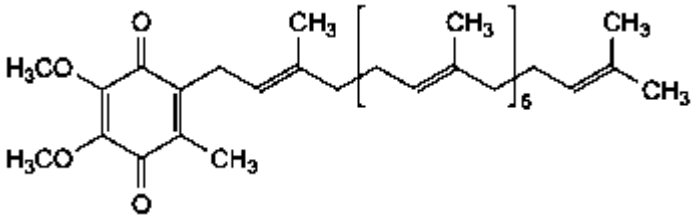
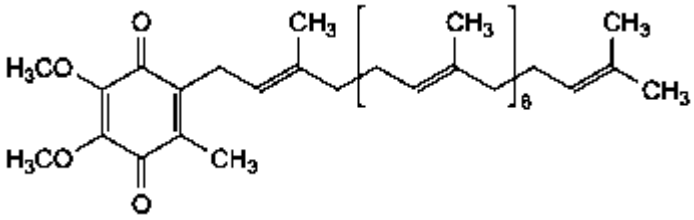


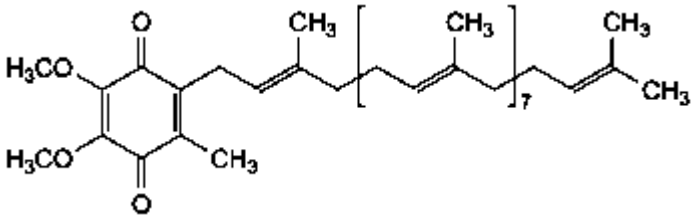
A. 2,3-dimethoxy-5-methylbenzene-1,4-diol,



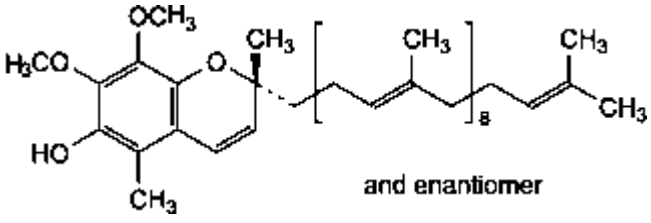
B. 2-[(*all-E*)-3,7,11,15,19,23,27-heptamethyloctadocosa-2,6,10,14,18,22,26-heptaenyl]-5,6-dimethoxy-3-methylbenzene-1,4-dione (ubiquinone-7),



C. 5,6-dimethoxy-3-methyl-2-[(*all-E*)-3,7,11,15,19,23,27,31-octamethyldotriaconta-2,6,10,14,18,22,26,30-octaenyl]benzene-1,4-dione (ubiquinone-8),



D. 5,6-dimethoxy-3-methyl-2-[(*all-E*)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaenyl]benzene-1,4-dione (ubiquinone-9),



E. (2*RS*)-7,8-dimethoxy-2,5-dimethyl-2-[(*all-E*)-4,8,12,16,20,24,28,32,36-nonamethylheptatriaconta-3,7,11,15,19,23,27,31,35-nonaenyl]-2*H*-1-benzopyran-6-ol (ubicromenol),

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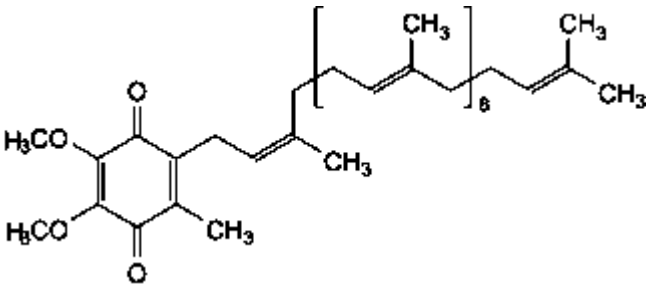

F. 2-[(2*Z*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-3,7,11,15,19,23,27,31,35,39-decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-5,6-dimethoxy-3-methylbenzene-1,4-dione (ubidecarenone (*Z*)-isomer),

G. unknown structure.

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Undecenoic Acid

General Notices

(Undecylenic Acid, Ph. Eur. monograph 0461)

$C_{11}H_{20}O_2$ 184.3 *112-38-9*

Ph Eur

DEFINITION

Undec-10-enoic acid.

Content

97.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

White or very pale yellow, crystalline mass or colourless or pale yellow liquid.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in fatty and essential oils.

IDENTIFICATION

A. Refractive index (2.2.6): 1.447 to 1.450, determined at 25 ± 0.5 °C.

B. Freezing point (2.2.18): 21 °C to 24 °C.

C. To 2.0 g add 2 mL of freshly distilled *aniline R* and boil under a reflux condenser for 10 min. Allow to cool and add 30 mL of *ether R*. Shake with 3 quantities, each of 20 mL, of *dilute hydrochloric acid R* and then with 20 mL of *water R*. Evaporate the organic layer to dryness on a water-bath. After recrystallising twice from *ethanol (70 per cent V/V) R* and drying *in vacuo* for 3 h, the residue melts (2.2.14) at 66 °C to 68 °C.

D. Dissolve 0.1 g in a mixture of 2 mL of *dilute sulfuric acid R* and 5 mL of *glacial acetic acid R*. Add dropwise 0.25 mL of *potassium permanganate solution R*. The colour of the potassium permanganate is discharged.

TESTS

Peroxide value (2.5.5, *Method A*)

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Peroxide value (*2.5.5, Method A*)

Maximum 10.

Fixed and mineral oils

To 1.0 g add 5 mL of *sodium carbonate solution R* and 25 mL of *water R* and boil for 3 min. The hot solution is not more opalescent than reference suspension II (*2.2.1*).

Water-soluble acids

To 1.0 g add 20 mL of *water R* heated to 35-45 °C and shake for 2 min. Cool and filter the aqueous layer through a moistened filter. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Degree of unsaturation

Dissolve 85.0 mg in a mixture of 5 mL of *dilute hydrochloric acid R* and 30 mL of *glacial acetic acid R*. Using 0.05 mL of *indigo carmine solution R1* as indicator, added towards the end of the titration, titrate with *0.0167 M bromide-bromate* until the colour changes from blue to yellow. 8.9 mL to 9.4 mL of *0.0167 M bromide-bromate* is required. Carry out a blank titration.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 0.50 g.

ASSAY

Dissolve 0.750 g in 10 mL of *ethanol (96 per cent) R*. Titrate with *0.5 M sodium hydroxide* using 0.1 mL of *phenolphthalein solution R* as indicator, until a pink colour is obtained.

1 mL of *0.5 M sodium hydroxide* is equivalent to 92.14 mg of $C_{11}H_{20}O_2$.

STORAGE

In a non-metallic container, protected from light.

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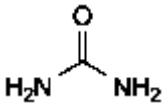
Urea

General Notices

(Ph. Eur. monograph 0743)



CH_4N_2O 60.1 *57-13-6*

Action and use

Keratolytic.

Preparation

Urea Cream

Ph Eur

DEFINITION

Carbamide.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or transparent crystals, slightly hygroscopic.

Solubility

Very soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

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A. Melting point (2.2.14): 132 °C to 135 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *urea CRS*.

C. Dissolve 0.1 g in 1 mL of *water R*. Add 1 mL of *nitric acid R*. A white, crystalline precipitate is formed.

D. Heat 0.5 g in a test tube until it liquefies and the liquid becomes turbid. Cool, dissolve in a mixture of 1 mL of *dilute sodium hydroxide solution R* and 10 mL of *water R* and add 0.05 mL of *copper sulfate solution R*. A reddish-violet colour is produced.

TESTS

Solution S

Dissolve 10.0 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

To 2.5 mL of solution S add 7.5 mL of *water R*.

Alkalinity

To 2.5 mL of solution S add 7.5 mL of *water R*, 0.1 mL of *methyl red solution R* and 0.4 mL of *0.01 M hydrochloric acid*. The solution is red to orange.

Biuret

Maximum 0.1 per cent.

To 10 mL of solution S add 5 mL of *water R*, 0.5 mL of a 5 g/L solution of *copper sulfate pentahydrate R* and 0.5 mL of *strong sodium hydroxide solution R*. Allow to stand for 5 min. Any reddish-violet colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 10 mL of a 0.2 g/L solution of *biuret R*.

Ammonium (2.4.1)

Maximum 500 ppm, determined on 0.1 mL of solution S.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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Dissolve 0.2000 g in *water R* and dilute to 50.0 mL with the same solvent. Introduce 1.0 mL of the solution into a combustion flask. Add 4 g of a powdered mixture of 100 g of *dipotassium sulfate R*, 5 g of *copper sulfate pentahydrate R* and 2.5 g of *selenium R*, and 3 glass beads. Wash any adhering particles from the neck into the flask with 5 mL of *sulfuric acid R*, allowing it to run down the sides of the flask, and mix the contents by rotation. Close the mouth of the flask loosely, for example by means of a glass bulb with a short stem, to avoid excessive loss of sulfuric acid. Heat gradually at first, then increase the temperature until there is vigorous boiling with condensation of sulfuric acid in the neck of the flask; take precautions to prevent the upper part of the flask from becoming overheated. Continue the heating for 30 min. Cool, dissolve the solid material by cautiously adding to the mixture 25 mL of *water R*, cool again and place in a steam-distillation apparatus. Add 30 mL of *strong sodium hydroxide solution R* and distil immediately by passing steam through the mixture. Collect the distillate in 15 mL of a 40 g/L solution of *boric acid R* to which has been added 0.2 mL of *methyl red mixed solution R* and enough *water R* to cover the tip of the condenser. Towards the end of the distillation, lower the receiver so that the tip of the condenser is above the surface of the acid. Take precautions to prevent any water on the outer surface of the condenser from reaching the contents of the receiver. Titrate the distillate with *0.01 M sulfuric acid*.

1 mL of *0.01 M sulfuric acid* is equivalent to 0.6006 mg of CH_4N_2O.

STORAGE

In an airtight container.

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Urea Cream

General Notices

DEFINITION

Urea Cream contains Urea in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of urea, CH_4N_2O

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel precoated plate (Merck silica gel 60 plates are suitable). Apply separately to the plate 10 µL of each of the following solutions. For solution (1) disperse with heating a quantity of the cream containing 50 mg of Urea in 1 mL of *water*, cool, add 4 mL of *acetone*, mix and filter. For solution (2) dissolve 50 mg of *urea* in 1 mL of *water* and add 4 mL of *acetone*. Solution (3) is a mixture of equal volumes of solutions (1) and (2). For the first development use *2,2,4-trimethylpentane* as the mobile phase. Remove the plate and allow it to dry in air. For the second development use as the mobile phase a mixture of 99 volumes of *absolute ethanol* and 1 volume of 13.5M *ammonia*. After removal of the plate, allow it to dry in air and spray with a solution containing 0.5% w/v of *4-dimethylaminobenzaldehyde* and 0.5% v/v of *sulfuric acid* in *absolute ethanol*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows a single, compact principal spot.

B. To a quantity containing 0.1 g of Urea add 50 mL of *water* and heat until dispersed, cool in ice and filter through glass wool. Adjust the pH of the filtrate, which may not be clear, to between 6.0 and 7.0 using 0.1M *hydrochloric acid* or 0.1M *sodium hydroxide* as necessary. To 5 mL add 5 mL of a 0.1% w/v suspension of *urease-active meal* and allow to stand for 30 minutes in a stoppered flask at 37°. When the resulting solution is heated in a water bath, a vapour is produced that turns moist *red litmus paper* blue.

TESTS

Ammonia

Not more than 2.0% with respect to the content of urea, CH_4N_2O (determined in the Assay) when determined by the following method.

Prepare a 0.035% w/v solution of *ammonium sulfate* in 1M *sulfuric acid* (solution A). Carry out the method for *ion-selective potentiometry*, Appendix VIII E, using an ammonia-selective electrode. Determine the response slope of the electrode using standard ammonia solutions and measure the emf in the following solutions. For solution (1) shake a quantity of the cream (w_1 g) containing 40 mg of Urea with 5 mL of 1M *sulfuric acid* to disperse, warming if necessary, add 10 mL of *2,2,4-trimethylpentane*, shake for 2 minutes and centrifuge. Dilute 3 mL of the aqueous layer to 50 mL with *water* and to 20 mL of the resulting solution add 4 mL of 1M *sodium hydroxide*. Prepare solution (2) in the

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same manner but shaking a quantity of the cream (w_2 g) containing 40 mg of Urea with 5 mL of solution A in place of 5 mL of 1M *sulfuric acid*.

Calculate C_1 and hence the concentration of ammonia in the cream from the expression:

$$\Delta E = a \log(w_2/w_1 + C_2/C_1)$$

where	ΔE	=	the difference in the emf, in mV, obtained with the two solutions,
	a	=	the response slope in mV per decade,
	C_1	=	the concentration of ammonia in solution (1) as % w/v,
	C_2	=	the concentration of standard added ammonia in solution (2) as % w/v (this is 0.0129 times the concentration of ammonium sulfate in solution A as % w/v), namely 0.000451% w/v.

ASSAY

Shake a quantity containing 42 mg of Urea with 150 mL of hot *water* for 20 minutes, allow to cool and dilute to 500 mL with *water*. Filter through a fine glass microfibre filter paper (Whatman GF/C is suitable), transfer 1 mL of the filtrate to a 100 mL graduated flask, add 2 mL of a 0.1% w/v suspension of *urease-active meal*, stopper the flask and allow to stand for 15 minutes at 37°. Immediately add 25 mL of a solution containing 12 g of *sodium salicylate* and 0.24 g of *sodium nitroprusside* in 200 mL and 25 mL of a solution prepared by diluting a volume of *sodium hypochlorite solution* containing the equivalent of 0.66 g of available chlorine with 0.2M *sodium hydroxide* to 1000 mL. Mix well, allow to stand at 37° for 5 minutes and dilute to 100 mL with *water*. Measure the *absorbance* of the resulting solution at the maximum at 665 nm, Appendix II B, using in the reference cell a solution prepared in the same manner but using 1 mL of *water* in place of 1 mL of the filtrate. Repeat the operation using 42 mg of *urea BPCRS* in place of the cream being examined. Calculate the content of CH_4N_2O from the *absorbances* obtained using the declared content of CH_4N_2O in *urea BPCRS.*

STORAGE

Urea Cream should be stored in accordance with the manufacturer's instructions.

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Urofollitropin

General Notices

(Ph. Eur. monograph 0958)

97048-13-0

Action and use

Follicle-stimulating hormone.

Preparation

Urofollitropin Injection

Ph Eur

DEFINITION

Dried preparation containing menopausal gonadotrophin obtained from the urine of post-menopausal women. It has follicle-stimulating activity and no or virtually no luteinising activity.

Potency

Minimum 90 IU of follicle-stimulating hormone (hFSH) per milligram.

Ratio of the number of units of luteinising hormone (interstitial-cell-stimulating hormone) [hLH(ICSH)] to the number of units of follicle-stimulating hormone Maximum 1/60.

PRODUCTION

It is prepared by suitable collection and extraction procedures followed by purification steps.

The method of preparation includes steps that have been shown to remove and/or inactivate extraneous agents. In addition, the process is designed to minimise microbial contamination.

CHARACTERS

Appearance

Almost white or slightly yellowish powder.

Solubility

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Soluble in water.

IDENTIFICATION

When administered to immature female rats as prescribed in the assay, it causes enlargement of the ovaries.

TESTS

Residual luteinising activity

The International Units of FSH and LH are the activities contained in stated amounts of the International Standard of human urinary follicle-stimulating hormone and luteinising hormone (interstitial-cell-stimulating hormone) which consists of a mixture of a freeze-dried extract of urine of post-menopausal women with lactose. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Use immature female rats approximately 21 days old and having masses such that the difference between the heaviest and the lightest rat is not more than 10 g. Assign the rats at random to 4 equal groups of at least 6 animals. If sets of 4 litter mates are available, assign one litter mate at random from each set to each group and mark according to litter.

Inject subcutaneously into each rat 50 IU of *serum gonadotrophin R* on the first day and 25 IU of *chorionic gonadotrophin R* on the fourth day, each in 0.5 mL of *phosphate-albumin buffered saline pH 7.2 R*.

Choose 3 doses of the reference preparation such that the smallest dose produces a depletion of the ovarian ascorbic acid content in all the rats and the largest dose does not produce a maximal depletion in all the rats. Use doses in geometric progression; as an initial approximation, total doses of 0.5 IU, 1.0 IU and 2.0 IU may be tried although the dose to be used will depend on the sensitivity of the animals.

Choose a dose of the preparation to be examined expected to contain 60 *X* IU of follicle-stimulating hormone (hFSH), in which *X* = the number of International Units of hLH in the middle dose of the reference preparation.

Dissolve separately the total quantities of the preparation to be examined and of the reference preparation in 1.0 mL of *phosphate-albumin buffered saline pH 7.2 R*. Inject into a tail vein to each separate group of rats 6 days after the injection of chorionic gonadotrophin. Exactly 4 h after the injection, euthanise the rats and remove the ovaries from each animal. Remove any extraneous fluid and tissue from the ovaries and weigh the ovaries immediately.

Treat the combined ovaries from each rat separately, as follows. Crush and homogenise within 2 min in a freshly prepared 25 g/L solution of *metaphosphoric acid R* at a temperature of 4 °C and dilute to 7 mL with the same solution. Allow the homogenate to stand for 30 min at 4 °C and centrifuge at 4 °C at approximately 2500 *g*. Filter the supernatant, if necessary, through a 0.22 µm filter.

Prepare a fresh solution consisting of a mixture of 2 mL of a 45.3 g/L solution of *sodium acetate R* adjusted to pH 7 with *acetic acid R*, 3 mL of *water R* and 2 mL of *dichlorophenolindophenol standard solution R*. Mix 2 mL of this solution with 2 mL of the clear supernatant. 30 s after mixing, measure the absorbance (*2.2.25*) of the solution at the maximum at about 520 nm. Use as reference a solution with a known content of *ascorbic acid CRS* in a 25 g/L solution of *metaphosphoric acid R*, treated by the same process.

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Calculate the amount of ascorbic acid from the ascorbic acid standard curve obtained and express in milligrams per 0.1 g of ovary to obtain the ascorbic acid content of the ovaries. Calculate the mean and its variance of the ascorbic acid content of the ovaries of the rats treated with the preparation to be examined.

For each dose-group of the reference preparation, plot the mean ascorbic acid content of the ovaries as a function of the logarithm of the dose and analyse the regression of the ascorbic acid content on the logarithm of the dose injected, using standard methods of analysis (the method of least squares).

The test is not valid unless:

— the slope constant *b* is significant at the 0.05 significance level;

— for the groups treated with the reference preparation, the sum of squares due to linear regression is equal to at least 95 per cent of the total sum of squares of the ascorbic acid content;

— the within-group variance of the ascorbic acid content of the group receiving the preparation to be examined is not significantly different at the 0.05 significance level from the within-group variance of the ascorbic acid content of the groups receiving the reference preparation.

The mean ascorbic acid content of the ovaries of the rats treated with the preparation to be examined is not significantly lower than that of the rats treated with the middle dose of the reference preparation (calculated from the regression equation) at the 0.05 significance level.

Water (*2.5.32*)

Maximum 5.0 per cent.

Bacterial endotoxins (*2.6.14, Method C*)

Less than 0.40 IU per International Unit of urofollitropin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

The follicle-stimulating activity of urofollitropin is estimated by comparing under given conditions its effect in enlarging the ovaries of immature rats treated with chorionic gonadotrophin with the same effect of the International Standard preparation of human urinary follicle-stimulating hormone and luteinising hormone or of a reference preparation calibrated in International Units. The International Units of FSH and LH are the activities contained in stated amounts of the International Standard of human urinary follicle-stimulating hormone and luteinising hormone (interstitial-cell-stimulating hormone) which consists of a mixture of a freeze-dried extract of urine of post-menopausal women with lactose. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Use immature female rats of the same strain, 19-28 days old, differing in age by not more than 3 days and having masses such that the difference between the heaviest and the lightest rat is not more than 10 g. Assign the rats at random to 6 equal groups of at least 5 animals. If sets of 6 litter mates are available, assign one litter mate from each set to each group and mark according to litter.

Choose 3 doses of the reference preparation and 3 doses of the preparation to be examined such that the smallest dose produces a positive response in some of the rats and the largest dose does not produce a maximal response in all the rats. Use doses in geometric

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progression and as an initial approximation total doses of 1.5 IU, 3.0 IU and 6.0 IU may be tried although the dose will depend on the sensitivity of the animals used, which may vary widely.

Dissolve separately the total quantities of the preparation to be examined and of the reference preparation corresponding to the daily doses to be used in sufficient *phosphate-albumin buffered saline pH 7.2 R* such that the daily dose is administered in a volume of about 0.5 mL. The buffer solution shall contain in the daily dose not less than 14 IU of chorionic gonadotrophin to ensure complete luteinisation. Add a suitable antimicrobial preservative such as 4 g/L of phenol or 0.02 g/L of thiomersal. Store the solutions at 5 ± 3 °C.

Inject subcutaneously into each rat the daily dose allocated to its group. Repeat the injection of each dose 24 h and 48 h after the first injection. About 24 h after the last injection, euthanise the rats and remove the ovaries from each animal. Remove any extraneous fluid and tissue from the ovaries and weigh the 2 combined ovaries of each animal immediately. Calculate the results by the usual statistical methods (for example, *5.3*) using the mass of the 2 combined ovaries as the response (a suitable correction of the organ mass with reference to the mass of the animal from which it was taken may be applied; an analysis of covariance may be used).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) of the estimated potency are not less than 64 per cent and not more than 156 per cent of the stated potency.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states:

— the number of International Units of follicle-stimulating hormone per container;

— the potency, in International Units of follicle-stimulating hormone per milligram.

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Urofollitropin Injection

General Notices

Action and use

Follicle-stimulating hormone.

DEFINITION

Urofollitropin Injection is a sterile solution of Urofollitropin in Sodium Chloride Infusion. It is prepared by dissolving Urofollitropin for Injection in the requisite amount of Sodium Chloride Infusion immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Urofollitropin Injection should be used immediately after preparation.

UROFOLLITROPIN FOR INJECTION

DEFINITION

Urofollitropin for Injection is a sterile material consisting of Urofollitropin with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Potency

The estimated potency is not less than 80% and not more than 125% of the stated potency.

CHARACTERISTICS

An almost white or slightly yellow powder.

IDENTIFICATION

Causes enlargement of the ovaries of immature female rats when administered as directed in the Assay.

TESTS

Acidity or alkalinity

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Dissolve the contents of the sealed container in 3 mL of *water* (solution A). The pH is 6.0 to 8.0, Appendix V L.

Clarity and colour of solution

Solution A is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method I.

Residual luteinising activity

Comply with the test described under Urofollitropin.

Water

Comply with the test described under Urofollitropin.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C, using Method C. Dissolve the contents of the sealed container in *water BET* to give a solution containing 75 IU of urofollitropin per mL (solution A). The endotoxin limit concentration of solution A is 30 IU of endotoxin per mL. Carry out the test using a suitable dilution of solution A as described under Method C.

ASSAY

Carry out the Assay described under Urofollitropin. The fiducial limits of error are not less than 64% and not more than 156% of the stated potency.

STORAGE

The sealed container should be protected from light.

LABELLING

The label of the sealed container states the number of IU (Units) of follicle-stimulating hormone activity contained in it.

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Urokinase

General Notices

(Ph. Eur. monograph 0695)

9039-53-6

Action and use

Plasminogen activator; fibrinolytic; enzyme.

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DEFINITION

Enzyme, obtained from human urine, that activates plasminogen. It consists of a mixture of low-molecular-mass (LMM) (M_r 33 000) and high-molecular-mass (HMM) (M_r 54 000) forms, the high-molecular-mass form being predominant.

Potency

Minimum 70 000 IU per milligram of protein.

PRODUCTION

It is prepared by suitable collection and extraction procedures followed by purification steps.

The method of preparation includes steps that have been shown to remove and/or inactivate extraneous agents. In addition, the process is designed to minimise microbial contamination and vasoactive substances.

CHARACTERS

Appearance

White or almost white, amorphous powder.

Solubility

Soluble in water.

IDENTIFICATION

A. Place separately in 2 haemolysis tubes 0.5 mL of citrated human plasma and 0.5 mL of citrated bovine plasma and maintain in a water-bath at 37 °C. To each tube add 0.1 mL of a solution containing a quantity of the substance to be examined equivalent to 1000 IU/mL in

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phosphate buffer solution pH 7.4 R and 0.1 mL of a solution containing a quantity of *human thrombin R* equivalent to 20 IU/mL in *phosphate buffer solution pH 7.4 R*. Shake immediately. In both tubes, a clot forms and lyses within 30 min.

B. Carry out identification by a suitable immunodiffusion test.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 10 mg in 10 mL of *water R*.

Thromboplastic contaminants

Test solutions Dissolve suitable quantities of the substance to be examined in *barbital buffer solution pH 7.4 R* to obtain solutions with activities of 5000 IU/mL, 2500 IU/mL, 1250 IU/mL, 625 IU/mL and 312 IU/mL.

To each of 6 haemolysis tubes 1 cm in internal diameter add 0.1 mL of *citrated rabbit plasma R*. Allocate the test solutions 1 to each of 5 of the tubes; add to each tube 0.1 mL of the solution allocated to it and to the 6^{th} tube add 0.1 mL of *barbital buffer solution pH 7.4 R* (blank). Incubate the tubes at 25 ± 0.5 °C for 5 min and add 0.1 mL of a 3.675 g/L solution of *calcium chloride R*. Measure with a stop-watch the coagulation time for each tube. Plot the shortening of the recalcification time (clotting time of the blank minus clotting time measured) against log concentration in International Units. Extrapolate the best-fitting straight line through the 5 points until it reaches the log-concentration axis. The urokinase activity at the intersection point, which represents the limit concentration for coagulant activity (zero coagulant activity), is not less than 150 IU/mL.

Molecular fractions

Size-exclusion chromatography (*2.2.30*).

Test solution Dissolve about 1 mg in 1.0 mL of *0.02 M phosphate buffer solution pH 8.0 R*. Prepare immediately before use.

Column:

— *size*: *l* = 0.9 m, Ø = 16 mm;

— *stationary phase*: *cross-linked dextran for chromatography R3*;

— *temperature*: 5 °C.

Mobile phase 17.5 g/L solution of *sodium chloride R* in *0.02 M phosphate buffer solution pH 8.0 R*.

Flow rate 0.1 mL/min.

Apply the test solution to the head of the column rinsing twice with 0.5 mL portions of the buffer and carry out the elution. The eluate may be collected in fractions of 1 mL. Measure the absorbance (*2.2.25*) of the eluate at the maximum at 280 nm and plot the individual values on a graph. Draw perpendicular lines towards the axis of the abscissae from the minima before the HMM peak, between the HMM and the LMM peaks, and after the LMM peak, thus identifying the fractions to be considered in calculating the HMM/LMM activity ratio. Pool the

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HMM fractions and, separately, the LMM fractions. Determine separately the urokinase activity in International Units of each of the fraction pools by the method prescribed under Assay. The ratio of the urokinase activity in the HMM fraction pool to that in the LMM fraction pool is not less than 2.0.

Total protein

Determine the nitrogen content, using 10 mg, by the method of sulfuric acid digestion (2.5.9) and calculate the quantity of protein by multiplying by 6.25.

ASSAY

The potency of urokinase is determined by comparing its capacity to activate plasminogen to form plasmin with the same capacity of a reference preparation of urokinase calibrated in International Units; the formation of plasmin is measured by the determination of the lysis time of a fibrin clot under given conditions.

The International Unit is the activity contained in a stated amount of the International Reference Preparation, which consists of freeze-dried urokinase with lactose. The equivalence in International Units of the International Reference Preparation is stated by the World Health Organization.

Unless otherwise prescribed, use *phosphate buffer solution pH 7.4 R* containing 30 g/L of *bovine albumin R* for the preparation of the solutions and dilutions used in the assay.

Test solution Prepare a solution of the substance to be examined expected to have an activity of 1000 IU/mL.

Reference solution Prepare a solution of a reference preparation having an activity of 1000 IU/mL.

Keep the test solution and the reference solution in iced water and use within 6 h. Prepare 3 serial 1.5-fold dilutions of the reference preparation such that the longest clot-lysis time is less than 20 min and the shortest clot-lysis time is greater than 3 min. Prepare 3 similar dilutions of the test solution. Keep the solutions in iced water and use within 1 h. Use 24 tubes 8 mm in diameter. Label the tubes T_1, T_2 and T_3 for the dilutions of the test solution and S_1, S_2 and S_3 for the dilutions of the reference solution, allocating 4 tubes to each dilution. Place the tubes in iced water. Into each tube, introduce 0.2 mL of the appropriate dilution, 0.2 mL of *phosphate buffer solution pH 7.4 R* containing 30 g/L of *bovine albumin R* and 0.1 mL of a solution of *human thrombin R* having an activity of not less than 20 IU/mL. Place the tubes in a water-bath at 37 °C and allow to stand for 2 min to attain temperature equilibrium. Using an automatic pipette, introduce into the bottom of the 1st tube 0.5 mL of a 10 g/L solution of *bovine euglobulins R*, ensuring mixing. At intervals of 5 s, introduce successively into the remaining tubes 0.5 mL of a 10 g/L solution of *bovine euglobulins R*. Using a stop-watch, measure for each tube the time in seconds that elapses between the addition of the euglobulins solution and the lysis of the clot. Plot the logarithms of the lysis times for the substance to be examined and for the reference preparation against the logarithms of the concentration and calculate the activity of the substance to be examined using the usual statistical methods.

The estimated potency is not less than 90 per cent and not more than 111 per cent of the stated potency. The confidence limits (P = 0.95) of the estimated potency are not less than 80 per cent and not more than 125 per cent of the stated potency.

STORAGE

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In an airtight container, protected from light, at a temperature not exceeding 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states the potency in International Units per milligram of protein.

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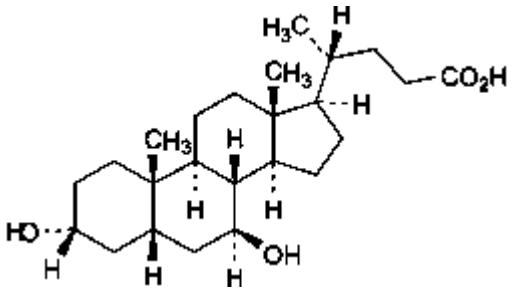
Ursodeoxycholic Acid

General Notices

(Ph. Eur. monograph 1275)



$C_{24}H_{40}O_4$ 392.6 *128-13-2*

Action and use

Bile acid; treatment of gallstones.

Preparations

Ursodeoxycholic Acid Capsules

Ursodeoxycholic Acid Tablets

Ursodeoxycholic Acid Oral Suspension

Ph Eur

DEFINITION

3α,7β-Dihydroxy-5β-cholan-24-oic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

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Practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in acetone, practically insoluble in methylene chloride.

mp

About 202 °C.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ursodeoxycholic acid CRS*.

B. Examine the chromatograms obtained in the test for impurity C.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 10 mg in 1 mL of *sulfuric acid R*. Add 0.1 mL of *formaldehyde solution R* and allow to stand for 5 min. Add 5 mL of *water R*. The suspension obtained is greenish-blue.

TESTS

Specific optical rotation (*2.2.7*)

+ 58.0 to + 62.0 (dried substance).

Dissolve 0.500 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Impurity C

Thin-layer chromatography (*2.2.27*).

Solvent mixture *water R*, *acetone R* (10:90 *V/V*).

Test solution (a) Dissolve 0.40 g of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 40 mg of *ursodeoxycholic acid CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 20 mg of *lithocholic acid CRS* (impurity C) in the solvent mixture and dilute to 10.0 mL with the solvent mixture (solution A). Dilute 2.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) To 5 mL of solution A add 10 mg of *chenodeoxycholic acid CRS* (impurity A) and dilute to 50 mL with the solvent mixture.

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Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *methylene chloride R* (1:30:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 120 °C for 10 min.

Detection Spray immediately with a 47.6 g/L solution of *phosphomolybdic acid R* in a mixture of 1 volume of *sulfuric acid R* and 20 volumes of *glacial acetic acid R* and heat at 120 °C until blue spots appear on a lighter background.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated principal spots.

Limit Test solution (a):

— *impurity C*: any spot due to impurity C is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *methanol R*, mobile phase (10:90 *V/V*).

Test solution Dissolve 60 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *ursodeoxycholic acid for system suitability CRS* (containing impurities A and H) in 1.0 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C ± 1 °C.

Mobile phase Mix 30 volumes of *acetonitrile R*, 37 volumes of a 0.78 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 3 with *phosphoric acid R*, and 40 volumes of *methanol R*.

Flow rate 0.8 mL/min.

Detection Refractometer at 35 ± 1 °C.

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Injection 150 µL.

Run time 4 times the retention time of ursodeoxycholic acid.

Identification of impurities Use the chromatogram supplied with *ursodeoxycholic acid for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and H.

Relative retention With reference to ursodeoxycholic acid (retention time = about 14 min): impurity H = about 0.9; impurity A = about 2.8.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity H and ursodeoxycholic acid.

Limits:

— *impurity A*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 mL of *ethanol (96 per cent) R*, previously neutralised to 0.2 mL of *phenolphthalein solution R*. Add 50 mL of *water R* and titrate with *0.1 M sodium hydroxide* until a pink colour is obtained.

1 mL of *0.1 M sodium hydroxide* is equivalent to 39.26 mg of $C_{24}H_{40}O_4$.

IMPURITIES

Specified impurities *A, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E, F, G, H, I.*

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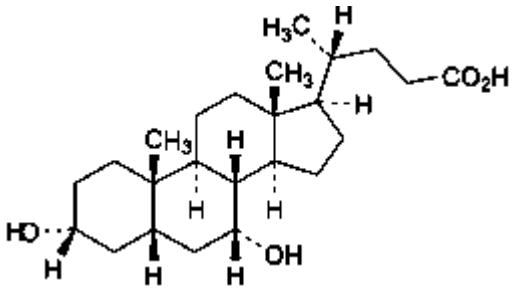
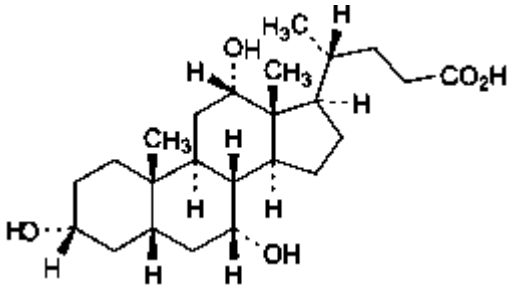
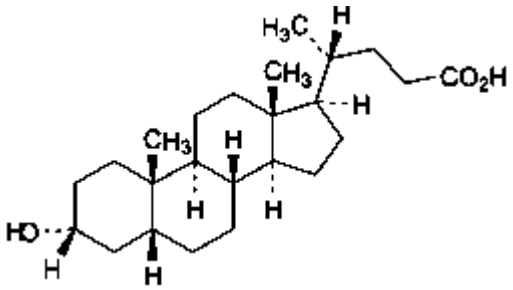


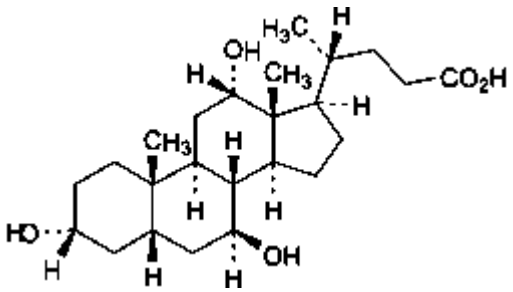
A. 3α,7α-dihydroxy-5β-cholan-24-oic acid (chenodeoxycholic acid),



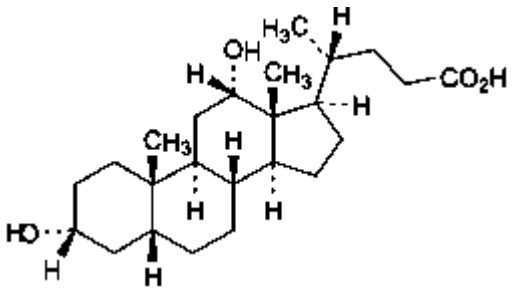
B. 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid (cholic acid),



C. 3α-hydroxy-5β-cholan-24-oic acid (lithocholic acid),



D. 3α,7β,12α-trihydroxy-5β-cholan-24-oic acid (ursocholic acid),



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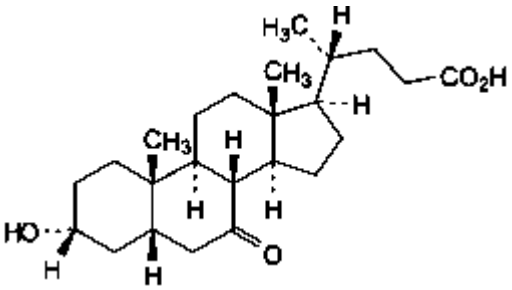
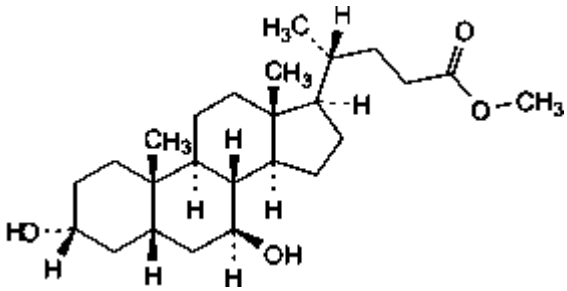
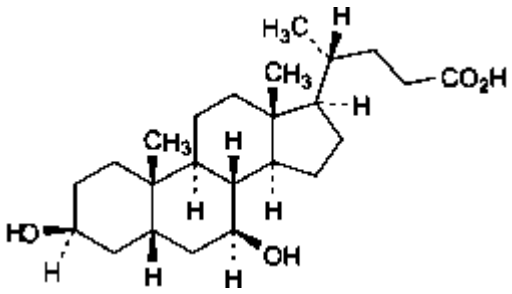
E. 3α,12α-dihydroxy-5β-cholan-24-oic acid (deoxycholic acid),



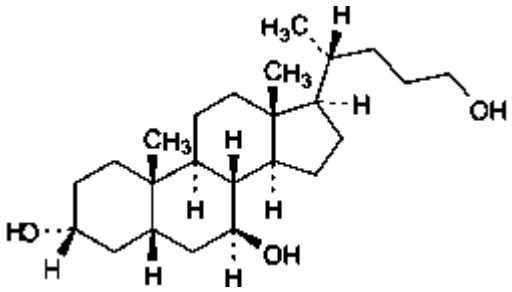
F. 3α-hydroxy-7-oxo-5β-cholan-24-oic acid,



G. methyl 3α,7β-dihydroxy-5β-cholan-24-oate,



H. 3β,7β-dihydroxy-5β-cholan-24-oic acid,



I. 5β-cholane-3α,7β,24-triol.

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Ursodeoxycholic Acid Capsules

General Notices

Action and use

Bile acid; treatment of gallstones.

DEFINITION

Ursodeoxycholic Acid Capsules contain Ursodeoxycholic Acid.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of ursodeoxycholic acid, $C_{24}H_{40}O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the contents of the capsules containing 0.1 g of Ursodeoxycholic Acid with 10 mL of *ethanol* (*96%*), centrifuge and evaporate the supernatant liquid to dryness in a stream of nitrogen in a water bath at room temperature. Dry the residue at room temperature at a pressure of 0.7 kPa for 2 hours. The *infrared absorption spectrum*, Appendix II A, of the dried residue is concordant with the *reference spectrum* of ursodeoxycholic acid (*RS 402*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of phosphate buffer of pH 7.5, prepared using equal volumes of 0.05M *potassium dihydrogen orthophosphate* and 0.05M *disodium hydrogen orthophosphate*, and adjusting the pH to 7.5 using 1M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) After 45 minutes withdraw a sample of the medium and filter. Dilute, if necessary, with sufficient dissolution medium to produce a solution expected to contain 0.028% w/v of Ursodeoxycholic Acid.

(2) Add 0.7 mL of 0.1M *sodium hydroxide* to 28 mg of *ursodeoxycholic acid BPCRS* and add sufficient dissolution medium to produce 100 mL, mix with the aid of ultrasound for 20 minutes and leave to cool at room temperature.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used with an injection volume of 250 µL.

DETERMINATION OF CONTENT

Calculate the total content of ursodeoxycholic acid, $C_{24}H_{40}O_4$, in the medium from the chromatograms obtained and using the declared content of $C_{24}H_{40}O_4$ in *ursodeoxycholic acid BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in Solvent A.

Solvent A 20 volumes of *methanol* and 80 volumes of the mobile phase.

(1) Add a quantity of the contents of the capsules containing 250 mg of Ursodeoxycholic Acid to 15 mL of Solvent A and mix with the aid of ultrasound for 15 minutes. Dilute to 50 mL and filter (0.45-µm PVDF filter is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.5% w/v of *ursodeoxycholic acid impurity standard BPCRS* and 0.0055% w/v of *chenodeoxycholic acid BPCRS* (impurity A).

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Uptisphere HDO C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a refractive index detector.

(f) Inject 8 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 5 times the retention time of ursodeoxycholic acid.

MOBILE PHASE

25 volumes of *acetonitrile*, 34 volumes of *methanol* and 47 volumes of a solution prepared by dissolving 0.8 g of *sodium dihydrogen orthophosphate dihydrate* in 1000 mL of *water* and adjusting the pH to 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to ursodeoxycholic acid (retention time, about 5 minutes) are: 7-ketolithocholic acid (impurity F), about 1.3 and chenodeoxycholic acid, about 2.8.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ursodeoxycholic acid and 7-ketolithocholic acid is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peaks corresponding to chenodeoxycholic acid is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peak* is not greater than 4.2 times the area of the principal peak in the chromatogram obtained with solution (2) (2.1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh a quantity of the mixed contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the mixed contents of the capsules containing 0.125 g of Ursodeoxycholic Acid add 15 mL of *methanol*, mix with the aid of ultrasound for 10 minutes and dilute to 50 mL with the mobile phase.
(2) Dissolve 50 mg of *ursodeoxycholic acid BPCRS* in 2 mL of *methanol* with the aid of ultrasound for 10 minutes and dilute to 20 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Superspher 100 RP 18E is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 30 µL of each solution.

MOBILE PHASE

To 40 volumes of *acetonitrile R1* add 60 volumes of 0.001M *potassium dihydrogen orthophosphate*, allow to equilibrate to room temperature, adjust to pH 2.0 with *orthophosphoric acid* (*85%*) and filter.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{40}O_4$ using the declared content of $C_{24}H_{40}O_4$ in *ursodeoxycholic acid BPCRS*.

IMPURITIES

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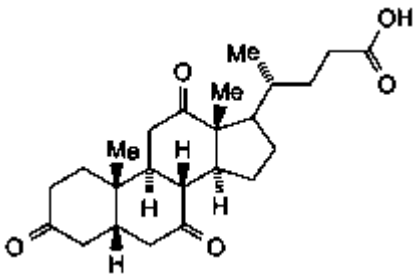
The impurities limited by the requirements of this monograph include A, D, E and F listed under Ursodeoxycholic Acid and the following:



1. 3,7,12-trioxo-(5β)-cholan-24-oic acid (dehydrocholic acid).

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Ursodeoxycholic Acid Oral Suspension

General Notices

Action and use

Bile acid; treatment of gallstones.

DEFINITION

Ursodeoxycholic Acid Oral Suspension is a suspension of Ursodeoxycholic Acid in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ursodeoxycholic acid, $C_{24}H_{40}O_4$

95.0 to 105.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. Weigh a quantity of the oral suspension containing 50 mg of Ursodeoxycholic Acid into a test tube, add 5 mL of *sulfuric acid* and allow to dissolve. Add 0.5 mL *formaldehyde solution*, allow to stand for 5 minutes and add 25 mL *water*. The suspension obtained is greyish-blue.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.8 to 5.2, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in Solvent A.

Solvent A 20 volumes of *methanol* and 80 volumes of mobile phase.

(1) Add a quantity of the oral suspension containing 250 mg of Ursodeoxycholic Acid to 15 mL of Solvent A and mix with the aid of ultrasound for 15 minutes. Dilute to 50 mL and filter (0.45-µm PVDF filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.5% w/v of *ursodeoxycholic acid impurity standard BPCRS* and 0.0055% w/v of *chenodeoxycholic acid BPCRS* (impurity A).

(4) Dilute 1 volume of solution (2) to 10 volumes.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Uptisphere HDO C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a refractive index detector.

(f) Inject 8 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 5 times the retention time of ursodeoxycholic acid.

MOBILE PHASE

25 volumes of *acetonitrile*, 34 volumes of *methanol* and 47 volumes of a solution prepared by dissolving 0.8 g of *sodium dihydrogen orthophosphate dihydrate* in 1000 mL of *water* and adjusting the pH to 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to ursodeoxycholic acid (retention time, about 5 minutes) are: 7-ketolithocholic acid (impurity F), about 1.3 and chenodeoxycholic acid, about 2.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ursodeoxycholic acid and 7-ketolithocholic acid is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peaks corresponding to chenodeoxycholic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in Solvent A, as described under Related substances.

(1) Add a weighed quantity of the oral suspension containing 250 mg of Ursodeoxycholic Acid to 15 mL of Solvent A and mix with the aid of ultrasound for 15 minutes. Dilute to 50 mL and filter (0.45-µm PVDF filter is suitable).

(2) 0.5% w/v of *ursodeoxycholic acid BPCRS*.

(3) 0.5% w/v of *ursodeoxycholic acid impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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The conditions described under Related substances may be used.

SYSTEM SUITABILITY

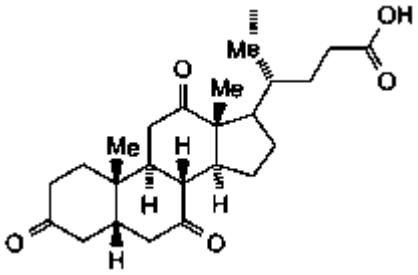
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ursodeoxycholic acid and 7-ketolithocholic acid is at least 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{24}H_{40}O_4$, weight in volume, using the declared content of $C_{24}H_{40}O_4$ in *ursodeoxycholic acid BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include A, D, E and F listed under Ursodeoxycholic Acid and the following:



1. 3,7,12-trioxo-(5β)-cholan-24-oic acid (dehydrocholic acid).

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Ursodeoxycholic Acid Tablets

General Notices

Action and use

Bile acid; treatment of gallstones.

DEFINITION

Ursodeoxycholic Acid Tablets contain Ursodeoxycholic Acid. They may be coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ursodeoxycholic acid, $C_{24}H_{40}O_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 0.1 g of Ursodeoxycholic Acid with 10 mL of *ethanol* (*96%*), centrifuge and evaporate the supernatant liquid to dryness in a stream of nitrogen in a water bath at room temperature. Dry the residue at room temperature at a pressure of 0.7 kPa for 2 hours. The *infrared absorption spectrum*, Appendix II A, of the dried residue is concordant with the *reference spectrum* of ursodeoxycholic acid (*RS 402*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of phosphate buffer as the dissolution medium, prepared using 0.68% w/v *potassium dihydrogen orthophosphate* adjusted to pH 8.0 using 2M *sodium hydroxide* at a temperature of 37°.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) After 45 minutes withdraw a sample of the dissolution medium and filter. Dilute with dissolution medium, if necessary, to produce a solution containing 0.017% w/v of Ursodeoxycholic Acid.

(2) Dissolve 17 mg of *ursodeoxycholic acid BPCRS* in 1 mL of *ethanol* (*96%*) and dilute to 100 mL with the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable), fitted with a stainless steel guard column packed with the same material (Lichrospher 100-RP 18E is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°C for both columns.

(e) Use a detection wavelength of 210 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

280 volumes of *acetonitrile R1* and 720 volumes of a 0.05M phosphate buffer prepared by dissolving 6.81 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 6.5 with 2M *sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the total content of ursodeoxycholic acid, $C_{24}H_{40}O_4$, in the medium using the declared content of $C_{24}H_{40}O_4$ in *ursodeoxycholic acid BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in Solvent A.

Solvent A 20 volumes of *methanol* and 80 volumes of the mobile phase.

(1) Add a quantity of the tablets containing 250 mg of Ursodeoxycholic Acid to 15 mL of Solvent A and mix with the aid of ultrasound for 15 minutes. Dilute to 50 mL and filter (0.45-µm PVDF filter is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.5% w/v of *ursodeoxycholic acid impurity standard BPCRS* and 0.0055% w/v of *chenodeoxycholic acid BPCRS* (impurity A).

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Uptisphere HDO C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a refractive index detector.

(f) Inject 8 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of ursodeoxycholic acid.

MOBILE PHASE

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25 volumes of *acetonitrile*, 34 volumes of *methanol* and 47 volumes of a solution prepared by dissolving 0.8 g of *sodium dihydrogen orthophosphate dihydrate* in 1000 mL of *water* and adjusting the pH to 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to ursodeoxycholic acid (retention time, about 5 minutes) are: 7-ketolithocholic acid (impurity F), about 1.3 and chenodeoxycholic acid, about 2.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ursodeoxycholic acid and 7-ketolithocholic acid is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of the peak due to chenodeoxycholic acid is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peak* is not greater than 4.2 times the area of the principal peak in the chromatogram obtained with solution (2) (2.1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D using the following solutions in Solvent B.

Solvent B Prepare a solution containing 535 mL of *water*, 6.0 g of *sodium dihydrogen orthophosphate dihydrate*, 2.0 g of *disodium hydrogen orthophosphate dihydrate*, 65 mL of *tetrabutylammonium hydroxide solution* and 400 mL of *acetonitrile R1*.

(1) Mix a quantity of the powdered tablets containing 0.3 g of Ursodeoxycholic Acid with 20 mL of solvent B with the aid of ultrasound for 15 minutes, shake intermittently and filter, if necessary.
(2) 1.5% w/v of *ursodeoxycholic acid BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of ursodeoxycholic acid.

MOBILE PHASE

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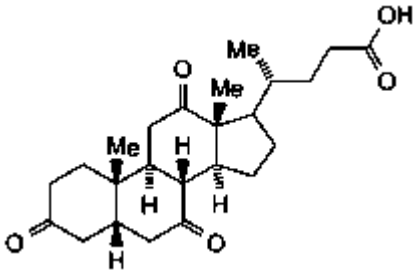
500 volumes of *acetonitrile R1* and 500 volumes of a solution containing 1.2% w/v of *sodium dihydrogen orthophosphate dihydrate*, 0.4% w/v of *disodium hydrogen orthophosphate dihydrate* and 1.08% w/v of *tetrabutylammonium hydrogen sulfate* in *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{40}O_4$ in the tablets using the declared content of $C_{24}H_{40}O_4$ in *ursodeoxycholic acid BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include A, D, E and F listed under Ursodeoxycholic Acid and the following:



1. 3,7,12-trioxo-(5β)-cholan-24-oic acid (dehydrocholic acid).

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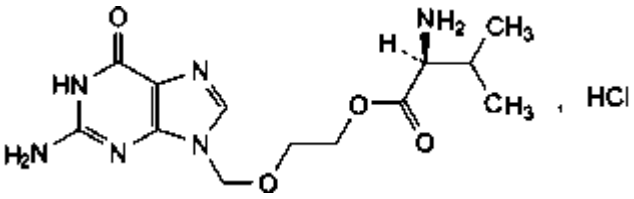
Valaciclovir Hydrochloride

General Notices

(Ph. Eur. monograph 1768)



$C_{13}H_{21}ClN_6O_4$ 360.8 *124832-27-5*

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

Preparation

Valaciclovir Tablets

Ph Eur

DEFINITION

2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-valinate hydrochloride.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

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Carry out either tests A, B, C, E or tests A, B, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *anhydrous valaciclovir hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *anhydrous ethanol R* and evaporate to dryness in a desiccator, under high vacuum, over *diphosphorus pentoxide R*. Record new spectra using the residues.

B. It gives reaction (a) of chlorides (2.3.1).

C. It complies with the limit for impurity R given in test A for related substances.

D. Optical rotation (2.2.7): laevorotatory.

Dissolve 2.50 g in *water R* and dilute to 50.0 mL with the same solvent.

E. Water (see Tests).

TESTS

Impurities E, F and G

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.250 g of the substance to be examined in 2 mL of *water R* and dilute to 5.0 mL with *ethanol (96 per cent) R*.

Reference solution (a) Dissolve 5 mg of *valaciclovir impurity D CRS*, 5.0 mg of *valaciclovir impurity E CRS*, 5.0 mg of *valaciclovir impurity G CRS* and 8.4 mg of *valaciclovir impurity F para-toluenesulfonate CRS* in a mixture of 2 mL of *water R* and 6 mL of *ethanol (96 per cent) R*, and dilute to 10.0 mL with *ethanol (96 per cent) R*.

Reference solution (b) Dilute 3.0 mL of reference solution (a) to 10.0 mL with *ethanol (96 per cent) R*.

Reference solution (c) Dilute 2.0 mL of reference solution (a) to 10.0 mL with *ethanol (96 per cent) R*.

Reference solution (d) Dilute 0.5 mL of reference solution (a) to 10.0 mL with *ethanol (96 per cent) R*.

Plate *TLC silica gel F_{254} plate R* (2-10 µm).

Pretreatment Wash the plate with *methanol R* until the solvent front has migrated over at least 4/5 of the plate; allow the plate to dry.

Mobile phase *concentrated ammonia R*, *tetrahydrofuran R*, *methanol R*, *methylene chloride R* (3:12:34:54 *V/V/V/V*); use freshly prepared mobile phase.

Application 4 µL of the test solution and reference solutions (b), (c) and (d).

Development Over 4/5 of the plate.

Drying In a current of air.

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Detection Examine in ultraviolet light at 254 nm for impurities E and G; spray with a 0.1 g/L solution of *fluorescamine R* in *ethylene chloride R* and examine in ultraviolet light at 365 nm for impurity F.

Retardation factors Impurity A = about 0; impurity B = about 0.2; valaciclovir = about 0.3; impurity C = about 0.5; impurity D = about 0.6; impurity E = about 0.7; impurity F = about 0.75; impurity G = about 0.79; impurity C is masked by the leading edge of the spot due to valaciclovir; impurities F and G may co-elute, but this does not adversely affect their quantification because they are visualised differently.

System suitability The chromatograms obtained with reference solutions (b), (c) and (d) each show 3 clearly separated spots when examined under ultraviolet light at 254 nm, due to impurities D, E and G.

Limits:

— *impurity E*: any spot due to impurity E is not more intense than the corresponding spot in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity F*: any spot due to impurity F is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.3 per cent calculated as hydrochloride salt);

— *impurity G*: any spot due to impurity G is not more intense than the corresponding spot in the chromatogram obtained with reference solution (d) (0.05 per cent).

Related substances

A. Impurities A, B, I and R. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 50.0 mg of the substance to be examined in a 0.5 per cent *V/V* solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 2.5 mg of *valaciclovir for system suitability CRS* (containing impurities A, B, C, D, H, I, J, M and R) in a 0.5 per cent *V/V* solution of *hydrochloric acid R* and dilute to 5.0 mL with the same solution.

Reference solution (b) Dissolve 50.0 mg of *anhydrous valaciclovir hydrochloride CRS* in a 0.5 per cent *V/V* solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution.

Reference solution (c) Dilute 3.0 mL of the test solution to 100.0 mL with a 0.5 per cent *V/V* solution of *hydrochloric acid R*. Dilute 1.0 mL of this solution to 100.0 mL with a 0.5 per cent *V/V* solution of *hydrochloric acid R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *crown-ether silica gel for chiral separation R* (5 µm);

— *temperature*: 10 °C.

Mobile phase *perchloric acid R*, *methanol R*, *water for chromatography R* (0.5:5:95 *V/V/V*).

Flow rate 0.75 mL/min.

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Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 1.5 times the retention time of valaciclovir.

Identification of impurities Use the chromatogram supplied with *valaciclovir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A + B, C + R, D, I and M.

Relative retention With reference to valaciclovir (retention time = about 21 min): impurities A and B = about 0.2; impurity I = about 0.4; impurities C and R = about 0.6; impurity D = about 0.7; impurity M = about 1.3.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurities C and R.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurities A and B by 0.7;

— *impurity R*: maximum 3.0 per cent; for the calculation, subtract the content of impurity C as determined in test B for related substances from the content of the coeluting impurities C and R as determined in this test;

— *sum of impurities A and B*: maximum 2.0 per cent;

— *impurity I*: maximum 0.2 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.03 per cent); disregard any peaks due to impurities other than A + B, C + R or I.

B. Liquid chromatography (2.2.29): use the normalisation procedure. *Use the solutions within 24 h of preparation.*

Solvent mixture *ethanol (96 per cent) R*, *water R* (20:80 *V/V*).

Test solution Dissolve 40 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2.5 mg of *valaciclovir for system suitability CRS* (containing impurities A, B, C, D, H, I, J, M and R) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylhexylsilyl silica gel for chromatography R* (5 µm);

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— *temperature*: 15 °C.

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *water for chromatography R* (0.2:100 *V/V*);

— *mobile phase B*: *trifluoroacetic acid R*, *methanol R2* (0.2:100 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 35	90 → 60	10 → 40

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *valaciclovir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, H, I, J and M.

Relative retention With reference to valaciclovir (retention time = about 19 min): impurity A = about 0.3; impurity B = about 0.4; impurity H = about 0.5; impurity C = about 1.06; impurity I = about 1.09; impurity D = about 1.2; impurity J = about 1.3; impurity M = about 1.6.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to valaciclovir;

— the chromatogram obtained is similar to the chromatogram supplied with *valaciclovir for system suitability CRS*.

Limits:

— *impurity M*: maximum 1.5 per cent;

— *impurity D*: maximum 0.5 per cent;

— *impurity C*: maximum 0.3 per cent;

— *impurities H, J*: for each impurity, maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *disregard limit*: 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent); disregard the peaks due to impurities A, B and I.

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Limit:

— *total for tests A and B*: maximum 5.0 per cent.

Chloride

9.4 to 9.9 per cent (anhydrous and solvent-free substance).

Dissolve 0.350 g in 100 mL of *water R* and add 0.2 mL of *nitric acid R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M silver nitrate*. Use a silver indicator electrode and a silver-silver chloride reference electrode or a combined silver electrode. Discard the result from the first titration, which is used to condition the electrodes. Carry out a blank titration.

1 mL of *0.1 M silver nitrate* is equivalent to 3.543 mg of Cl.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modification.

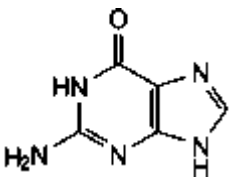
Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{13}H_{21}ClN_6O_4$ taking into account the assigned content of *anhydrous valaciclovir hydrochloride CRS*.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J, M, R.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *K, L, N, O, P, Q.*



A. 2-amino-1,9-dihydro-6*H*-purin-6-one (guanine),

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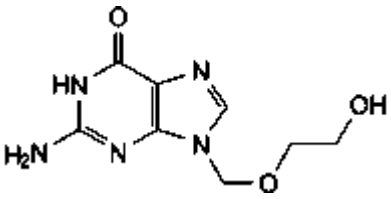
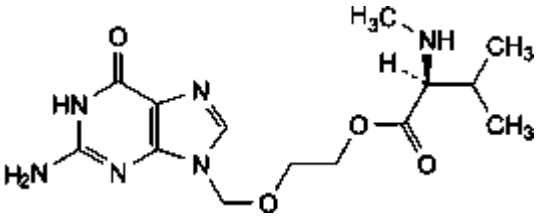
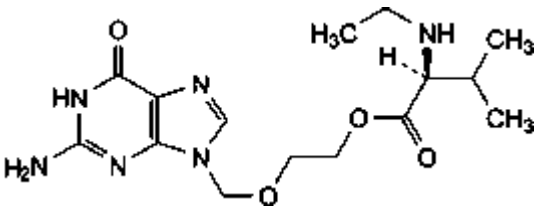


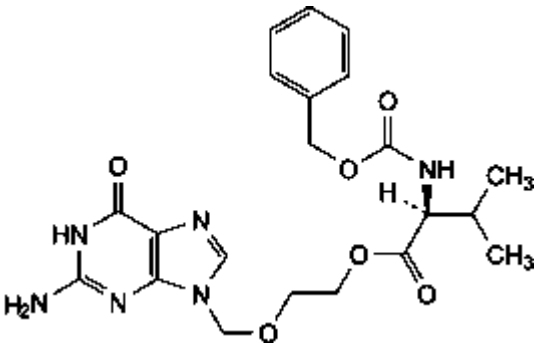
B. 2-amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one (aciclovir),



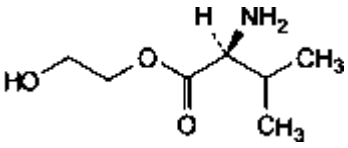
C. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-methyl-L-valinate,



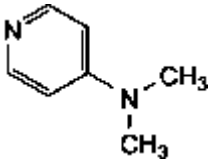
D. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-ethyl-L-valinate,



E. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-[(benzyloxy)carbonyl]-L-valinate,



F. 2-hydroxyethyl L-valinate,



G. *N,N*-dimethylpyridin-4-amine,

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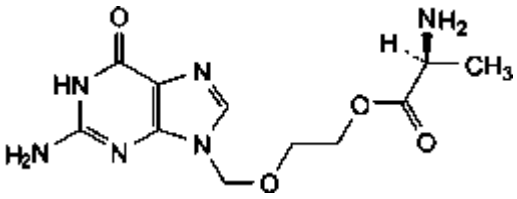
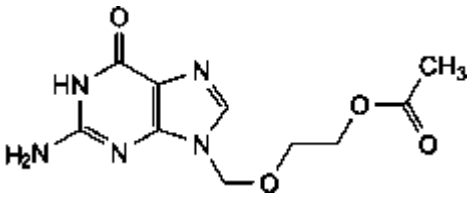
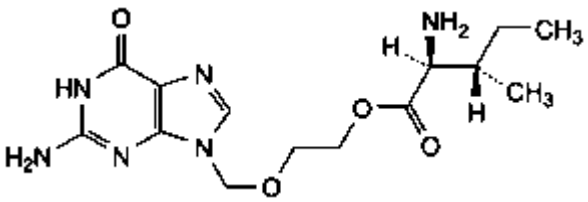


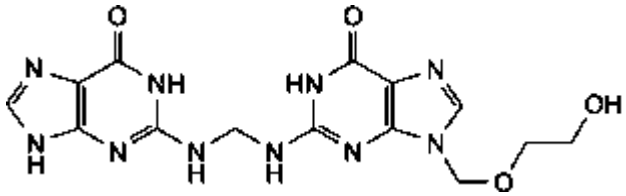
H. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-alaninate,



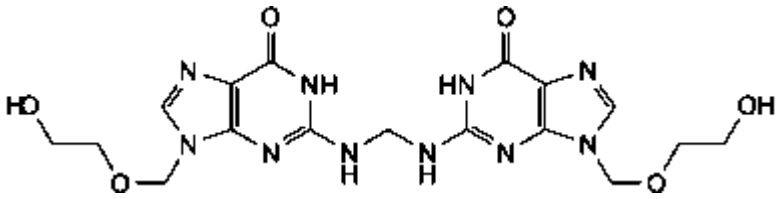
I. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate,



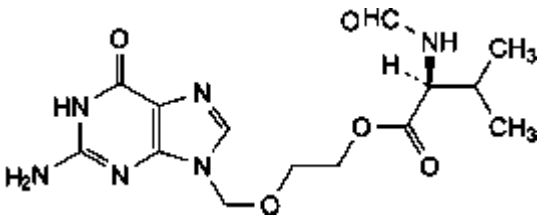
J. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-isoleucinate,



K. 9-[(2-hydroxyethoxy)methyl]-2-[[[(6-oxo-6,9-dihydro-1*H*-purin-2-yl)amino]methyl]amino]-1,9-dihydro-6*H*-purin-6-one,



L. 2,2′-(methylenediazanediyl)bis[9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one],



M. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-formyl-L-valinate,

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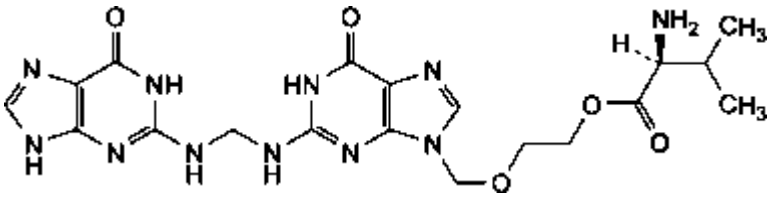
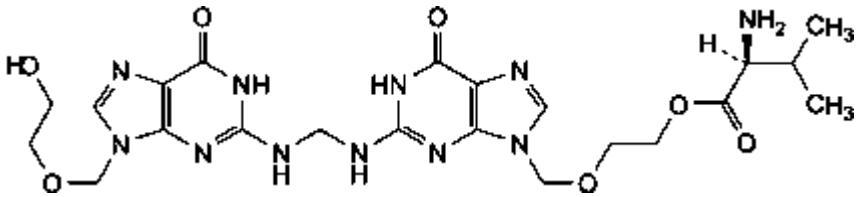
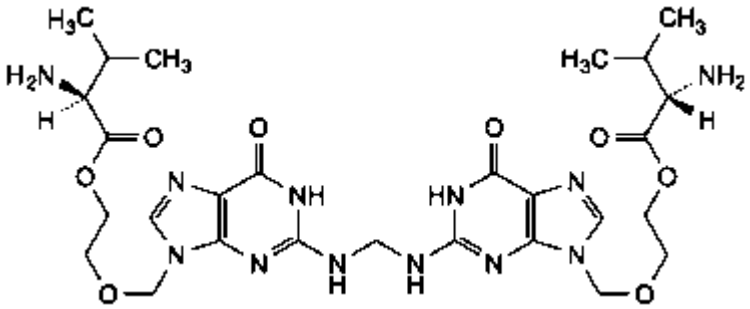


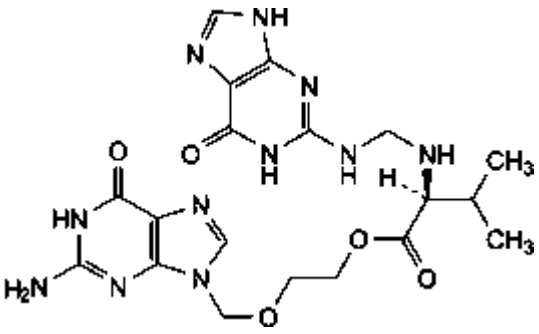
N. 2-[[6-oxo-2-[[[(6-oxo-6,9-dihydro-1*H*-purin-2-yl)amino]methyl]amino]-1,6-dihydro-9*H*-purin-9-yl]methoxy]ethyl L-valinate,



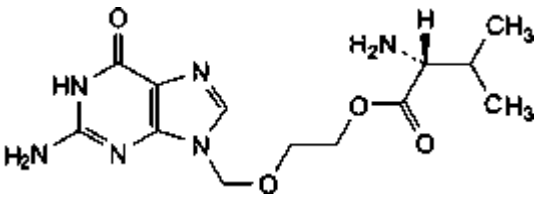
O. 2-[[2-[[[[9-[(2-hydroxyethoxy)methyl]-6-oxo-6,9-dihydro-1*H*-purin-2-yl]amino]methyl]amino]-6-oxo-1,6-dihydro-9*H*-purin-9-yl]methoxy]ethyl L-valinate,



P. [methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxyethan-2,1-diyl]] di-L-valinate,



Q. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-[[(6-oxo-6,9-dihydro-1*H*-purin-2-yl)amino]methyl]-L-valinate,



R. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl D-valinate.

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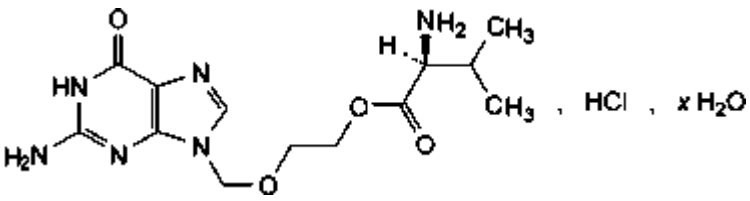
Valaciclovir Hydrochloride Hydrate

General Notices

Valaciclovir Hydrochloride, Hydrated

(Ph. Eur. monograph 2751)



$C_{13}H_{21}ClN_6O_4,xH_2O$ 360.8 (anhydrous substance) *1218948-84-5*

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

Preparation

Valaciclovir Tablets

Ph Eur

DEFINITION

2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-valinate hydrochloride hydrate.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Freely soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in acetonitrile.

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It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve the substance to be examined in the minimum volume of water R, evaporate to dryness at room temperature and record the spectrum using the residue.

Comparison Repeat the operations using anhydrous valaciclovir hydrochloride CRS.

B. It complies with the limit for impurity R (see test A for related substances).

C. Water (see Tests).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Impurities G and S

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.250 g of the substance to be examined in 2 mL of water R and dilute to 5.0 mL with ethanol (96 per cent) R.

Reference solution Dissolve 5.0 mg of valaciclovir impurity G CRS and 5.0 mg of valaciclovir impurity S CRS in a mixture of 2 mL of water R and 6 mL of ethanol (96 per cent) R and dilute to 10.0 mL with ethanol (96 per cent) R. Dilute 0.5 mL of the solution to 10.0 mL with ethanol (96 per cent) R.

Plate TLC silica gel F_{254} plate R (2-10 µm).

Pretreatment Wash the plate with methanol R until the solvent front has migrated over at least 4/5 of the plate; allow to dry in air.

Mobile phase concentrated ammonia R, tetrahydrofuran R, methanol R, methylene chloride R (3:12:34:54 *V/V/V/V*); use freshly prepared mobile phase.

Application 4 µL.

Development Over 4/5 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Valaciclovir = about 0.3; impurity S = about 0.7; impurity G = about 0.8.

System suitability The chromatogram obtained with the reference solution shows 2 clearly separated spots due to impurities S and G.

Limits:

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— *impurity G*: any spot due to impurity G is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.05 per cent);

— *impurity S*: any spot due to impurity S is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.05 per cent).

Related substances

A. Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 50.0 mg of the substance to be examined in a 0.5 per cent *V/V* solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 2.5 mg of *valaciclovir for system suitability CRS* (containing impurities A, B, C, D, H, M and R) in a 0.5 per cent *V/V* solution of *hydrochloric acid R* and dilute to 5.0 mL with the same solution.

Reference solution (b) Dissolve 50.0 mg of *anhydrous valaciclovir hydrochloride CRS* in a 0.5 per cent *V/V* solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution.

Reference solution (c) Dilute 3.0 mL of the test solution to 100.0 mL with a 0.5 per cent *V/V* solution of *hydrochloric acid R*. Dilute 1.0 mL of this solution to 100.0 mL with a 0.5 per cent *V/V* solution of *hydrochloric acid R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *crown-ether silica gel for chiral separation R* (5 µm);

— *temperature*: 10 °C.

Mobile phase *perchloric acid R*, *methanol R*, *water for chromatography R* (0.5:5:95 *V/V/V*).

Flow rate 0.75 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time 1.5 times the retention time of valaciclovir.

Identification of impurities Use the chromatogram supplied with *valaciclovir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A + B, C + R, D and M.

Relative retention With reference to valaciclovir (retention time = about 17 min): impurities A and B = about 0.2; impurities C and R = about 0.6; impurity D = about 0.7; impurity M = about 1.3.

System suitability Reference solution (a):

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— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurities C and R.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurities A and B by 0.7;

— *impurity R*: maximum 3.0 per cent; for the calculation, subtract the content of impurity C as determined in test B for related substances from the content of the coeluting impurities C and R as determined in this test;

— *sum of impurities A and B*: maximum 2.0 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.03 per cent); disregard any peaks due to impurities other than A + B and C + R.

B. Liquid chromatography (2.2.29): use the normalisation procedure. *Use the solutions within 24 h of preparation.*

Solvent mixture ethanol (96 per cent) R, water R (20:80 *V/V*).

Test solution Dissolve 80 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 1.6 mg of valaciclovir for system suitability CRS (containing impurities A, B, C, D, H, M and R) in the solvent mixture and dilute to 2.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of valaciclovir impurity P CRS in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped phenylhexylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 15 °C.

Mobile phase:

— *mobile phase A*: trifluoroacetic acid R, water for chromatography R (0.2:100 *V/V*);

— *mobile phase B*: trifluoroacetic acid R, methanol R2 (0.2:100 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
5 - 35	90 → 60	10 → 40
35 - 45	60	40

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *valaciclovir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, H and M; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity P.

Relative retention With reference to valaciclovir (retention time = about 20 min): impurity A = about 0.3; impurity B = about 0.4; impurity H = about 0.5; impurity C = about 1.06; impurity D = about 1.2; impurity M = about 1.6; impurity P = about 2.0.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to valaciclovir.

Limits:

— *impurity M*: maximum 0.6 per cent;

— *impurity D*: maximum 0.3 per cent;

— *impurity C*: maximum 0.2 per cent;

— *impurities H, P*: for each impurity, maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *disregard limit*: 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent); disregard the peaks due to impurities A and B.

Limit:

— *total for tests A and B*: maximum 4.0 per cent.

Water (2.5.12)

4.5 per cent to 11.0 per cent, determined on 0.100 g.

Sulfated ash (2.4.14)

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Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in test A for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{13}H_{21}ClN_6O_4$ taking into account the assigned content of *anhydrous valaciclovir hydrochloride CRS*.

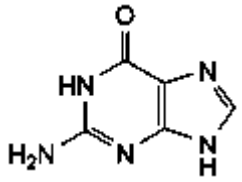
STORAGE

In an airtight container.

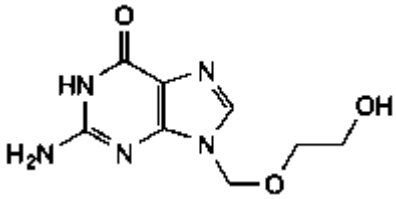
IMPURITIES

Specified impurities *A, B, C, D, G, H, M, P, R, S.*

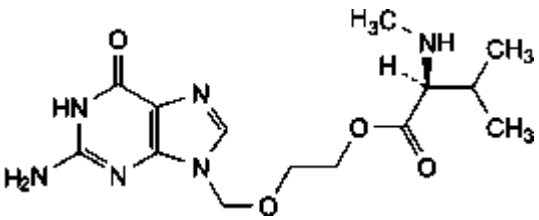
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *I, J, N.*



A. 2-amino-1,9-dihydro-6*H*-purin-6-one (guanine),



B. 2-amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one (aciclovir),



C. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-methyl-L-valinate,

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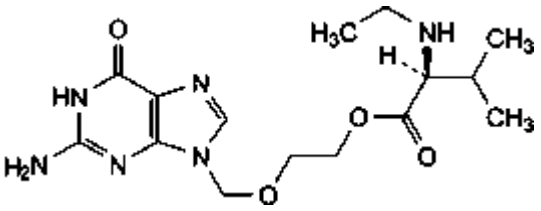
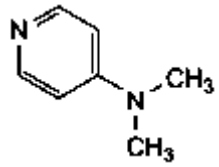
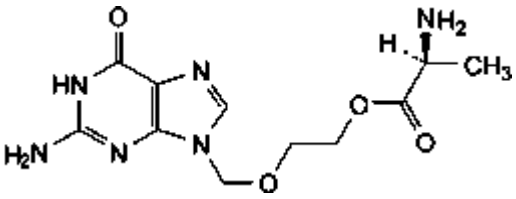


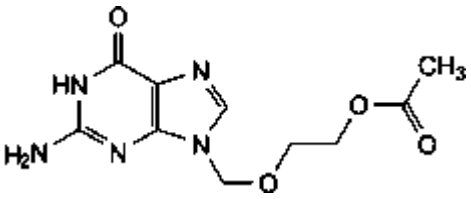
D. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-ethyl-L-valinate,



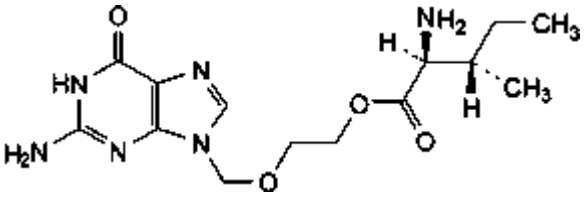
G. *N*,*N*-dimethylpyridin-4-amine,



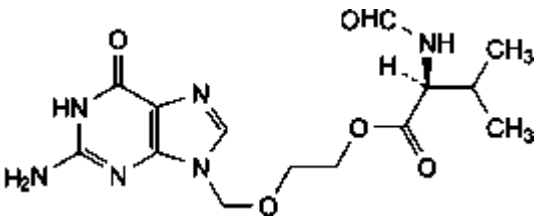
H. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-alaninate,



I. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate,



J. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-isoleucinate,



M. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-formyl-L-valinate,

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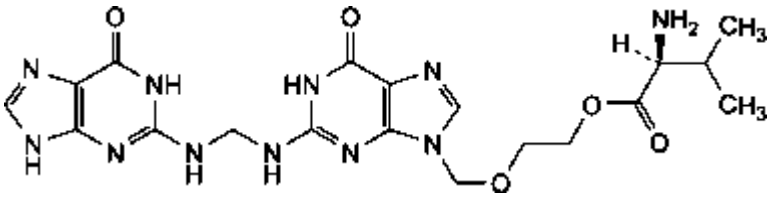
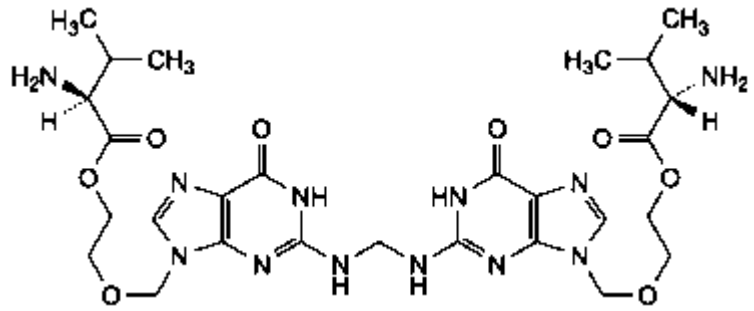
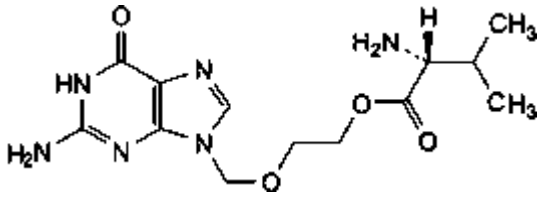


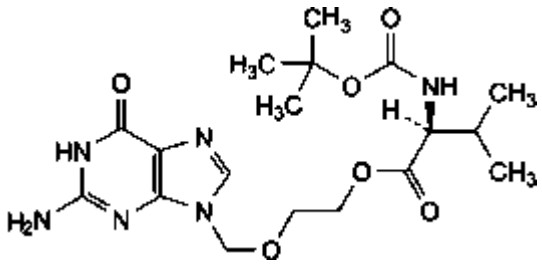
N. 2-[[6-oxo-2-[[[(6-oxo-6,9-dihydro-1*H*-purin-2-yl)amino]methyl]amino]-1,6-dihydro-9*H*-purin-9-yl]methoxy]ethyl L-valinate,



P. [methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxyethan-2,1-diyl]] di-L-valinate,



R. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl D-valinate,



S. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-(*tert*-butoxycarbonyl)-L-valinate.

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Valaciclovir Tablets

General Notices

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Valaciclovir Tablets contain Valaciclovir Hydrochloride or Valaciclovir Hydrochloride Hydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of valaciclovir, $C_{13}H_{20}N_6O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 50 mg of valaciclovir with 20 mL of *methanol,* filter (Whatman GF/C is suitable), evaporate the filtrate and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Valaciclovir Hydrochloride *(RS 481)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 10-mL sample of the medium and filter using a 0.45-µm filter. Dilute with sufficient *0.1M hydrochloric acid*, if necessary, to contain the equivalent of 0.00278% w/v of valaciclovir.

(2) 0.0031% w/v of *valaciclovir hydrochloride BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm).

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

5 volumes of *acetonitrile* and 95 volumes of 0.1% v/v *orthophosphoric acid* in *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* is not greater than 2.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{20}N_6O_4$ in the medium using the declared content of $C_{13}H_{20}N_6O_4$ in *valaciclovir hydrochloride BPCRS*.

LIMITS

The amount of valaciclovir released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 0.1% v/v of *orthophosphoric acid* in *water*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 2.5 g of valaciclovir in 600 mL of 0.1M *hydrochloric acid* with the aid of ultrasound for 10 minutes. Allow to cool and dilute to 1000 mL with 0.1M *hydrochloric acid*. Dilute 4 mL of the resulting solution to 100 mL with solvent A, mix, filter through a 0.45-µm glass fibre filter (Whatman Uniprep is suitable) and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) Mix, with the aid of ultrasound 10 mL of a solution containing 0.004% w/v of *aciclovir BPCRS* in *0.1M hydrochloric acid* with 300 mL of a 0.0166% w/v solution of *valaciclovir hydrochloride BPCRS* in solvent A and dilute to 500 mL with solvent A.

(5) 0.01% w/v of *valaciclovir impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.0 mm) packed with *silica gel for chromatography, crown ether* (5 µm) (Diacel Chiral Phase Crownpack CR (+) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.75 mL per minute.

(d) Use a column temperature of 10°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

(g) Inject solution (1) and continue the chromatography for twice the retention time of valaiciclovir.

MOBILE PHASE

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1 volume of *methanol* and 19 volumes of 0.1% v/v *orthophosphoric acid* in *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to valaciclovir (about 4.5 minutes) are: aciclovir, about 0.5; impurity R, about 0.8; impurity I, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5):

the *symmetry factor* of the peak due to valaciclovir is not greater than 2;

the *resolution* between the peaks due to impurity R and valaciclovir is at least 1.3.

LIMITS

Identify any peak corresponding to aciclovir using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity R is not greater than 3 times the area of peak due to valaciclovir in the chromatogram obtained with solution (2) (3.0%);

the area of any peak corresponding to aciclovir (impurity B) is not greater than twice the area of the peak due to valaciclovir in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity I is not greater than half the area of peak due to valaciclovir in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the peak due to valaciclovir in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5.5 times the area of the peak due to valaciclovir in the chromatogram obtained with solution (2) (5.5%).

Disregard any peak with an area less than 0.5 times the area of the peak due to valaciclovir in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 0.1% v/v *orthophosphoric acid* in *water*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 2.5 g of valaciclovir in 600 mL of 0.1M *hydrochloric acid* with the aid of ultrasound for 10 minutes. Allow to cool and dilute to 1000 mL with 0.1M *hydrochloric acid*. Dilute 4 mL to 100 mL with solvent A, mix, filter through a 0.45-µm glass fibre filter (Whatman Uniprep is suitable) and use the filtrate.
(2) 0.011% w/v of *valaciclovir hydrochloride BPCRS* in solvent A.

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(3) Mix, with the aid of ultrasound 10 mL of a solution containing 0.004% w/v of *aciclovir BPCRS* in *0.1M hydrochloric acid* with 300 mL of a 0.0166% w/v solution of *valaciclovir hydrochloride BPCRS* in solvent A and dilute to 500 mL with solvent A.

(4) 0.01% w/v of *valaciclovir impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *symmetry factor* of the peak due to valaciclovir is not greater than 2;

the *resolution* between the peaks due to impurity R and valaciclovir is at least 1.3.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{20}N_6O_4$ in the tablets using the declared content of $C_{13}H_{20}N_6O_4$ in *valaciclovir hydrochloride BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of valaciclovir.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, I and R listed under Valaciclovir Hydrochloride.

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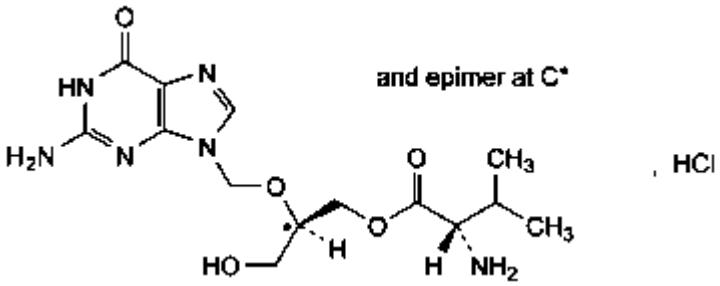
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Valganciclovir Hydrochloride

General Notices

(Ph. Eur. monograph 2930)



$C_{14}H_{23}ClN_6O_5$ 390.8 *175865-59-5*

Ph Eur

DEFINITION

(2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl L-valinate hydrochloride.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *valganciclovir hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Impurity T (see Tests).

C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Impurity T

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 10.0 mg of the substance to be examined in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Reference solution Dissolve 5 mg of *valganciclovir containing impurity T CRS* in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 25 mL with the same solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.0 mm;

— *stationary phase*: *crown-ether silica gel for chiral separation R* (5 µm).

Mobile phase A 16.2 g/L solution of *perchloric acid R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 5 °C.

Injection 10 µL.

Run time Twice the retention time of the 1st peak due to valganciclovir ((*R*)-ester).

Identification of impurities Use the chromatogram supplied with *valganciclovir containing impurity T CRS* and the chromatogram obtained with the reference solution to identify the peaks due to impurity T (isomers 1 and 2).

Relative retention With reference to valganciclovir (retention time of the 1st peak ((*R*)-ester) = about 11 min): impurity T (isomer 1) = about 0.64; impurity T (isomer 2) = about 0.67; 2nd peak due to valganciclovir ((*S*)-ester) = about 1.1.

System suitability Reference solution:

— *resolution*: minimum 3.5 between the 2nd peak due to impurity T (isomer 2) and the 1st peak due to valganciclovir ((*R*)-ester).

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Limit:

— *impurity T*: maximum 3.0 per cent for the sum of the 2 isomers; disregard any peak other than the peaks due to impurity T (isomers 1 and 2) and valganciclovir ((*R*)-ester and (*S*)-ester).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 10.0 mg of the substance to be examined in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Reference solution (a) Dissolve the contents of a vial of *valganciclovir for system suitability CRS* (containing impurities A, B, C, D and N) in 1 mL of a 0.103 g/L solution of *hydrochloric acid R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a 0.103 g/L solution of *hydrochloric acid R*. Dilute 1.0 mL of this solution to 10.0 mL with a 0.103 g/L solution of *hydrochloric acid R*.

Reference solution (c) Dissolve 10.0 mg of *valganciclovir hydrochloride CRS* in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: a 11.5 g/L solution of *ammonium dihydrogen phosphate R*, adjusted to pH 2.8 with *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	92	8
5 - 15	92 → 80	8 → 20
15 - 30	80 → 30	20 → 70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 5 °C.

Injection 20 µL of the test solution and reference solutions (a) and (b).

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Identification of impurities Use the chromatogram supplied with *valganciclovir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to valganciclovir (retention time of the 1st peak ((*R*)-ester) = about 7 min): impurity B = about 0.3; impurity A = about 0.4; impurity C = about 0.9; impurity D = about 1.3 (impurity D may be eluted as 1 or 2 peaks).

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to the 2 isomers of valganciclovir;

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the 1st peak due to valganciclovir ((*R*)-ester).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity B = 0.5;

— for each impurity, use the concentration of valganciclovir hydrochloride in reference solution (b) and the areas of the peaks due to valganciclovir ((*R*)-ester and (*S*)-ester).

Limits:

— *impurity A*: maximum 1.5 per cent;

— *impurity D*: maximum 0.5 per cent, for the sum of the areas of the 2 peaks;

— *impurity B*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total (including impurity N)*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent.

Diastereoisomer ratio

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification. Use the normalisation procedure.

Limit Test solution:

— the ratio of the area of the peak due to the (*R*)-ester of valganciclovir to the sum of the areas of the peaks due to the (*R*)-ester and (*S*)-ester of valganciclovir is between 0.45 and 0.55.

Impurity N

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

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Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dilute 2.5 mL of *triethylamine R* in 1000 mL of *water for chromatography R* and adjust to pH 3.0 with *trifluoroacetic acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	93	7
10 - 20	93 → 70	7 → 30

Identification of impurities Use the chromatogram supplied with *valganciclovir for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity N.

Relative retention With reference to valganciclovir (retention time of the 1st peak ((*R*)-ester) = about 7 min): impurity N (isomer 1) = about 1.2; impurity N (isomer 2) = about 1.3.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the 2nd peak due to valganciclovir ((*S*)-ester) and the 1st peak due to impurity N (isomer 1).

Calculation of percentage contents:

— for impurity N, use the concentration of valganciclovir hydrochloride in reference solution (b) and the areas of the peaks due to valganciclovir (*R*)-ester and (*S*)-ester.

Limit:

— *impurity N*: maximum 0.2 per cent for the sum of the 2 isomers.

Water (*2.5.12*)

Maximum 8.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection 20 µL of the test solution and reference solution (c).

Calculate the percentage content of $C_{14}H_{23}ClN_6O_5$ (sum of the 2 isomers of valganciclovir hydrochloride) taking into account the assigned content of *valganciclovir hydrochloride CRS*.

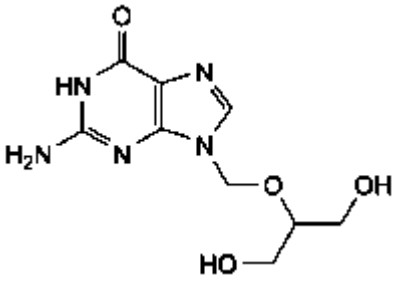
STORAGE

In an airtight container.

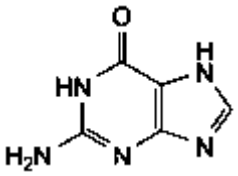
IMPURITIES

Specified impurities *A, B, D, N, T.*

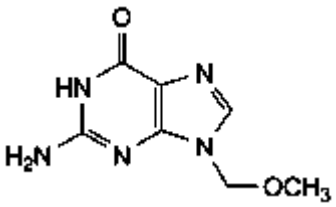
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F, H, I, J, K, L, M, O, P, Q, R, S.*



A. 2-amino-9-[[(1,3-dihydroxypropan-2-yl)oxy]methyl]-1,9-dihydro-6*H*-purin-6-one (ganciclovir),



B. 2-amino-1,7-dihydro-6*H*-purin-6-one (guanine),



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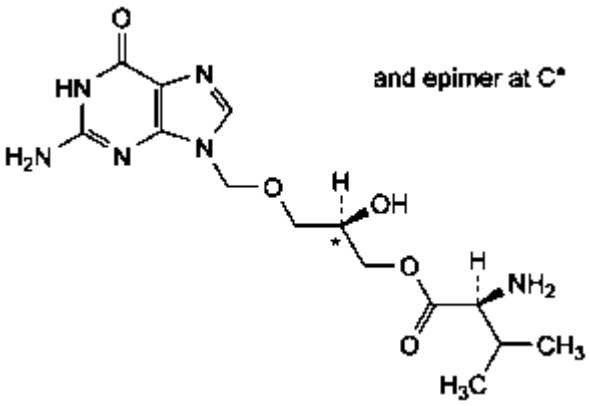
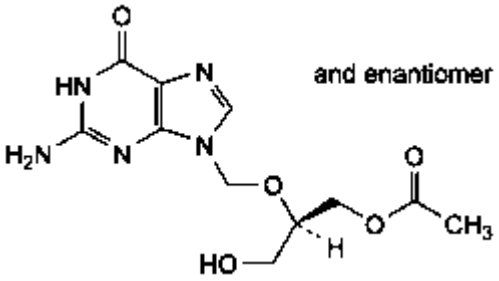
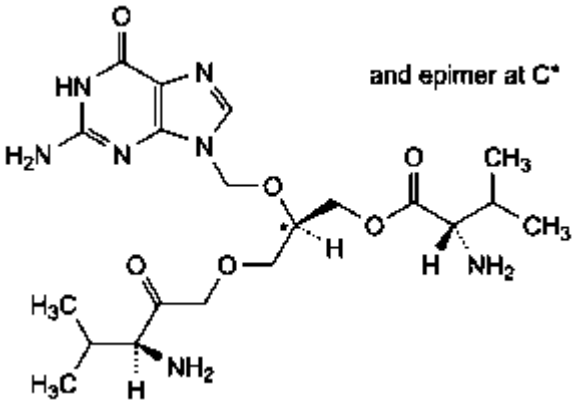
C. 2-amino-9-(methoxymethyl)-1,9-dihydro-6*H*-purin-6-one,



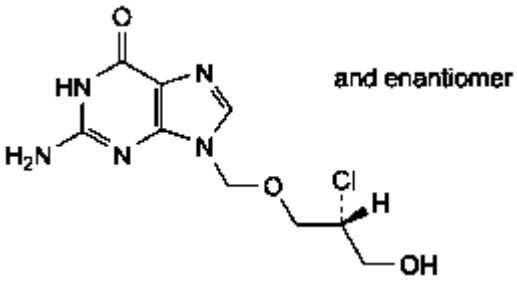
D. (2*RS*)-3-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-2-hydroxypropyl L-valinate,



E. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl acetate,



F. (2*RS*)-3-[[(3*S*)-3-amino-4-methyl-2-oxopentyl]oxy]-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]propyl L-valinate,



H. 2-amino-9-[[(2*RS*)-2-chloro-3-hydroxypropoxy]methyl]-1,9-dihydro-6*H*-purin-6-one,

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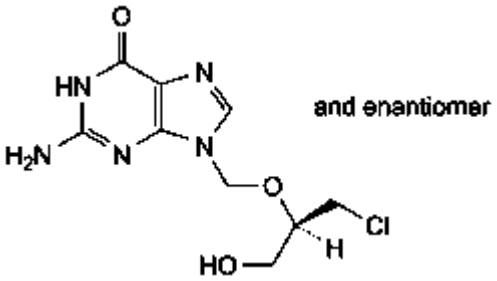
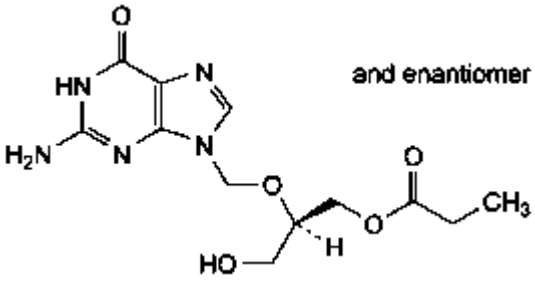
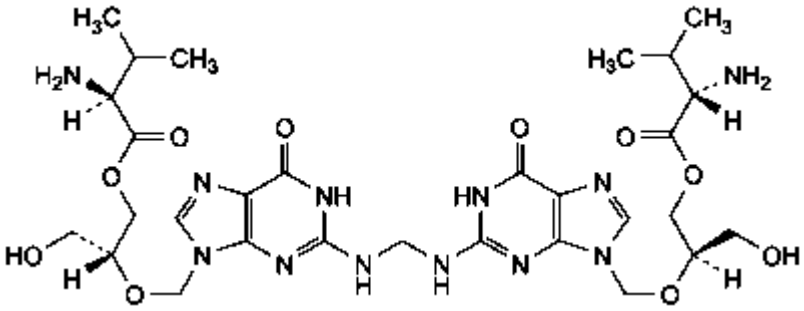


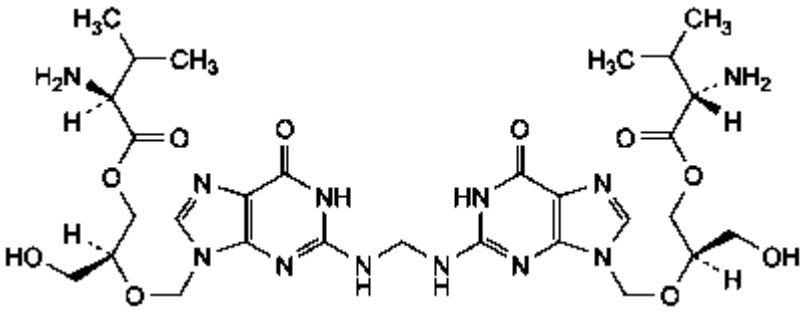
I. 2-amino-9-[[[(2*RS*)-1-chloro-3-hydroxypropan-2-yl]oxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



J. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl propanoate,



K. [methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxy[(2*R*)-3-hydroxypropane-2,1-diyl]]] di-L-valinate,



L. (2*R*)-3-hydroxy-2-[[2-[[[[9-[[[(2*S*)-1-hydroxy-3-(L-valyloxy)propan-2-yl]oxy]methyl]-6-oxo-1,6-dihydro-9*H*-purin-2-yl]amino]methyl]amino]-6-oxo-1,6-dihydro-9*H*-purin-9-yl]methoxy]propyl L-valinate,

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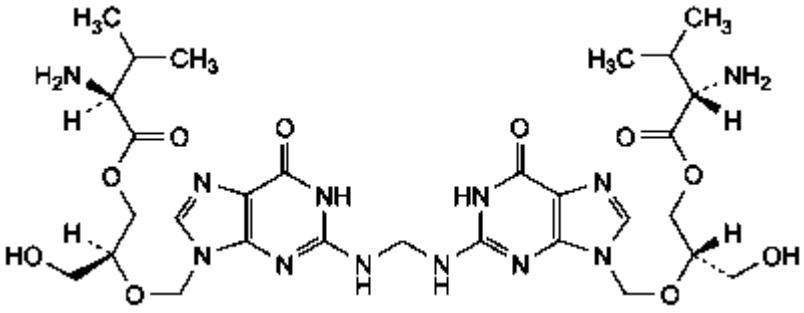
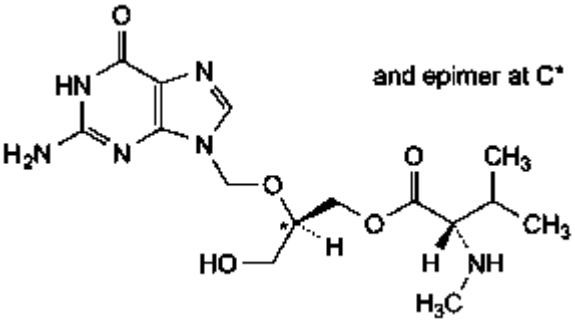
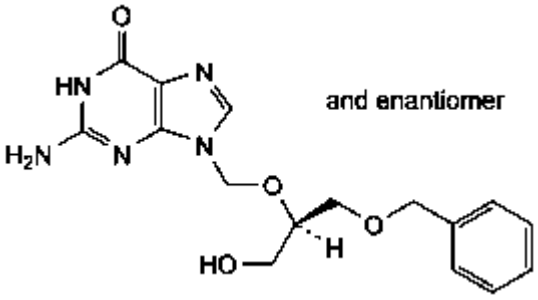


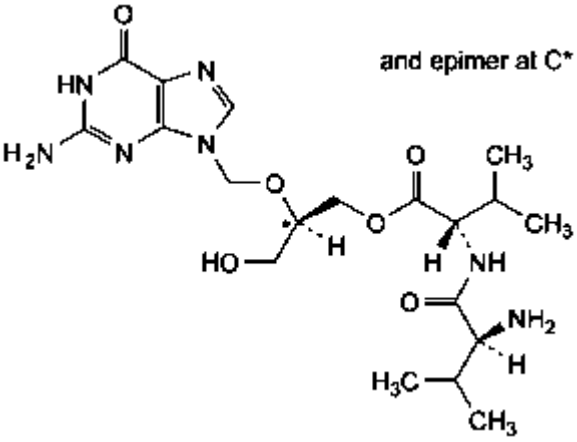
M. [methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxy[(2*S*)-3-hydroxypropane-2,1-diyl]]] di-L-valinate,



N. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl *N*-methyl-L-valinate,



O. 2-amino-9-[[[(2*RS*)-1-(benzyloxy)-3-hydroxypropan-2-yl]oxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



P. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl L-valyl-L-valinate,

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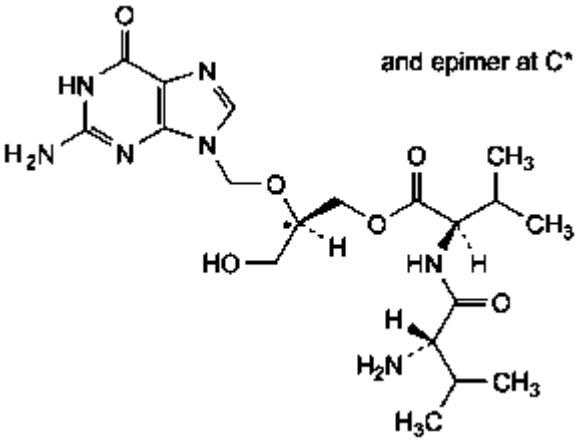
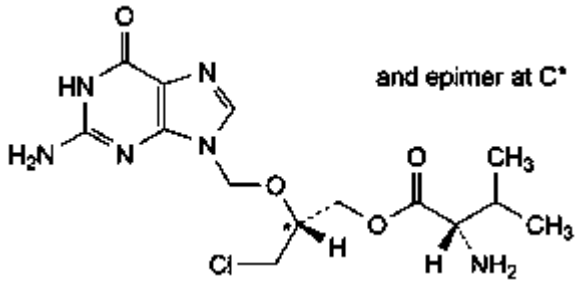
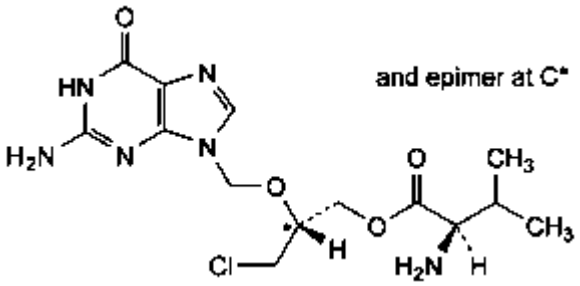


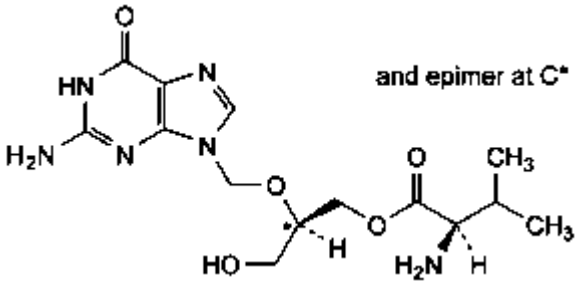
Q. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl D-valyl-D-valinate,



R. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-chloropropyl L-valinate,



S. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-chloropropyl D-valinate,



T. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl D-valinate.

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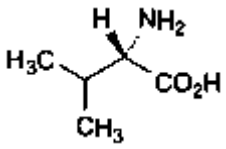
Valine

General Notices

(Ph. Eur. monograph 0796)



$C_5H_{11}NO_2$ 117.1 *72-18-4*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-methylbutanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

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A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *valine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Reference solution Dissolve 10 mg of *valine CRS* in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the same solution.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*)

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 2.5 g in *water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

+ 26.5 to + 29.0 (dried substance).

Dissolve 2.00 g in *hydrochloric acid R1* and dilute to 25.0 mL with the same acid.

Ninhydrin-positive substances

Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled,

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keeping the ratios of concentrations between all solutions as described.

Solution A *dilute hydrochloric acid R1* or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* (impurity B) and 30 mg of *leucine R* (impurity C) in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Reference solution (e) Dissolve 30.0 mg of *isoleucine R* (impurity B) in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurities B and C.

Calculation of percentage contents:

— for impurity B, use the concentration of impurity B in reference solution (e);

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of valine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *impurity B at 570 nm*: maximum 0.4 per cent;

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

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The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dissolve 0.5 g in *distilled water R* and dilute to 15 mL with the same solvent.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 11.71 mg of $C_5H_{11}NO_2$.

STORAGE

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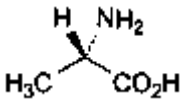
Protected from light.

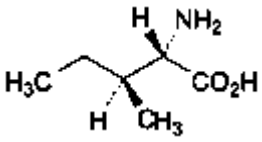
IMPURITIES

Specified impurities B.

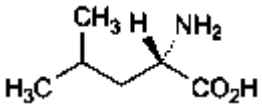
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C.



A. (2*S*)-2-aminopropanoic acid (alanine),



B. (2*S*,3*S*)-2-amino-3-methylpentanoic acid (isoleucine),



C. (2*S*)-2-amino-4-methylpentanoic acid (leucine).

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Valproic Acid

General Notices

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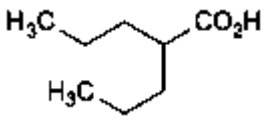

$C_8H_{16}O_2$ 144.2 *99-66-1*

Action and use

Antiepileptic.

Ph Eur

DEFINITION

2-Propylpentanoic acid.

Content

99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

Colourless or very slightly yellow, clear liquid, slightly viscous.

Solubility

Very slightly soluble in water, miscible with ethanol (96 per cent) and with methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *valproic acid CRS*.

TESTS

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Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Dissolve 2.0 g in *dilute sodium hydroxide solution R* and dilute to 10 mL with the same alkaline solution.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 0.500 g of the substance to be examined in *heptane R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *valproic acid for system suitability CRS* (containing impurity K) in 1.0 mL of *heptane R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *heptane R*.

Column:

— *material*: wide-bore fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *macrogol 20 000 2-nitroterephthalate R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 8 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	80
	5 - 15	80 → 150
	15 - 28.3	150 → 190
	28.3 - 30	190
Injection port		220
Detector		220

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to valproic acid (retention time = about 17 min): impurity K = about 0.97.

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System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity K and valproic acid.

Limits:

— *impurity K*: not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.03 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 25 mL of *ethanol (96 per cent) R*. Add 2 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 14.42 mg of $C_8H_{16}O_2$.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *K*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I, J, L*.

A. pentanoic acid (valeric acid),

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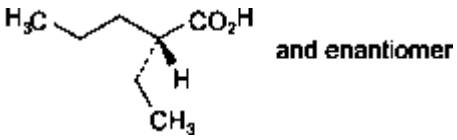
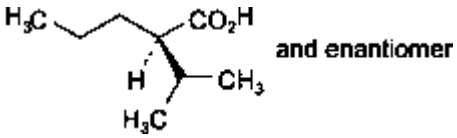
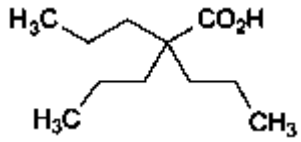


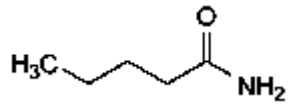
B. (2*RS*)-2-ethylpentanoic acid,



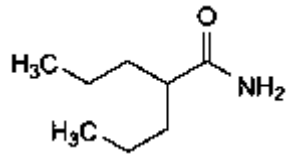
C. (2*RS*)-2-(1-methylethyl)pentanoic acid,



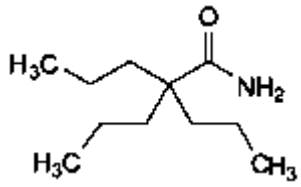
D. 2,2-dipropylpentanoic acid,



E. pentanamide (valeramide),

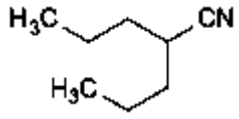


F. 2-propylpentanamide,



G. 2,2-dipropylpentanamide,

H. pentanenitrile (valeronitrile),



I. 2-propylpentanenitrile,

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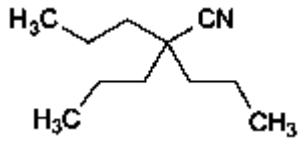
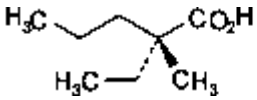
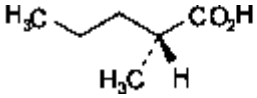


J. 2,2-dipropylpentanenitrile,


and enantiomer

K. (2*RS*)-2-ethyl-2-methylpentanoic acid,


and enantiomer

L. (2*RS*)-2-methylpentanoic acid.

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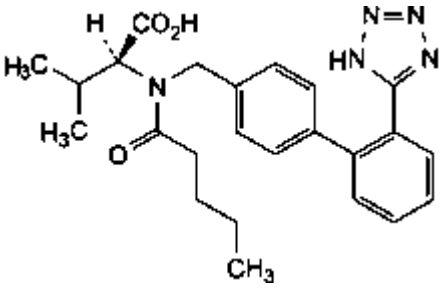
Valsartan

General Notices

(Ph. Eur. monograph 2423)



$C_{24}H_{29}N_5O_3$ 435.5 *137862-53-4*

Action and use

Angiotensis II (AT_1) receptor antagonist.

Preparations

Valsartan Capsules

Valsartan Tablets

Ph Eur

DEFINITION

(2*S*)-3-Methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in valsartan should be avoided or limited as much as possible. For this reason, manufacturers of valsartan for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in valsartan. The general chapter 2.5.42. *N-Nitrosamines in active substances* is available to assist manufacturers.

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CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride.

IDENTIFICATION

Carry out either tests A, B or tests A, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *valsartan CRS*.

B. Enantiomeric purity (see Tests).

C. Specific optical rotation (2.2.7): -69.0 to -64.0 (anhydrous substance).

Dissolve 0.200 g in *methanol R* and dilute to 20.0 mL with the same solvent.

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *valsartan for peak identification CRS* (containing impurity A) in the mobile phase and dilute to 5 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (5 µm).

Mobile phase *trifluoroacetic acid R*, *2-propanol R*, *hexane R* (0.1:15:85 *V/V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Run time 1.5 times the retention time of valsartan.

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Identification of impurities Use the chromatogram supplied with *valsartan for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to valsartan (retention time = about 13 min): impurity A = about 0.6.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity A and valsartan.

Limit:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *valsartan for system suitability CRS* (containing impurity C) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R*, *acetonitrile R1*, *water for chromatography R* (1:500:500 *V/V/V*).

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Run time 6 times the retention time of valsartan.

Identification of impurities Use the chromatogram supplied with *valsartan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to valsartan (retention time = about 5 min): impurity C = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity C and valsartan.

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Limits:

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 2.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.170 g in 70 mL of *2-propanol R*. Titrate with *0.1 M tetrabutylammonium hydroxide in 2-propanol*, determining the endpoint potentiometrically (2.2.20). Perform all operations under nitrogen.

1 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 21.78 mg of $C_{24}H_{29}N_5O_3$.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities *A, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*

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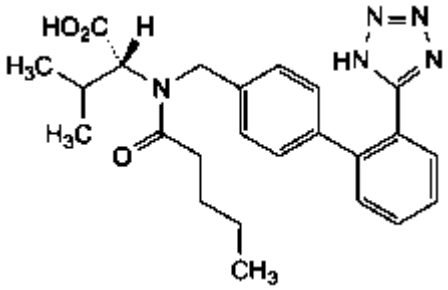
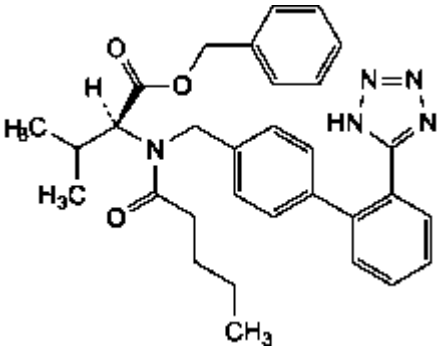
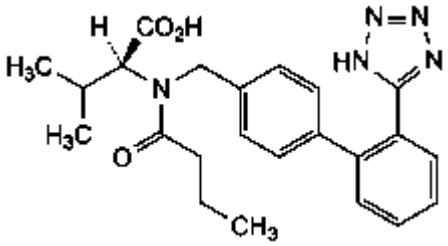


A. (2*R*)-3-methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid,



B. benzyl (2*S*)-3-methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoate,



C. (2*S*)-2-[butanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-3-methylbutanoic acid.

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Valsartan Capsules

General Notices

Action and use

Angiotensin II (AT_1) receptor antagonist.

DEFINITION

Valsartan Capsules contain Valsartan.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of valsartan, $C_{24}H_{29}N_5O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing 50 mg of Valsartan with 20 mL of *dichloromethane* for 10 minutes, filter, evaporate the filtrate to dryness under a stream of nitrogen and dry the residue at 105° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Valsartan (*RS 473*). Disregard any bands occurring between 1250 and 1325 cm^{-1}.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium to give a solution expected to contain 0.004% w/v of Valsartan, at the maximum at 250 nm, Appendix II B, using *phosphate buffer pH 6.8* in the reference cell.

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(2) Measure the *absorbance* of a 0.004% w/v solution of *valsartan BPCRS* in *phosphate buffer pH 6.8*, at the maximum at 250 nm, Appendix II B, using *phosphate buffer pH 6.8* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of valsartan, $C_{24}H_{29}N_5O_3$, in the medium from the absorbances obtained and using the declared content of $C_{24}H_{29}N_5O_3$, in *valsartan BPCRS*.

LIMITS

The amount of valsartan released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 50 mg of Valsartan with 80 mL of the mobile phase with the aid of ultrasound, add sufficient mobile phase to produce 100 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(3) Dissolve the contents of a vial of *valsartan for system suitability EPCRS* (containing impurity C) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucelosil-100 C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.4 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for 6 times the retention time of valsartan.

MOBILE PHASE

1 volume of *glacial acetic acid*, 500 volumes of *acetonitrile R1* and 500 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to valsartan (retention time = about 5 minutes) is: impurity C = about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and valsartan is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 7 times the area of principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the mixed contents of 20 capsules containing 50 mg of Valsartan, add 80 mL of the mobile phase and mix with the aid of ultrasound. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

(2) 0.005% w/v of *valsartan BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *valsartan for system suitability EPCRS* (containing impurity C) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and valsartan is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{29}N_5O_3$ in the capsules using the declared content of $C_{24}H_{29}N_5O_3$ in *valsartan BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Valsartan.

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Valsartan Tablets

General Notices

Action and use

Angiotensin II (AT_1) receptor antagonist.

DEFINITION

Valsartan Tablets contain Valsartan.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of valsartan, $C_{24}H_{29}N_5O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Valsartan with 20 mL of *dichloromethane* for 10 minutes, filter, evaporate the filtrate to dryness under a stream of nitrogen and dry the residue at 105° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Valsartan (*RS 473*). Disregard any bands occurring between 1250 and 1325 cm^{-1}.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium to give a solution expected to contain 0.004% w/v of Valsartan, at the maximum at 250 nm, Appendix II B, using *phosphate buffer pH 6.8* in the reference cell.

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(2) Measure the *absorbance* of a 0.004% w/v solution of *valsartan BPCRS* in *phosphate buffer pH 6.8* at the maximum at 250 nm, Appendix II B, using *phosphate buffer pH 6.8* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of valsartan, $C_{24}H_{29}N_5O_3$, in the medium from the absorbances obtained and using the declared content of $C_{24}H_{29}N_5O_3$, in *valsartan BPCRS*.

LIMITS

The amount of valsartan released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Valsartan with 80 mL of the mobile phase with the aid of ultrasound, add sufficient mobile phase to produce 100 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(3) Dissolve the contents of a vial of *valsartan for system suitability EPCRS* (containing impurity C) in 1.0 mL on the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucelosil-100 C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.4 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for 6 times the retention time of valsartan.

MOBILE PHASE

1 volume of *glacial acetic acid*, 500 volumes of *acetonitrile R1* and 500 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to valsartan (retention time, about 5 minutes) is: impurity C, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and valsartan is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of Valsartan, add 80 mL of the mobile phase and mix with the aid of ultrasound. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.
(2) 0.005% w/v of *valsartan BPCRS* in the mobile phase.
(3) Dissolve the contents of a vial of *valsartan for system suitability EPCRS* (containing impurity C) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and valsartan is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{29}N_5O_3$ in the tablets using the declared content of $C_{24}H_{29}N_5O_3$ in *valsartan BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Valsartan.

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Vancomycin Capsules

General Notices

Action and use

Glycopeptide antibacterial.

DEFINITION

Vancomycin Capsules contain Vancomycin Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

IDENTIFICATION

A. In the test for Related substances and vancomycin B, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.
The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

B. The contents of the capsules yield reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium and filter. Dilute to 100 IU/mL with *water*, if necessary, and carry out the *microbiological assay of antibiotics*, Appendix XIV A.

LIMITS

The amount of vancomycin released is not less than 85% (Q) of the stated amount.

Related substances and vancomycin B

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation* procedure.

(1) Shake a quantity of the capsule contents containing 0.1 g of Vancomycin Hydrochloride with 20 mL of *water*, dilute to 25 mL and filter.

(2) 0.4% w/v of *vancomycin for system suitability EPCRS*.

(3) Expose 4 mg of *vancomycin for system suitability EPCRS* to 80-100% relative humidity at 42 ± 2° for at least 7 days. Allow to cool. Add 1 mL of *water* and dissolve the sample with the aid of ultrasound (generation of impurities B, D, E, G, and L).

(4) Dilute 1 volume of solution (2) to 100 volumes with 0.1% v/v of *acetic acid*. Dilute 1 volume of this solution to 10 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *end-capped, charged-surface, ethylene-bridged, octadecylsilyl silica gel for chromatography (hybrid material)* (1.7 µm) (Acquity CSH C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 280 nm.

(f) Use an autosampler temperature of 5°.

(g) Inject 2 µL of each solution.

MOBILE PHASE

Mobile phase A 3 volumes of *acetonitrile*, 4 volumes of *methanol* and 93 volumes of a 0.7% w/v solution of *tris(hydroxymethyl)aminomethane* previously adjusted to pH 8.1 with a 20% v/v solution of *glacial acetic acid*.

Mobile phase B 10 volumes of *acetonitrile*, 40 volumes of *methanol* and 50 volumes of a 0.7% w/v solution of *tris(hydroxymethyl)aminomethane* previously adjusted to pH 8.1 with a 20% v/v solution of *glacial acetic acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-7	88	12	isocratic
7-21	88→75	12→25	linear gradient
21-35	75→25	25→75	linear gradient
35-37	25	75	isocratic
37-38	25→88	75→12	linear gradient
38-45	88	12	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to vancomycin B (retention time, about 19 minutes) are: impurity E, about 0.4; impurity L, about 0.66; impurity B, about 0.70; impurity A, about 0.76; impurity F, about 0.82; impurity G, about 0.90; impurity H, about 0.94; impurity M, about 1.11; impurity I, about 1.14; impurity J, about 1.20; impurity D, about 1.24; impurity K, about 1.5 and impurity C, about 1.9.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity L and impurity B is between 1.5 to 5.0;

the *resolution* between the peaks due to impurity G and impurity H is between 1.5 to 4.0.

If the *resolution* between the peaks due to impurities L and B is greater than 5.0, adjust the pH of solution A to a lower value. If the *resolution* between the peaks due to impurities G and H is greater than 4.0, adjust the pH of solution A to a higher value.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to vancomycin impurities A, C, F, H, I, J, K and M using the chromatogram obtained with solution (2) and any peaks corresponding to vancomycin impurities B, D, E, G, and L using the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1), integrate all peaks present with an area greater than the area of the principal peak in the chromatogram obtained with solution (4) to determine the total peak area. Calculate the percentage content of each of the components and impurities by *normalisation*:

the content of vancomycin B is not less than 81.0%;

the area of any peak due to impurities G or J is not greater than 3.2%;

the area of any peak due to impurities A, D or H is not greater than 3.0%;

the area of any peak due to impurity L is not greater than 2.1%;

the sum of the areas of any peaks due to impurities B and E is not greater than 2.0%;

the area of any peak due to impurity C is not greater than 2.0%;

the area of any peak due to impurity I is not greater than 1.8%;

the area of any peak due to impurities F or M is not greater than 1.5%;

the area of any peak due to impurity K is not greater than 1.2%;

the area of any other *secondary peak* is not greater than 0.8%;

the sum of the areas of all the *secondary peaks* is not greater than 19.0%.

ASSAY

Weigh and mix the contents of 20 capsules. Dissolve a quantity of the mixed contents containing 1,000,000 IU of vancomycin as completely as possible in sufficient *water* to produce 1000 mL. Dilute 10 mL to 100 mL and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

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The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 110.0% of the stated number of IU.

LABELLING

The label of the sealed container states (1) the total number of IU (Units) contained in it; (2) the number of IU (Units) per mg in each capsule.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Vancomycin Hydrochloride.

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Vancomycin Eye Drops

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Glycopeptide antibacterial.

DEFINITION

Vancomycin Eye Drops are a sterile solution of Vancomycin Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

IDENTIFICATION

A. In the test for Vancomycin B, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (4).

B. Yield reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 2.5 to 4.5, Appendix V L.

Vancomycin B

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Use the solutions within 4 hours of preparation.

(1) Dilute a volume of the eye drops with sufficient mobile phase A to produce a solution containing about 0.2% w/v of Vancomycin Hydrochloride.

(2) Dilute 1 volume of solution (1) to 25 volumes with mobile phase A.

(3) Dilute 1 volume of solution (2) to 40 volumes with mobile phase A.

(4) Heat a 0.050% w/v solution of *vancomycin hydrochloride EPCRS* in mobile phase A at 65° for 24 hours and allow to cool.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

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(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A To 4 volumes of *triethylamine* add 1996 volumes of *water* and adjust to pH 3.2 with *orthophosphoric acid* (solution A). Add 10 volumes of *tetrahydrofuran* and 70 volumes of *acetonitrile* to 920 volumes of solution A.

Mobile phase B Add 10 volumes of *tetrahydrofuran* and 290 volumes of *acetonitrile* to 700 volumes of solution A.

Use the following gradient.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-13	100	0	isocratic
13-21	100→0	0→100	linear gradient
21-25	0	100	isocratic
25-35	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the principal peak has a *signal-to-noise ratio* of at least 5;

in the chromatogram obtained with solution (2), the *symmetry factor* of the vancomycin peak is not greater than 1.6;

in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 5.0.

LIMITS

Not less than 88.0%, calculated using the following expression:

$$\frac{A_b \times 100}{A_b + \left(\frac{A_t}{25}\right)}$$

where,

A_b = area of the peak corresponding to vancomycin B in the chromatogram obtained with solution (2);

A_t = sum of the areas of the peaks corresponding to impurities in the chromatogram obtained with solution (1).

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using solutions (1), (2) and (3) described under Vancomycin B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Vancomycin B may be used.

LIMITS

In the chromatogram obtained with solution (1) calculate the percentage content of each impurity using the following expression:

$$\frac{\left(\frac{A_i}{25}\right) \times 100}{A_b + \left(\frac{A_t}{25}\right)}$$

where,

A_i	=	area of an impurity peak in the chromatogram obtained with solution (1),
A_b	=	area of the peak corresponding to vancomycin B in the chromatogram obtained with solution (2),
A_t	=	sum of the areas of the peaks corresponding to impurities in the chromatogram obtained with solution (1).

The content of any impurity is not greater than 4.0% and the sum of the contents of any such impurities is not greater than 12.0%.

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

The upper fiducial limit of error is not less than 95.0% and the lower fiducial limit of error is not more than 115.0% of the stated content.

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Vancomycin for Infusion

General Notices

Action and use

Glycopeptide antibacterial.

DEFINITION

Vancomycin for Infusion is a sterile material consisting of Vancomycin Hydrochloride with or without excipients. It is supplied in a sealed container. It may be used to prepare a solution for oral administration.

If intended for administration as an Infusion, the contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

If intended for administration as an Oral Solution, the contents of the sealed container comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids and with the following requirements.

IDENTIFICATION

A. In the test for Related substances and Vancomycin B, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.
The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

B. Yield reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH of a solution containing 5% w/v of Vancomycin Hydrochloride, 2.5 to 4.5, Appendix V L.

Clarity of solution

A solution containing 10.0% w/v of Vancomycin Hydrochloride is *clear*, Appendix IV A. The *absorbance* of the solution at 450 nm is not greater than 0.10, Appendix II B.

Related substances and vancomycin B

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation* proceedure.

(1) Dissolve a quantity of the powder containing 0.1 g of Vancomycin Hydrochloride with 20 mL of *water* and dilute to 25 mL.

(2) 0.4% w/v of *vancomycin for system suitability EPCRS*.

(3) Expose 4 mg of *vancomycin for system suitability EPCRS* to 80-100% relative humidity at 42 ± 2° for at least 7 days. Allow to cool. Add 1 mL of *water* and dissolve the sample with the aid of ultrasound (generation of impurities B, D, E, G, and L).

(4) Dilute 1 volume of solution (2) to 100 volumes with 0.1% v/v of *acetic acid*. Dilute 1 volume of this solution to 10 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *end-capped, charged-surface, ethylene-bridged, octadecylsilyl silica gel for chromatography (hybrid material)* (1.7 µm) (Acquity CSH C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 280 nm.

(f) Use an autosampler temperature of 5°.

(g) Inject 2 µL of each solution.

MOBILE PHASE

Mobile phase A 3 volumes of *acetonitrile*, 4 volumes of *methanol* and 93 volumes of a 0.7% w/v solution of *tris(hydroxymethyl)aminomethane* previously adjusted to pH 8.1 with a 20% v/v solution of *glacial acetic acid*.

Mobile phase B 10 volumes of *acetonitrile*, 40 volumes of *methanol* and 50 volumes of a 0.7% w/v solution of *tris(hydroxymethyl)aminomethane* previously adjusted to pH 8.1 with a 20% v/v solution of *glacial acetic acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-7	88	12	isocratic
7-21	88→75	12→25	linear gradient
21-35	75→25	25→75	linear gradient
35-37	25	75	isocratic
37-38	25→88	75→12	linear gradient
38-45	88	12	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to vancomycin B (retention time, about 19 minutes) are: impurity E, about 0.4; impurity L, about 0.66; impurity B, about 0.70; impurity A, about 0.76; impurity F, about 0.82; impurity G, about 0.90; impurity H, about 0.94; impurity M, about 1.11; impurity I, about 1.14; impurity J, about 1.20; impurity D, about 1.24; impurity K, about 1.5 and impurity C, about 1.9.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity L and impurity B is between 1.5 to 5.0;

the *resolution* between the peaks due to impurity G and impurity H is between 1.5 to 4.0.

If the *resolution* between the peaks due to impurities L and B is greater than 5.0, adjust the pH of solution A to a lower value. If the *resolution* between the peaks due to impurities G and H is greater than 4.0, adjust the pH of solution A to a higher value.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to vancomycin impurities A, C, F, H, I, J, K and M using the chromatogram obtained with solution (2) and any peaks corresponding to vancomycin impurities B, D, E, G, and L using the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1), integrate all peaks present with an area greater than the area of the principal peak in the chromatogram obtained with solution (4) to determine the total peak area. Calculate the percentage content of each of the components and impurities by *normalisation*:

the content of Vancomycin B is not less than 86.0%;

the area of any peak due to impurities A or H is not greater than 3.0%;

the sum of the areas of any peaks due to impurities B and E is not greater than 2.0%;

the area of any peak due to impurities D or J is not greater than 2.0% ;

the area of any peak due to impurity C is not greater than 1.7%;

the area of any peak due to impurities F or M is not greater than 1.5%;

the area of any peak due to impurities G, I or K is not greater than 1.2% ;

the area of any other *secondary peak* is not greater than 0.8%;

the sum of the areas of all the *secondary peaks* is not greater than 14.0%.

Water

Not more than 5.0% w/w, Appendix IX C. Use 0.5 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *tris-chloride buffer pH 7.4* prepared using *water BET* to give a solution containing 9000 IU of vancomycin per mL (solution A). The endotoxin limit concentration of solution A is 2.5 IU of endotoxin per mL.

ASSAY

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Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Mix the contents of the 10 containers and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

For a container of average content weight, the upper fiducial limit of error is not less than 95.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU.

LABELLING

The label of the sealed container states (1) the total number of IU (Units) contained in it; (2) the number of IU (Units) per mg; (3) if it has been approved for oral administration.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Vancomycin Hydrochloride.

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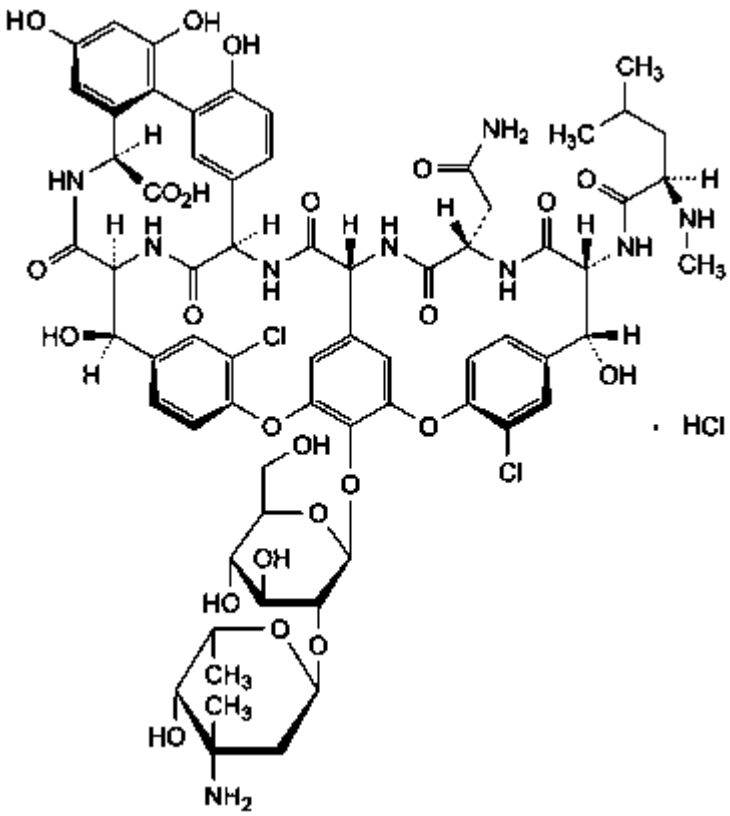
Vancomycin Hydrochloride

General Notices

(Ph. Eur. monograph 1058)



$C_{66}H_{76}Cl_3N_9O_{24}$ 1486

Action and use

Glycopeptide antibacterial.

Preparations

Vancomycin Capsules

Vancomycin Eye Drops

Vancomycin Infusion

Vancomycin Oral Solution

Ph Eur

DEFINITION

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DEFINITION

Monohydrochloride of (3*S*,6*R*,7*R*,8*M*,18*M*,22*R*,23*S*,26*S*,30a*M*,36*R*,38a*R*)-3-(2-amino-2-oxoethyl)-44-[[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-10,19-dichloro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)pentanamido]-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-22*H*-23,36-(azanomethano)-8,11:18,21-dietheno-13,16:31,35-dimetheno-1*H*,13*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid (vancomycin B hydrochloride).

Substance produced by certain strains of *Amycolatopsis orientalis*.

Potency

Minimum 1050 IU/mg (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Examine the chromatograms obtained in the test for vancomycin B and related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 450 nm is not greater than 0.10, and its absorbance at 370 nm is not greater than 0.65.

Dissolve 2.50 g in *water R* and dilute to 25.0 mL with the same solvent.

pH (*2.2.3*)

2.5 to 4.5.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Vancomycin B and related substances

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Liquid chromatography (2.2.29): use the normalisation procedure.

Solution A Dissolve 7.0 g of tris(hydroxymethyl)aminomethane R in approximately 950 mL of water for chromatography R. Measure the temperature of the solution. Considering the temperature dependency of the buffer, adjust the pH to 8.0-8.3 using a 20 per cent *V/V* solution of glacial acetic acid R in water for chromatography R and dilute to 1000 mL with water for chromatography R.

Test solution Dissolve 20.0 mg of the substance to be examined in water R and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 6 mg of vancomycin for system suitability CRS (containing impurities A, C, F, H, I, J, K and M) in 1.5 mL of water R.

Reference solution (b) In order to prepare impurities B, D, E, G and L *in situ*, expose 4 mg of vancomycin for system suitability CRS (containing impurities A, C, F, H, I, J, K and M) to 80-100 per cent relative humidity at 42 ± 2 °C for at least 7 days. Add 1 mL of water R and dissolve the sample completely using sonication.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with a 0.1 per cent *V/V* solution of acetic acid R. Dilute 1.0 mL of this solution to 10.0 mL with a 0.1 per cent *V/V* solution of acetic acid R.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: end-capped, charged surface, ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R (1.7 µm);

— *temperature*: 40 ± 2 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, methanol R, solution A (3:4:93 *V/V/V*);

— *mobile phase B*: acetonitrile R, methanol R, solution A (10:40:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	88	12
7 - 21	88 → 75	12 → 25
21 - 35	75 → 25	25 → 75
35 - 37	25	75

Flow rate 0.30 ± 0.02 mL/min.

Detection Spectrophotometer at 280 nm.

Autosampler Set at 5 °C.

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Injection 2 µL.

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, C, F, H, I, J, K and M; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, D, E, G and L.

Relative retention With reference to vancomycin B (retention time = about 19 min): impurity E = about 0.37; impurity L = about 0.66; impurity B = about 0.70; impurity A = about 0.76; impurity F = about 0.82; impurity G = about 0.90; impurity H = about 0.94; impurity M = about 1.11; impurity I = about 1.14; impurity J = about 1.20; impurity D = about 1.24; impurity K = about 1.50; impurity C = about 1.86.

System suitability:

— *resolution*: minimum 1.5 and maximum 4.0 between the peaks due to impurities G and H, and minimum 1.5 and maximum 5.0 between the peaks due to impurities L and B in the chromatogram obtained with reference solution (b). If the resolution between the peaks due to impurities G and H is greater than 4.0, adjust the pH of solution A to a higher value. If the resolution between the peaks due to impurities L and B is greater than 5.0, adjust the pH of solution A to a lower value;

— *signal-to-noise ratio*: minimum 10 for the peak due to vancomycin B in the chromatogram obtained with reference solution (c).

Limits:

— *vancomycin B*: minimum 91.0 per cent;

— *impurities A, H*: for each impurity, maximum 3.0 per cent;

— *sum of impurities B and E*: maximum 2.0 per cent;

— *impurity J*: maximum 1.6 per cent;

— *impurities D, F, M*: for each impurity, maximum 1.5 per cent;

— *impurities G, I, K*: for each impurity, maximum 1.2 per cent;

— *impurity C*: maximum 1.0 per cent;

— *any other impurity eluting before vancomycin B*: for each impurity, maximum 0.8 per cent, and not more than 5 such impurities exceed 0.30 per cent;

— *any other impurity eluting after vancomycin B*: for each impurity, maximum 0.8 per cent, and not more than 3 such impurities exceed 0.30 per cent;

— *total of impurities*: maximum 9.0 per cent;

— *reporting threshold*: 0.10 per cent.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.500 g.

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Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.00 g.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *vancomycin hydrochloride CRS* as the reference substance.

STORAGE

In an airtight container, protected from light at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

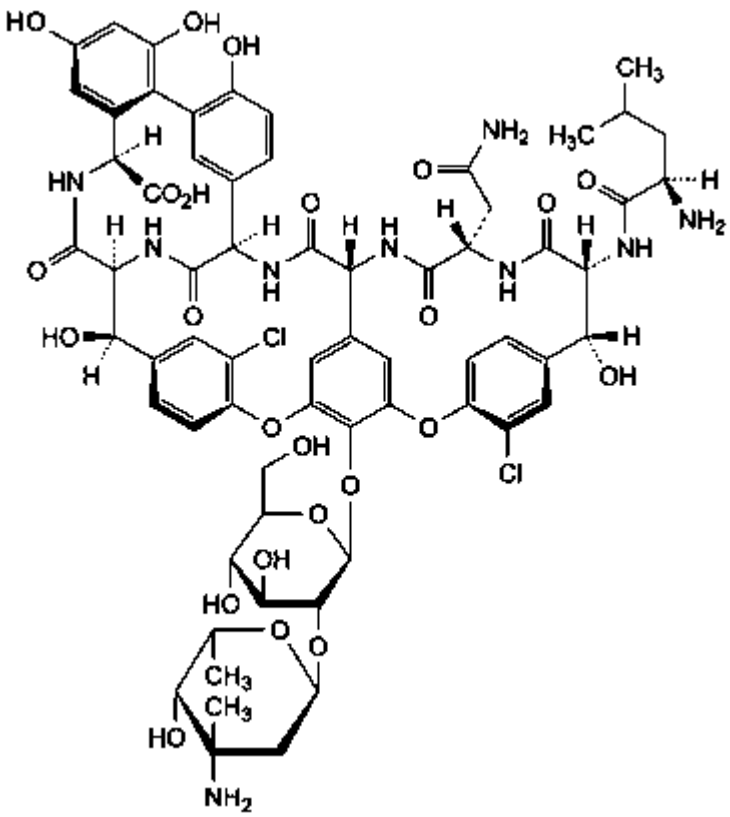
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J, K, M.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *L.*



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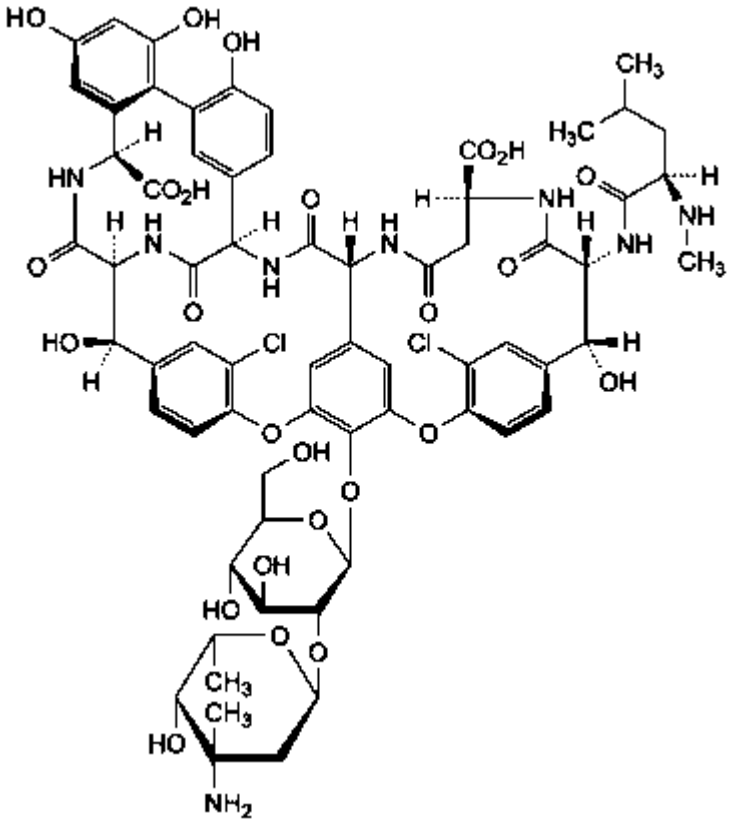
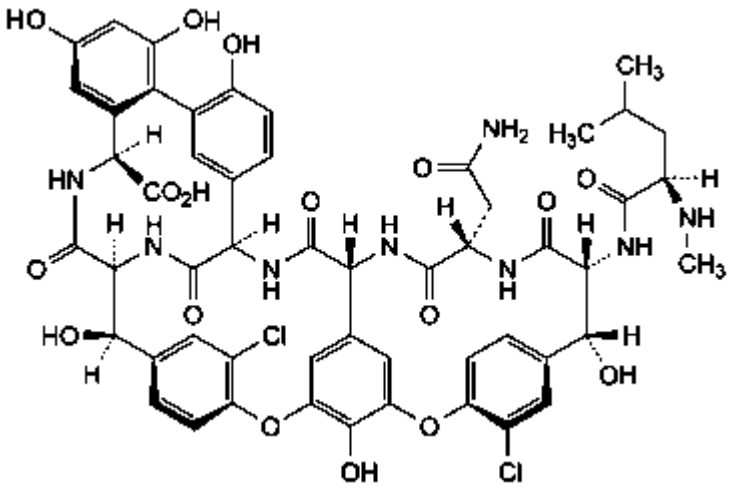
A. $N^{2.1}$-demethylvancomycin B,



B. (1.2*M*)-[L-β-Asp^3]vancomycin B (3.2-*syn*-chloro[L-β-Asp^3]vancomycin B) (CDP-1 major),



C. $O^{4.4}$-de-[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]vancomycin B (aglucovancomycin B),

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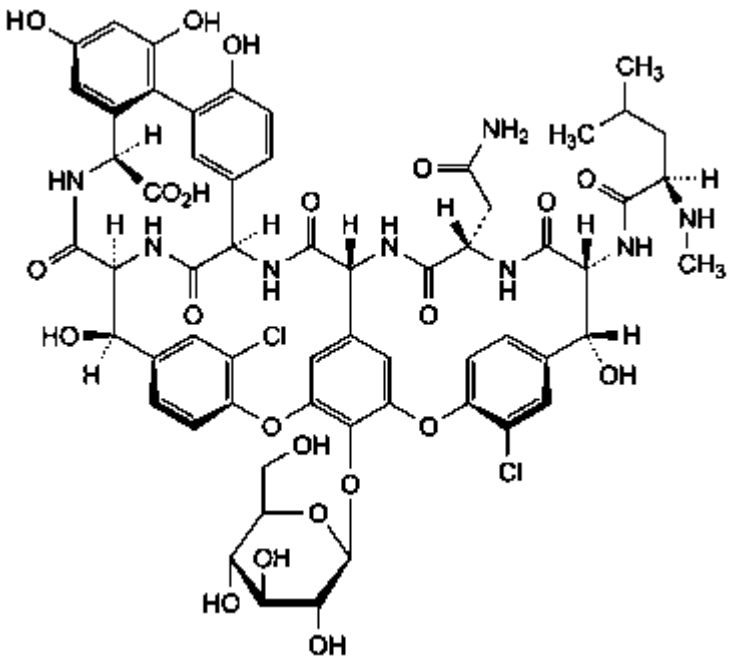
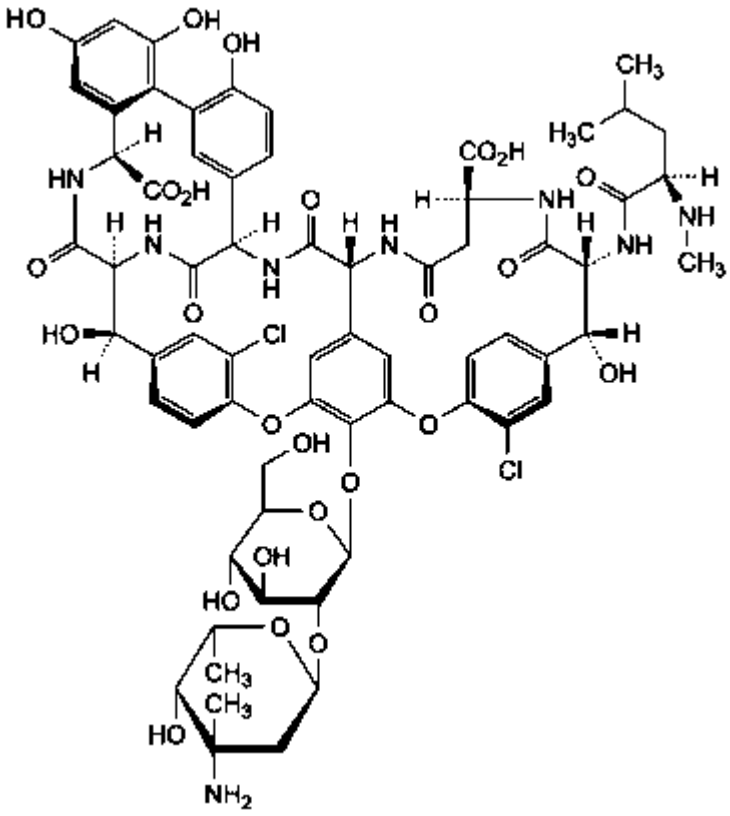


D. $O^{4.4}$-de-[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]-$O^{4.4}$-β-D-glucopyranosyl-vancomycin B (desvancosaminylvancomycin B),



E. [L-β-Asp^3]vancomycin B (CDP-1 minor),

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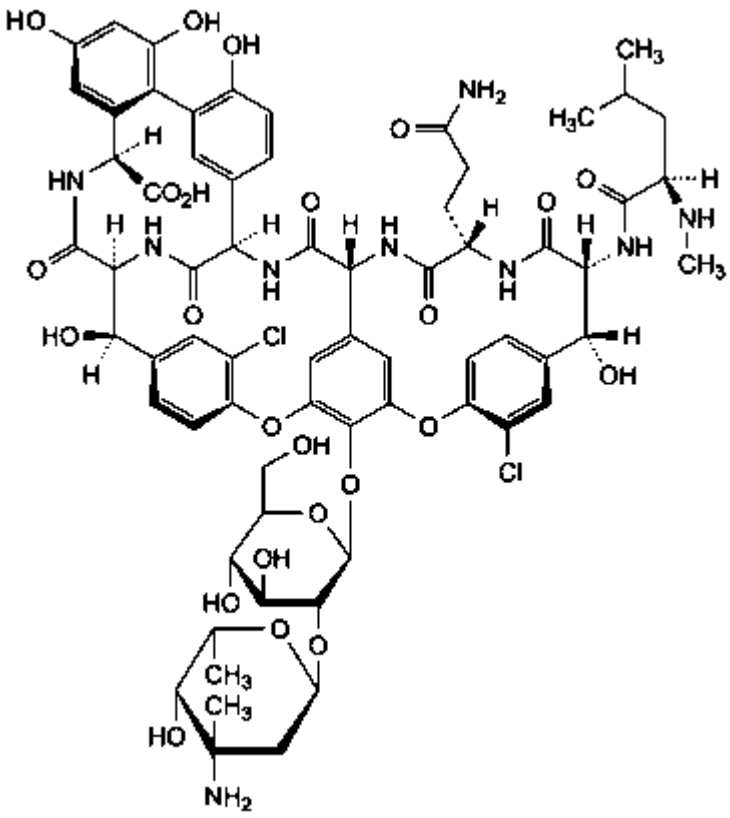
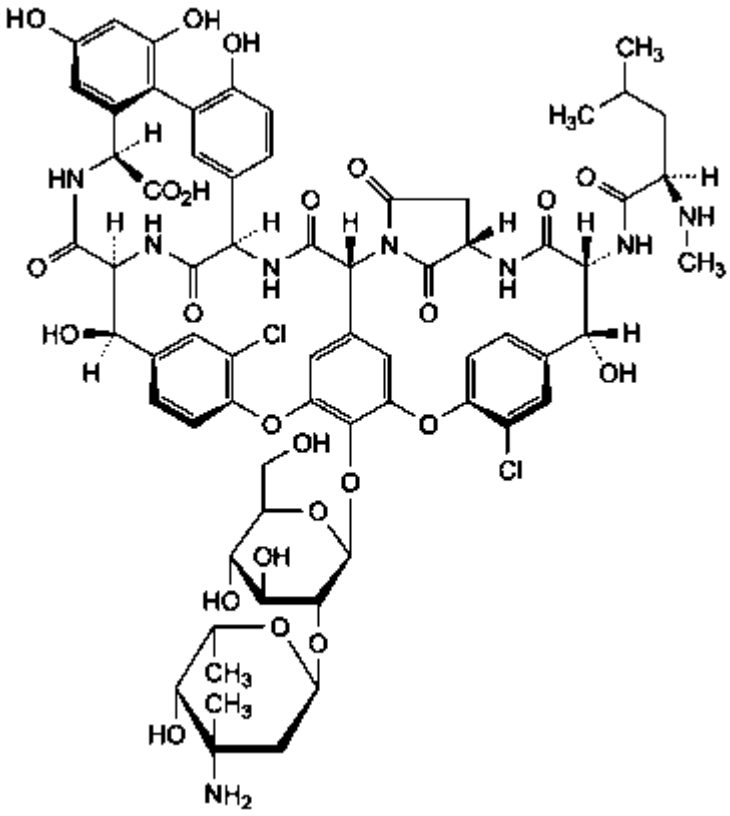


F. [L-α-Gln^{3}]vancomycin B,



G. 4.3,$N^{\alpha,4}$-anhydro-[L-α-Asp^{3}]vancomycin B,

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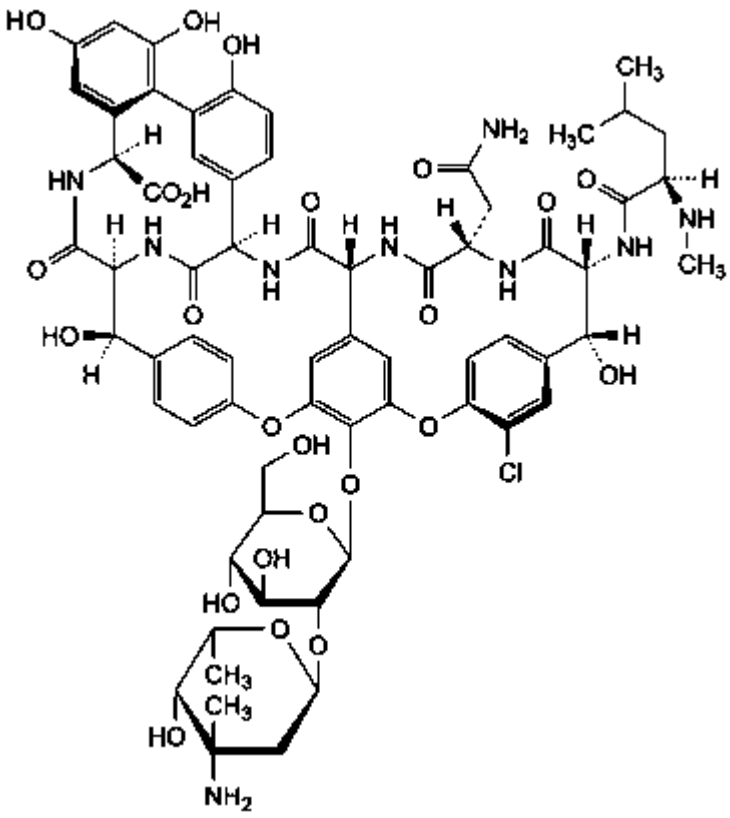
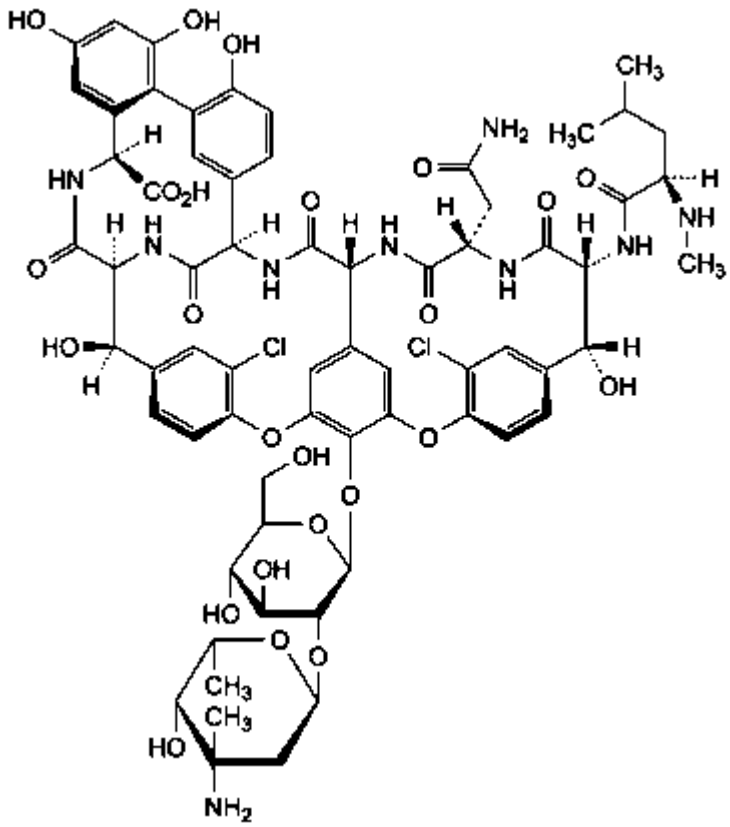


H. 3.6-dechlorovancomycin B (mono-dechloro-6-vancomycin B),



I. (1.2*M*)-vancomycin B (3.2-*syn*-chloro-vancomycin B),

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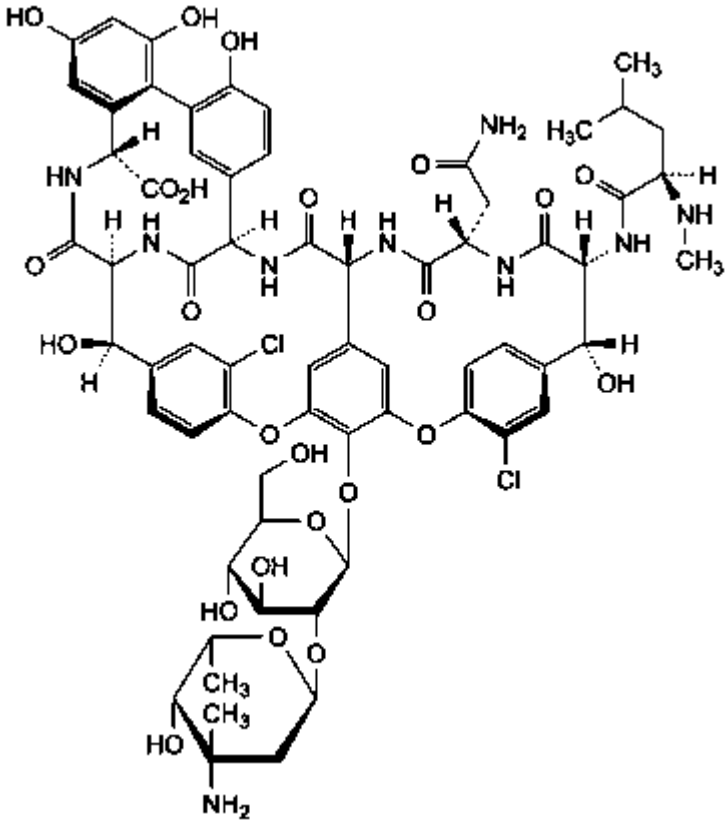
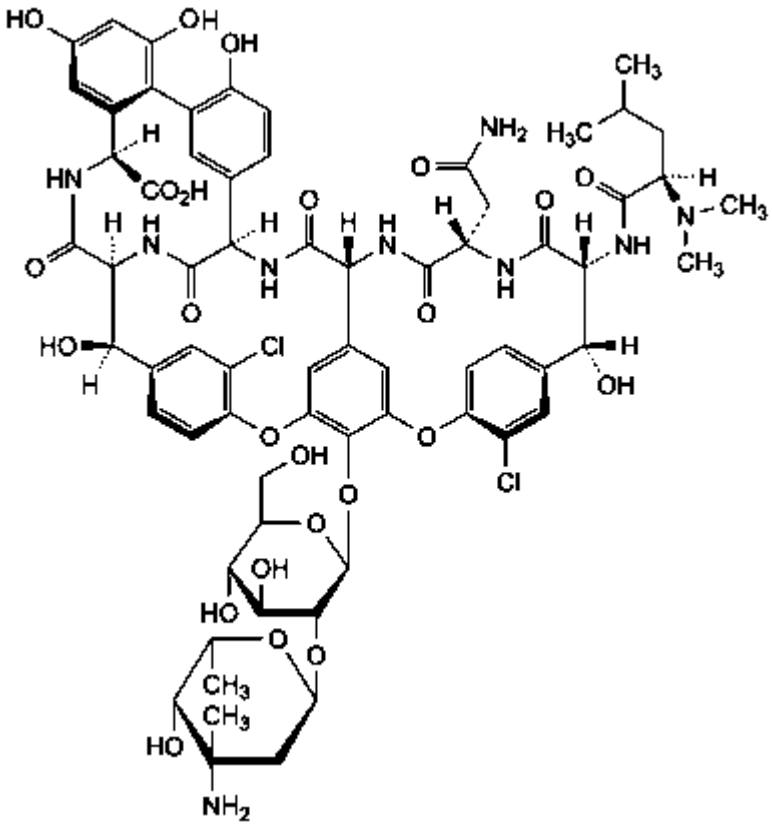


J. ($C^{\alpha,7}R$)-vancomycin B (26-*epi*-vancomycin B),



K. [*N*,*N*-dimethyl-D-Leu^{1}]vancomycin B,

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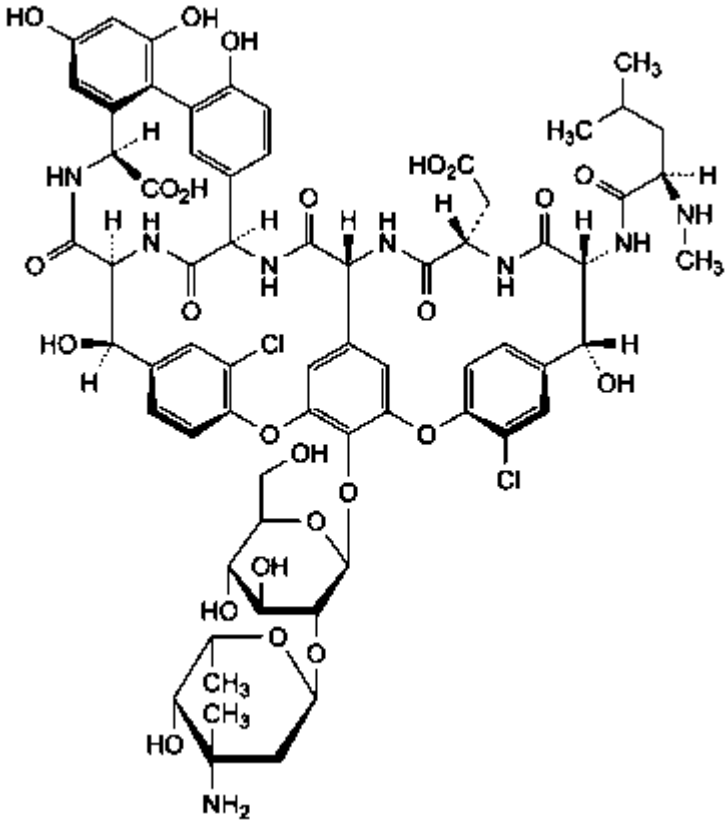

L. [L-α-Asp^{3}]vancomycin B),

M. unknown structure.

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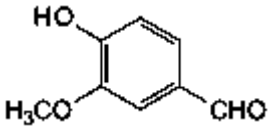
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Vanillin

General Notices

(Ph. Eur. monograph 0747)



$C_8H_8O_3$ 152.1 *121-33-5*

Ph Eur

DEFINITION

Vanillin contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 4-hydroxy-3-methoxybenzaldehyde, calculated with reference to the dried substance.

CHARACTERS

White or slightly yellowish, crystalline powder or needles, slightly soluble in water, freely soluble in ethanol (96 per cent) and in methanol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (2.2.14): 81 °C to 84 °C.

B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *vanillin CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for related substances in daylight after spraying. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To 5 mL of a saturated solution of the substance to be examined add 0.2 mL of *ferric chloride solution R1*. A blue colour is produced. Heat to 80 °C. The solution becomes brown. On cooling, a white precipitate is formed.

TESTS

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TESTS

Appearance of solution

Dissolve 1.0 g in *alcohol R* and dilute to 20 mL with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a) Dissolve 0.1 g of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 10 mg of *vanillin CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dilute 0.5 mL of test solution (a) to 100 mL with *methanol R*.

Apply to the plate 5 µL of each solution. Develop in an unsaturated tank over a path of 10 cm using a mixture of 0.5 volumes of *anhydrous acetic acid R*, 1 volume of *methanol R* and 98.5 volumes of *methylene chloride R*. Dry the plate in a current of cold air. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). Spray with *dinitrophenylhydrazine-aceto-hydrochloric solution R* and examine in daylight. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Reaction with sulfuric acid

Dissolve 50 mg in 5 mL of *sulfuric acid R*. After 5 min, the solution is not more intensely coloured than a mixture of 4.9 mL of yellow primary solution and 0.1 mL of red primary solution or a mixture of 4.9 mL of yellow primary solution and 0.1 mL of blue primary solution (*2.2.2, Method I*).

Loss on drying (*2.2.32*)

Not more than 1.0 per cent, determined on 1.000 g by drying in a desiccator for 4 h.

Sulfated ash (*2.4.14*)

Not more than 0.05 per cent, determined on 2.0 g.

ASSAY

Dissolve 0.120 g in 20 mL of *alcohol R* and add 60 mL of *carbon dioxide-free water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 15.21 mg of $C_8H_8O_3$.

STORAGE

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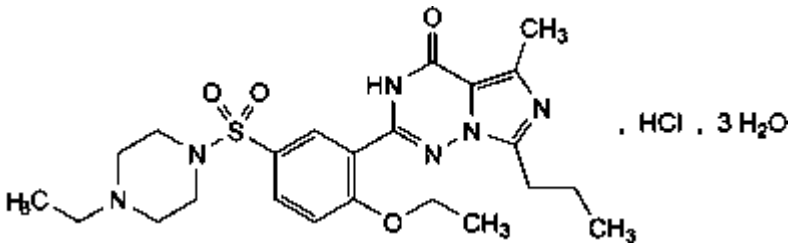
Vardenafil Hydrochloride Trihydrate

General Notices

(Ph. Eur. monograph 2782)



$C_{23}H_{33}ClN_6O_4S,3H_2O$ 579.1 *330808-88-3*

Action and use

Selective inhibitor of cyclic GMP-specific phosphodiesterase type V with vasodilator action; treatment of erectile dysfunction.

Preparations

Vardenafil Orodispersible Tablets

Vardenafil Tablets

Ph Eur

DEFINITION

2-[2-Ethoxy-5-[(4-ethylpiperazin-1-yl)sulfonyl]phenyl]-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one hydrochloride trihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly brown or yellow powder.

Solubility

Slightly soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *vardenafil hydrochloride CRS*.

B. Water (see Tests).

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light*.

Solvent mixture *acetonitrile R*, mobile phase A (20:80 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in 20 mL of *acetonitrile R* and dilute to 100.0 mL with mobile phase A.

Test solution (b) Dilute 15.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of *vardenafil hydrochloride CRS* in 20 mL of *acetonitrile R* and dilute to 100.0 mL with mobile phase A. Dilute 15.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *vardenafil for system suitability CRS* (containing impurity A) in 2 mL of *acetonitrile R* and dilute to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: solution containing 0.7 g/L of *disodium hydrogen phosphate dihydrate R* and 1.3 g/L of *potassium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
2 - 22	80 → 25	20 → 75
22 - 27	25	75

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *vardenafil for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to vardenafil (retention time = about 16 min): impurity A = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity A and vardenafil.

Calculation of percentage contents:

— for each impurity, use the concentration of vardenafil hydrochloride trihydrate in reference solution (b).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Sulfates (2.4.13)

Maximum 400 ppm.

Suspend 0.5 g in 20 mL of a 5.15 g/L solution of *hydrochloric acid R* and stir for 15 min. Filter if complete dissolution is not obtained.

Water (2.5.12)

8.8 per cent to 10.5 per cent, determined on 60.0 mg.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

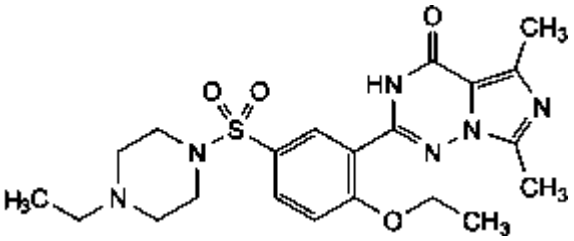
Injection 10 µL of test solution (b) and reference solution (a).

Calculate the percentage content of $C_{23}H_{33}ClN_6O_4S$ taking into account the assigned content of *vardenafil hydrochloride CRS*.

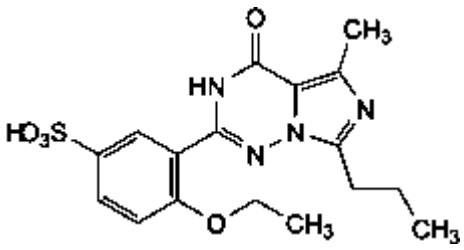
IMPURITIES

Specified impurities *A.*

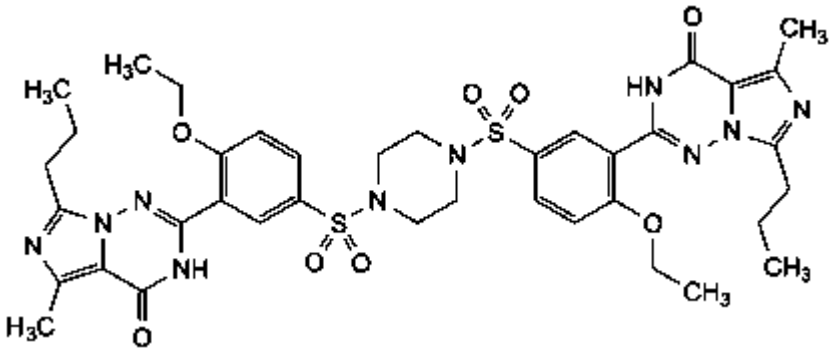
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C.*



A. 2-[2-ethoxy-5-[(4-ethylpiperazin-1-yl)sulfonyl]phenyl]-5,7-dimethylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one,



B. 4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-2-yl)benzenesulfonic acid,



C. 2,2′-[piperazine-1,4-diylbis[(sulfonyl)(4-ethoxybenzene-1,3-diyl)]]bis[5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one].

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Vardenafil Orodispersible Tablets

General Notices

Action and use

Selective inhibitor of cyclic GMP-specific phosphodiesterase type V with vasodilator action; treatment of erectile dysfunction.

DEFINITION

Vardenafil Orodispersible Tablets contain Vardenafil Hydrochloride Trihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of vardenafil, $C_{23}H_{32}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following.

(1) Disperse a quantity of the powdered tablets containing the equivalent of 20 mg of Vardenafil Hydrochloride Trihydrate in 100 mL of a solution of 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid* and filter.

(2) 0.02% *vardenafil hydrochloride EPCRS* in a solution of 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel* F_{254} *HPTLC plates* (Merck silica gel 60 F_{254} HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air, and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume each of *acetone*, of *cyclohexane* and of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

(1) Disperse a quantity of powdered tablets containing the equivalent of 10 mg of vardenafil in 50 mL of solvent A with the aid of ultrasound and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A.

(3) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

(4) 0.015% w/v of *vardenafil for system suitability EPCRS* solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Extend C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08% w/v of *ammonium acetate* in 90 volumes of *water* and 10 volumes of *acetonitrile*.

Mobile phase B 0.08% w/v of *ammonium acetate* in 10 volumes of *water* and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	80→0	20→100	linear gradient
20-21	0→80	100→20	linear gradient
21-25	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to vardenafil (retention time about 8 min) are: impurity B, about 0.2; impurity 1, about 0.5; impurity 2, about 0.55; impurity A, about 0.6 and impurity C, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to vardenafil and impurity A is not less than 5.0.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any peak due to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak due to impurity B or impurity 2is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 1 volumes of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

(1) Disperse a quantity of powdered tablets containing the equivalent of 10 mg of vardenafil in solvent A with the aid of ultrasound, dilute to 50 mL and filter.

(2) 0.0215% of *vardenafil hydrochloride EPCRS* in solvent A.

(3) 0.015% w/v of *vardenafil for system suitability EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to vardenafil and impurity A is not less than 5.0.

DETERMINATION OF CONTENT

Calculate the content of vardenafil, $C_{23}H_{32}N_6O_4S$, using the declared content of $C_{23}H_{32}N_6O_4S$, HCl, in *vardenafil hydrochloride EPCRS*.

Each mg of *vardenafil hydrochloride EPCRS* is equivalent to 0.9306 mg of vardenafil.

STORAGE

Vardenafil Orodispersible Tablets should be stored at a temperature not exceeding 25° and protected from moisture and light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Vardenafil Hydrochloride Trihydrate and:

1. 1-Ethyl-4-{4-ethoxy-3-[5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-2-yl]benzenesulfonyl}piperazine N^1-oxide

2. 2-[2-Ethoxy-5-(piperazine-1-sulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one

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Vardenafil Tablets

General Notices

Action and use

Selective inhibitor of cyclic GMP-specific phosphodiesterase type V with vasodilator action; treatment of erectile dysfunction.

DEFINITION

Vardenafil Tablets contain Vardenafil Hydrochloride Trihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of vardenafil, $C_{23}H_{32}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 20 mg of vardenafil in 100 mL of a solution of 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid* and filter.

(2) 0.02% w/v of *vardenafil hydrochloride EPCRS* in a solution of 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel F_{254} plates* (Merck silica gel 60 F_{254} HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air, and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume each of *acetone*, of *cyclohexane* and of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

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Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for liquid chromatography, Appendix III D, using the following solutions protected from light.

(1) After 30 minutes withdraw a sample of the medium. Use the filtered dissolution medium diluted, if necessary, to obtain a solution expected to contain the equivalent of 0.00025% w/v of vardenafil.

(2) 0.00027% w/v of *vardenafil hydrochloride EPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 3 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.8 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of 0.68% w/v *potassium dihydrogenphosphate* adjusted to pH 3.5 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of vardenafil, $C_{23}H_{32}N_6O_4S$, using the declared content of $C_{23}H_{32}N_6O_4S$, HCl, in *vardenafil hydrochloride EPCRS*.

Each mg of *vardenafil hydrochloride EPCRS* is equivalent to 0.9306 mg of vardenafil.

LIMITS

The amount of vardenafil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions

Solvent A 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

(1) Disperse a quantity of powdered tablets containing the equivalent of 10 mg of vardenafil in 50 mL of solvent A with the aid of ultrasound and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A.

(3) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

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(4) 0.015% w/v of *vardenafil for system suitability EPCRS* solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Extend C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08% w/v of *ammonium acetate* in 90 volumes of water and 10 volumes of *acetonitrile*.

Mobile phase B 0.08% w/v *ammonium acetate* in 10 volumes of water and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	80→0	20→100	linear gradient
20-21	0→80	100→20	linear gradient
21-25	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to vardenafil (retention time about 8 min) are: impurity B, about 0.2; impurity 1, about 0.5; impurity 2, about 0.55; impurity A, about 0.6 and impurity C, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to vardenafil and impurity A is not less than 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A or impurity 1 is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak due to impurity 2 is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

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the sum of the areas of all *secondary peaks*, excluding impurities A, 1 and 2, is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of vardenafil comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

(1) Shake one tablet with sufficient volume of solvent A to produce a solution expected to contain 0.02% w/v of vardenafil and filter.

(2) 0.0215% w/v of *vardenafil hydrochloride EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Extend C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08% w/v of *ammonium acetate* in 90 volumes of water and 10 volumes of *acetonitrile*.

Mobile phase B 0.08% w/v *ammonium acetate* in 10 volumes of water and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	70→10	30→90	linear gradient
10-11	10→70	90→30	linear gradient
11-15	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention time of the vardenafil peak is about 5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peak due to vardenafil and impurity A is not less than 4.0.

DETERMINATION OF CONTENT

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Calculate the content of vardenafil, $C_{23}H_{32}N_6O_4S$, using the declared content of $C_{23}H_{32}N_6O_4S$, in *vardenafil hydrochloride EPCRS*.

Each mg of *vardenafil hydrochloride EPCRS* is equivalent to 0.9306 mg of vardenafil.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of vardenafil

Use the average individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of vardenafil

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 1 volumes of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

(1) Disperse a quantity of powdered tablets containing the equivalent of 10 mg of vardenafil in solvent A with the aid of ultrasound, dilute to 50 mL and filter.

(2) 0.0215% w/v of *vardenafil hydrochloride EPCRS* in solvent A.

(3) 0.015% w/v of *vardenafil for system suitability EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to vardenafil and impurity A is not less than 5.0.

DETERMINATION OF CONTENT

Calculate the content of vardenafil, $C_{23}H_{32}N_6O_4S$, using the declared content of $C_{23}H_{32}N_6O_4S$, HCl, in *vardenafil hydrochloride EPCRS*.

Each mg of *vardenafil hydrochloride EPCRS* is equivalent to 0.9306 mg of vardenafil.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Vardenafil Hydrochloride Trihydrate and:

1. 1-Ethyl-4-{4-ethoxy-3-[5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-2-yl]benzenesulfonyl}piperazine N^1-oxide

2. 2-[2-Ethoxy-5-(piperazine-1-sulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one

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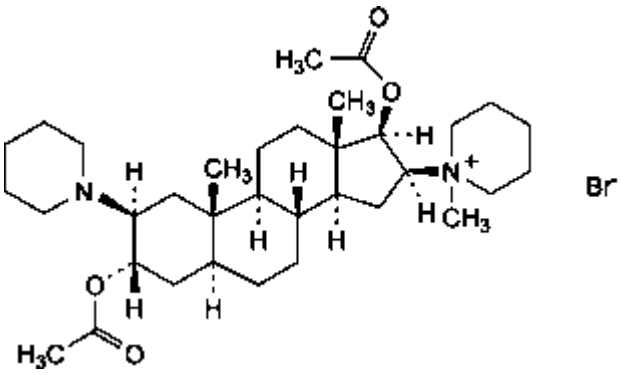
Vecuronium Bromide

General Notices

(Ph. Eur. monograph 1769)



$C_{34}H_{57}BrN_2O_4$ 638 *50700-72-6*

Action and use

Non-depolarizing neuromuscular blocker.

Preparation

Vecuronium Bromide for Injection

Ph Eur

DEFINITION

1-[3α,17β-Bis(acetyloxy)-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidin-1-ium bromide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white crystals or crystalline powder.

Solubility

Slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in acetonitrile and in anhydrous ethanol.

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IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *vecuronium bromide CRS*.

C. It gives reaction (a) of bromides (2.3.1).

TESTS

Solution S

Dissolve 0.500 g in a 5.15 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

+ 30.5 to + 35.0 (anhydrous substance), determined on solution S.

Impurity B

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methylene chloride R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of the substance to be examined and 5 mg of *pancuronium bromide CRS* (impurity B) in *methylene chloride R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 5.0 mg of *pancuronium bromide CRS* (impurity B) in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Plate *TLC silica gel plate R* (2-10 µm).

Mobile phase Dissolve 1 g of *sodium bromide R* in 5 mL of *water R*. Add 85 mL of *2-propanol R*, then 10 mL of *acetonitrile R*.

Application 1 µL.

Development In an unsaturated tank, over 2/3 of the plate.

Drying In air for 30 min.

Detection Spray with a 2.5 g/L solution of *iodine R* in a mixture of equal volumes of *methanol R* and *methylene chloride R*.

System suitability Reference solution (a):

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— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity B*: any spot due to impurity B is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solution A 0.2 g/L solution of *hydrochloric acid R* in *methanol R2*.

Test solution Dissolve 40 mg of the substance to be examined in solution A and dilute to 20.0 mL with solution A.

Reference solution (a) Dissolve 4 mg of *vecuronium for system suitability CRS* (containing impurities C and E) in solution A and dilute to 2.0 mL with the solution A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 135 volumes of an 18.0 g/L solution of *tetramethylammonium hydroxide R* previously adjusted to pH 6.9 with *phosphoric acid R*, 250 volumes of *methanol R2* and 615 volumes of *acetonitrile R1*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 4 °C.

Injection 20 µL.

Run time 5 times the retention time of vecuronium.

Identification of impurities Use the chromatogram supplied with *vecuronium for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and E.

Relative retention With reference to vecuronium (retention time = about 5 min): impurity C = about 0.8; impurity E = about 1.2.

System suitability:

— *signal-to-noise ratio*: minimum 28 for the principal peak in the chromatogram obtained with reference solution (b);

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— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 1.4;

— for each impurity, use the concentration of vecuronium bromide in reference solution (b).

Limits:

— *impurity C*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 4.0 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.450 g in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 63.8 mg of $C_{34}H_{57}BrN_2O_4$.

STORAGE

In an airtight container, protected from light and moisture.

IMPURITIES

Specified impurities B, C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, D, E, F.

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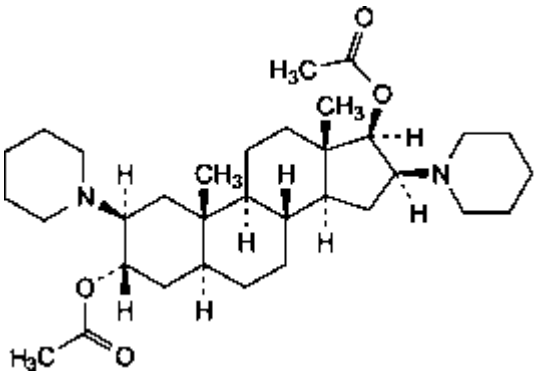
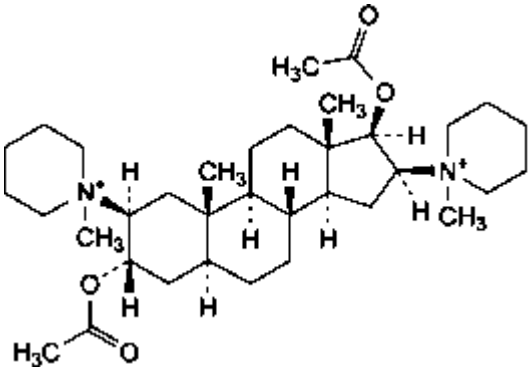
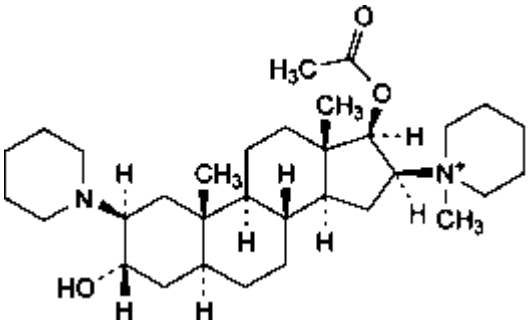


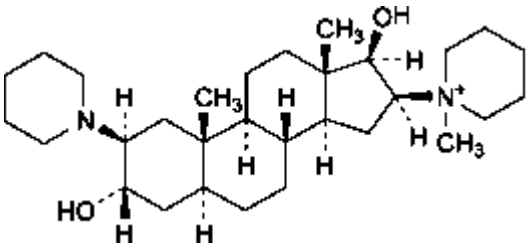
A. 2β,16β-di(piperidin-1-yl)-5α-androstane-3α,17β-diyl diacetate,



B. 1,1′-[3α,17β-bis(acetyloxy)-5α-androstane-2β,16β-diyl]bis(1-methylpiperidin-1-ium) (pancuronium),



C. 1-[17β-(acetyloxy)-3α-hydroxy-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidin-1-ium,



D. 1-[3α,17β-dihydroxy-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidin-1-ium,

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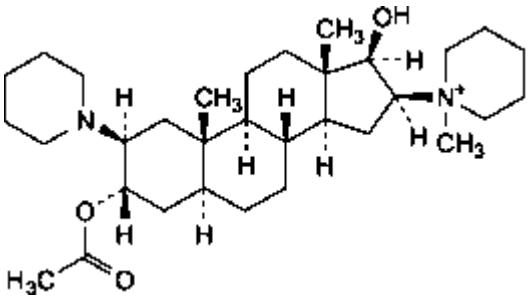
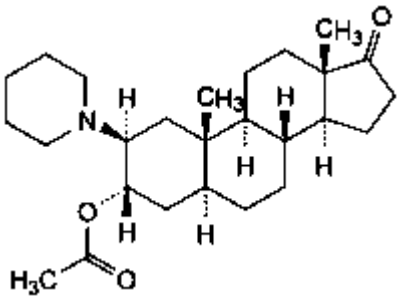


E. 1-[3α-(acetyloxy)-17β-hydroxy-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidin-1-ium,



F. 2β-(piperidin-1-yl)-17-oxo-5α-androstan-3α-yl acetate.

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Vecuronium Bromide for Injection

General Notices

Action and use

Non-depolarizing neuromuscular blocker.

DEFINITION

Vecuronium Bromide for Injection is a sterile material consisting of Vecuronium Bromide with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of vecuronium bromide, $C_{34}H_{57}BrN_2O_4$

93.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *dichloromethane*.

(1) Shake the contents of the sealed container in a sufficient volume of *dichloromethane* to produce a solution containing 0.1% w/v of Vecuronium Bromide. Filter and use the filtrate.

(2) 0.1% w/v of *vecuronium bromide BPCRS*.

(3) 0.1% w/v each of *vecuronium bromide BPCRS* and *pancuronium bromide EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with a 0.25% w/v solution of *iodine* in a mixture of equal volumes of *dichloromethane* and *methanol*.

MOBILE PHASE

Dissolve 1 g of *sodium bromide* in 5 mL of *water*. Add 85 mL of *propan-2-ol* and 10 mL of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in a 0.02% w/v solution of *hydrochloric acid* in *methanol R1*.

(1) Dissolve the contents of a sealed container in a sufficient volume to produce a solution containing 0.04% w/v of Vecuronium Bromide.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.04% w/v of *vecuronium for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 100 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for four times the retention time of vecuronium bromide.

MOBILE PHASE

135 volumes of 1.8% w/v *tetramethylammonium hydroxide* adjusted to pH 6.5 with *orthophosphoric acid*, 250 volumes of *methanol R1* and 615 volumes of *acetonitrile R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to vecuronium bromide and impurity E is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity A and impurity C using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity A and impurity C by the following correction factors respectively: 0.6 and 1.4.

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity C is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight,* Appendix XII C1, Powders for Parenteral Use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in a 0.02% w/v solution of *hydrochloric acid* in *methanol R1*.

(1) Dissolve a quantity of the mixed contents of the 10 containers containing 20 mg of Vecuronium Bromide in 100 mL.
(2) 0.02% w/v of *vecuronium bromide BPCRS*.
(3) 0.2% w/v of *vecuronium for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but with an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to vecuronium bromide and impurity E is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{34}H_{57}BrN_2O_4$ in a container of average content weight from the chromatograms obtained and from the declared content of $C_{34}H_{57}BrN_2O_4$ in *vecuronium bromide BPCRS*.

STORAGE

Vecuronium Bromide for Injection should be stored protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph those listed under Vecuronium Bromide.

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Vegetable Fatty Oils

General Notices

(Ph. Eur. monograph 1579)

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DEFINITION

Vegetable fatty oils are mainly solid or liquid triglycerides of fatty acids. They may contain small amounts of other lipids such as waxes, free fatty acids, partial glycerides or unsaponifiable matters. Vegetable fatty oils are obtained from the seeds, the fruit or the pit/stone/kernel of various plants by expression and/or solvent extraction, then possibly refined and hydrogenated. A suitable antioxidant may be added if necessary.

Virgin oil An oil obtained from raw materials of special quality by mechanical procedures (e.g. by cold expression or centrifugation).

Refined oil An oil obtained by expression and/or solvent extraction, and subsequently either alkali refining (followed by bleaching and any deodorisation) or physical refining.

Hydrogenated oil An oil obtained by expression and/or solvent extraction, and subsequently either alkali refining or physical refining, then possible bleaching, followed by drying, hydrogenation and subsequent bleaching and deodorisation.

Only alkali-refined oils are used in the manufacture of parenteral preparations.

PRODUCTION

Measures are taken to ensure that the oil complies with the limit for benzo[a]pyrene decided by the competent authority. A limit of 2.0 ppb is set in Commission Regulation (EC) No. 208/2005.

OBTENTION OF A CRUDE OIL

Where the plant has a high oil content, the oil is generally obtained by expression under heating followed by an extraction; where the plant has a low oil content, the oil is generally obtained by direct extraction.

Mechanical procedures

A. Expression

High-pressure screw-pressing It consists of some or all of the following steps: cleaning, drying, dehulling or decorticating, grinding, cooking and flaking.

During *cleaning* the foreign matter is eliminated. *Drying* may be necessary if the seed moisture content is higher than desirable for downstream processing. *Decorticating* is useful to obtain a high-protein meal by reduction of fibre and to reduce impurities in the oil.

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Cooking serves various purposes: completion of the breakdown of oil cells, lowering of the viscosity of the oil, coagulation of the protein in the meal, adjustment of the moisture level, sterilisation of the seed, detoxifying undesirable seed constituents (gossypol for cottonseed) and fixing certain phosphatides in the cake thus lowering subsequent refining losses. The efficacy of the expression process is such that only 3 per cent to 6 per cent of the oil is left in the cake.

Wet screw-pressing The bunches are loaded into cages (for palm fruit) and moved into a horizontal steriliser with application of live steam and heating. The purposes of this steriliser are inactivation of enzymes, loosening of the fruit on the bunch, coagulation of proteins, etc. After heating in a digester, the pulp is fed to a screw-press. The oil is centrifugally clarified and vacuum-dried.

Pre-pressing followed by solvent extraction The same sequence of steps is performed as above. The main function of pre-pressing is to obtain a cake of excellent permeability for the following solvent extraction stage. The extraction is performed either in a percolation-type or in an immersion-type apparatus. The efficacy of the solvent extraction process is such that residual oil levels in meal are generally below 1 per cent.

B. Centrifugation

Centrifugation separates the oily phase from the aqueous phase, which contains water-soluble components and residual solid particles. This operation can be carried out using:

— self-cleaning bowl or disc centrifuges;

— super-decanters, which are horizontal turbines equipped with a cylindrical bowl that tapers slightly at one end and which contains a continuously turning screw that scrapes the sides of the bowl; the screw and the bowl rotate at different speeds; the solid particles are discarded from the tapered end of the bowl and the oil flows out from the other end.

Solvent extraction

Prior to extraction, the following steps are carried out: the seeds are tempered for about a week at a temperature below 24 °C in order to loosen the hull from the seed and allow the seed moisture to attain equilibrium, then the seeds are cleaned, ground, dehulled and flaked. The most widely used solvent is a mixture of mainly *n*-hexane and methylpentanes (bp: 65-70 °C) commonly referred to as ‘hexane’. Due to the major fire and explosive risks of this mixture, liquified gases and supercritical gases may also be used.

REFINING

The objective of refining is to remove impurities and contaminants of the oil with the least possible damage to the triglycerides and with minimal loss of oil. The contents of the following substances are reduced:

— free fatty acids, which may cause deterioration of the oil by oxidation, a smoked taste when heated and a sharp flavour (by alkali refining);

— water, which favours the enzymatic hydrolysis reactions (by alkali refining, drying);

— partial glycerides, which may cause foaming and a bitter taste (by neutralisation, washing);

— phosphatides and phosphorous compounds, which have emulsifying properties and may cause deposits, a darkening of the oil when heated, a cloudy appearance and bad organoleptic stability (by alkali refining);

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— colouring matters such as chlorophyll (by alkali refining) and carotenoids (by bleaching);

— glycolipids, which may form colloidal solutions with water;

— free hydrocarbons, paraffin, waxes and resinous materials;

— metals (Fe, Cu, Pb, Sn, Pt, Pd, etc.), which are strong oxidation catalysts;

— pigments such as gossypol (in cottonseed oil) or mycotoxins such as aflatoxin (mainly in arachis seeds);

— pesticides;

— oxidation products (aldehydes, peroxides);

— proteins having possible allergic reactions;

— unsaponifiable matters (sterols, tocopherols and other vitamins);

— polycyclic aromatic hydrocarbons.

Alkali refining

It involves the following steps: degumming if necessary, neutralisation using alkali, washing and drying.

Degumming During this step of the refining, i.e. treatment with water and/or phosphoric acid and/or sodium chloride, the phosphatides, phosphorous compounds and metals are eliminated. The use of this step depends on the nature of the oil.

Neutralisation with alkali This step reduces the free-fatty-acid content below 0.1 per cent; the fatty acids are converted into oil-insoluble soaps, also called ‘soapstocks’. Other substances may be removed by adsorption on these soaps: mucilaginous substances, phosphatides, oxidation products, colouring matters, etc. All substances that become insoluble in the oil on hydration are removed. Neutralisation with alkali has the disadvantage of saponifying a portion of neutral oil if the neutralisation is not well conducted.

Washing This operation consists in removing the excess of soaps and alkali as well as the remaining traces of metals, phosphatides and other impurities, using hot water.

Drying The remaining water is eliminated under vacuum before any further steps, such as bleaching.

Physical refining

It involves a steam treatment of the oil under high vacuum at a temperature greater than 235 °C. This technique can only be applied to oils naturally low in phosphatides and metals (palm and coconut) or from which phosphatides and metals have been removed by an acid treatment using concentrated phosphoric acid followed by an adsorptive treatment with activated bleaching earth (for sunflower, rapeseed, soya-bean). Moreover, it cannot be used for heat-sensitive oils (cottonseed oil), which darken.

Bleaching

The common method of bleaching is by adsorption treatment of the oil, which is generally heated at 90 °C for 30 min under vacuum, with bleaching earth (natural or activated) or carbon (activated or not); synthetic silica adsorbents may also be added. Substances that have not

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been totally removed during refining are eliminated, for example carotenoids and chlorophyll.

Deodorisation

Deodorisation eliminates odours, volatile substances and any residual extraction solvents; it involves injecting dry vapour into the oil, which is kept under vacuum at a high temperature. Different temperatures are used according to the oil: 200-235 °C for 1.5-3 h or greater than 240 °C for 30 min.

One of the main side reactions is thermic decolourisation due to the destruction of carotenoids when the temperature is greater than 150 °C. This technique provokes a loss of substances that may be distilled (free fatty acids, sterols, tocopherols, part of the refined oil), and may cause *cis-trans* isomerisation of the unsaturated fatty-acid double bonds.

WINTERISATION

Elimination of solids and waxes by filtration at low temperature (also called dewaxing). These solids and waxes could affect the appearance of the oil and cause deposits.

HYDROGENATION

The hydrogenation of the dried and/or bleached oil is performed using a catalyst (e.g. Ni, Pt, Pd), at a temperature of about 100-200 °C under hydrogen pressure. The catalyst is then removed by filtration at 90 °C. The hydrogen must be pure: free of poisons for the catalyst, water-free, and low in carbon dioxide, methane and nitrogen contents. Small amounts of polymers may be obtained. *Trans*-fatty acids are formed during partial hydrogenation.

CHROMATOGRAPHIC PURIFICATION

In high-purity applications, mainly for parenteral uses, the oil may be further purified by passing the oil through a column containing an activated earth. A solvent may sometimes be used to improve the efficiency. High-polarity molecules, such as oxidised materials, acids, alcohols, partial glycerides and free sterols, are preferentially removed.

When the oil is used in the manufacture of parenteral preparations, the limits set in the monograph for the acid value, the peroxide value and the water content may be different.

LABELLING

The label states:

— where applicable, that the oil was obtained by expression or extraction;

— where applicable, that the oil is suitable for use in the manufacture of parenteral preparations.

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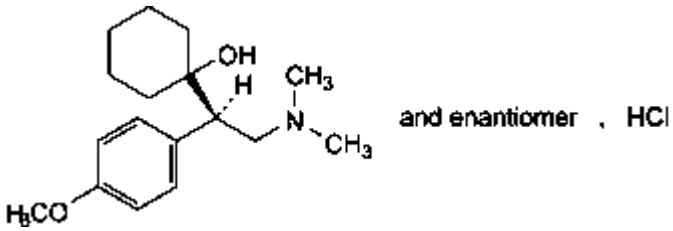
Venlafaxine Hydrochloride

General Notices

(Ph. Eur. monograph 2119)



$C_{17}H_{28}ClNO_2$ 313.9 *99300-78-4*

Action and use

Inhibition of 5HT and noradrenaline reuptake; antidepressant.

Preparations

Venlafaxine Prolonged-release Capsules

Venlafaxine Prolonged-release Tablets

Venlafaxine Tablets

Ph Eur

DEFINITION

1-[(1*RS*)-2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone.

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It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison venlafaxine hydrochloride CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in 2-propanol R, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Acidity or alkalinity

Dissolve 0.20 g in carbon dioxide-free water R and dilute to 10 mL with the same solvent. Add 0.05 mL of methyl red solution R and 0.1 mL of 0.01 M hydrochloric acid. The solution is pink. Not more than 0.2 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of venlafaxine for system suitability CRS (containing impurities D and F) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm) with a pore size of 10 nm.

Mobile phase Mix 510 volumes of acetonitrile R and 1490 volumes of a solution prepared as follows: dissolve 17 g of ammonium dihydrogen phosphate R in 1490 mL of water R and adjust to pH 4.4 using phosphoric acid R.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL.

Run time 10 times the retention time of venlafaxine.

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Relative retention With reference to venlafaxine (retention time = about 9 min): impurity D = about 0.9; impurity F = about 3.4.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity D and venlafaxine.

Limits:

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

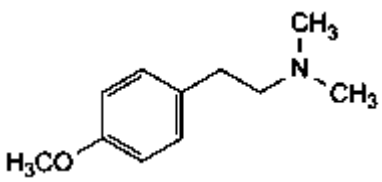
Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.39 mg of $C_{17}H_{28}ClNO_2$.

IMPURITIES

Specified impurities *F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, G, H.*



A. 2-(4-methoxyphenyl)-*N,N*-dimethylethanamine,

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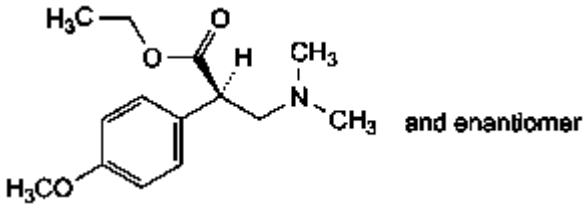
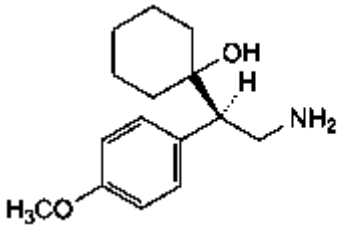


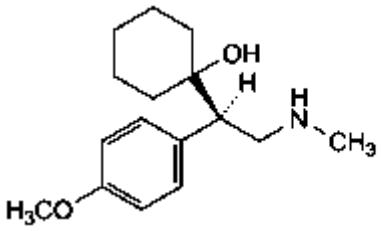
and enantiomer

B. ethyl (2*RS*)-3-(dimethylamino)-2-(4-methoxyphenyl)propanoate,



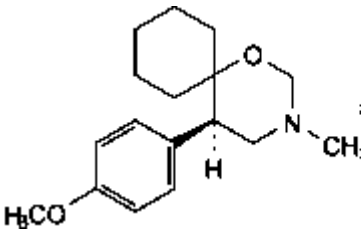
and enantiomer

C. 1-[(1*RS*)-2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol,



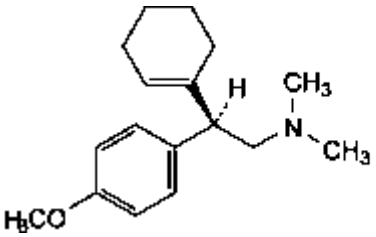
and enantiomer

D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol,



and enantiomer

E. (5*RS*)-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-azaspiro[5.5]undecane,



and enantiomer

F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-*N,N*-dimethylethanamine,

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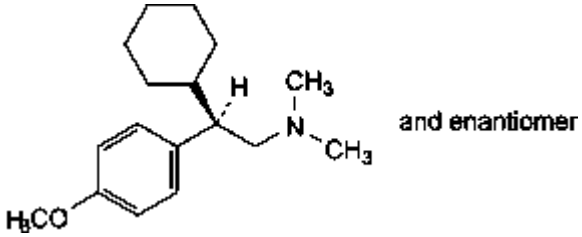
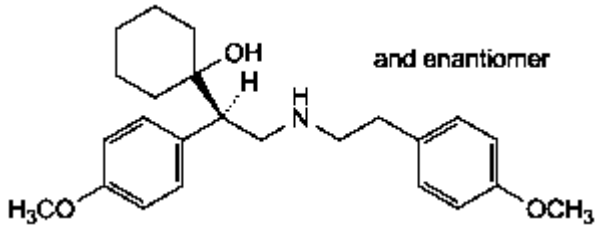


G. (2*RS*)-2-cyclohexyl-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine,



H. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]cyclohexanol.

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Venlafaxine Prolonged-release Capsules

General Notices

Prolonged-release Venlafaxine Capsules

Venlafaxine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Inhibition of 5HT and noradrenaline reuptake; antidepressant.

DEFINITION

Venlafaxine Prolonged-release Capsules contain Venlafaxine Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Venlafaxine Hydrochloride. The dissolution profile reflects the performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of venlafaxine, $C_{17}H_{27}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered capsule contents containing the equivalent of 0.35 g of venlafaxine with 100 mL of a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane* for 30 minutes, filter the extract through *anhydrous sodium sulfate* and evaporate the filtrate to dryness. Wash the residue with a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane*, filter and dry the residue. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of venlafaxine hydrochloride *(RS 439)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase A.

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(1) Mix with the aid of ultrasound, a quantity of the powdered capsule contents containing the equivalent of 200 mg of venlafaxine with 80 mL of a 2.4% v/v solution of *orthophosphoric acid*, shake for a further 30 minutes, cool, add sufficient *water* to produce 100 mL, mix and centrifuge; use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 500 volumes.

(3) 0.2% w/v of *venlafaxine impurity standard BPCRS*.

(4) Dilute 25 volumes of solution (2) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Partisil ODS 3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *triethylamine*, 20 volumes of *acetonitrile* and 80 volumes of *water* adjusted to pH 3.5 with *orthophosphoric acid*.

Mobile phase B 1 volume of *triethylamine*, 50 volumes of *acetonitrile* and 50 volumes of *water* adjusted to pH 3.5 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100→0	0→100	linear gradient
30-45	0	100	isocratic
45-48	0→100	100→0	re-equilibration
48-60	100	0	isocratic

Under the prescribed conditions, the retention time of venlafaxine is about 13 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity D or impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Mix the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the capsule contents containing the equivalent of 175 mg of venlafaxine for 30 minutes with 50 mL of *methanol*, add sufficient *methanol* to produce 100 mL, mix and filter. To 5 volumes of the filtrate add sufficient of the mobile phase to produce 100 volumes.

(2) 0.01% w/v of *venlafaxine hydrochloride BPCRS*.

(3) 0.01% w/v of *venlafaxine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C18 is suitable)

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile* and 80 volumes of a 1% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

Under the prescribed conditions, the retention time of venlafaxine is about 3.5 minutes. If necessary adjust the *acetonitrile* content of the mobile phase.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{27}NO_2$ in the capsules using the declared content of $C_{17}H_{27}NO_2$,HCl in *venlafaxine hydrochloride BPCRS*. Each mg of $C_{17}H_{27}NO_2$,HCl is equivalent to 0.884 mg of $C_{17}H_{27}NO_2$.

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LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of venlafaxine.

IMPURITIES

The impurities limited by the requirements of this monograph include:

D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol (European Pharmacopoeia impurity D);

F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-N,N-dimethylethanamine (European Pharmacopoeia impurity F).

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Venlafaxine Prolonged-release Tablets

General Notices

Prolonged-release Venlafaxine Tablets

Venlafaxine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Inhibition of 5HT and noradrenaline reuptake; antidepressant.

DEFINITION

Venlafaxine Prolonged-release Tablets contain Venlafaxine Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Venlafaxine Hydrochloride. The dissolution profile reflects the performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of venlafaxine, $C_{17}H_{27}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 0.35 g of venlafaxine with 100 mL of a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane* for 30 minutes, filter the extract through *anhydrous sodium sulfate* and evaporate the filtrate to dryness. Wash the residue with a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane*, filter and dry the residue. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of venlafaxine hydrochloride *(RS439)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing the equivalent of 200 mg of venlafaxine with 80 mL of a 2.4% v/v solution of *orthophosphoric acid*, shake for a further 30 minutes, cool, add sufficient *water* to produce 100 mL, mix and centrifuge; use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A, further dilute 1 volume of this solution to 5 volumes with mobile phase A.

(3) 0.2% w/v of *venlafaxine impurity standard BPCRS* in mobile phase A.

(4) Dilute 25 volumes of solution (2) to 100 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Partisil ODS 3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *triethylamine*, 20 volumes of *acetonitrile* and 80 volumes of *water* previously adjusted to pH 3.5 with *orthophosphoric acid*.

Mobile phase B 1 volume of *triethylamine*, 50 volumes of *acetonitrile* and 50 volumes of *water* previously adjusted to pH 3.5 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100→0	0→100	linear gradient
30-45	0	100	isocratic
45-48	0→100	100→0	re-equilibration
48-60	100	0	isocratic

When the chromatograms are recorded under the prescribed conditions, the retention time of venlafaxine is about 13 minutes. Retention times relative to venlafaxine are: impurity D, about 0.8; impurity F, about 1.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.5.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D or impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered tablets containing the equivalent of 175 mg of venlafaxine for 30 minutes with 50 mL of *methanol*, add sufficient *methanol* to produce 100 mL, mix and filter. Dilute 1 volume of the filtrate to 20 volumes with mobile phase.
(2) 0.01% w/v of *venlafaxine hydrochloride BPCRS*.
(3) 0.01% w/v of *venlafaxine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C18 is suitable)
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 226 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile* and 80 volumes of a 1% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

Under the prescribed conditions, the retention time of venlafaxine is about 3.5 minutes. If necessary, adjust the *acetonitrile* content of the mobile phase.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.0.

DETERMINATION OF CONTENT

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Calculate the content of $C_{17}H_{27}NO_2$ in the tablets using the declared content of $C_{17}H_{27}NO_2$,HCl in *venlafaxine hydrochloride BPCRS*.

Each mg of $C_{17}H_{27}NO_2$,HCl is equivalent to 0.884 mg of $C_{17}H_{27}NO_2$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of venlafaxine.

IMPURITIES

The impurities limited by the requirements of this monograph include:

D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol (European Pharmacopoeia impurity D);

F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine (European Pharmacopoeia impurity F).

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Venlafaxine Tablets

General Notices

Action and use

Inhibition of 5HT and noradrenaline reuptake; antidepressant.

DEFINITION

Venlafaxine Tablets contain Venlafaxine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of venlafaxine, $C_{17}H_{27}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 0.35 g of venlafaxine with 100 mL of a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane* for 30 minutes, filter and evaporate the filtrate to dryness. Wash the residue with a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane*, filter and dry the residue. The i*nfrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of venlafaxine hydrochloride *(RS 439)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, to give a solution expected to contain the equivalent of about 0.0025% w/v of venlafaxine, at the maximum at 274 nm, Appendix II B using *water* in the reference cell.

(2) Measure the *absorbance* of a 0.0025% w/v solution of *venlafaxine hydrochloride BPCRS* using *water* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of venlafaxine, $C_{17}H_{27}NO_2$, in the medium from the absorbances obtained and using the declared content of $C_{17}H_{27}NO_2$,HCl in *venlafaxine hydrochloride BPCRS*. Each mg of $C_{17}H_{27}NO_2$,HCl is equivalent to 0.884 mg of $C_{17}H_{27}NO_2$.

LIMITS

The amount of venlafaxine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase A.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 200 mg of venlafaxine with 80 mL of a 2.4% v/v solution of *orthophosphoric acid*, shake for a further 30 minutes, cool, add sufficient *water* to produce 100 mL, mix and centrifuge; use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 500 volumes.

(3) 0.2% w/v of *venlafaxine impurity standard BPCRS*.

(4) Dilute 25 volumes of solution (2) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Partisil ODS 3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *triethylamine*, 20 volumes of *acetonitrile* and 80 volumes of *water* adjusted to pH 3.5 with *orthophosphoric acid*.

Mobile phase B 1 volume of *triethylamine*, 50 volumes of *acetonitrile* and 50 volumes of *water* adjusted to pH 3.5 with *orthophosphoric acid*.

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Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100→0	0→100	linear gradient
30-45	0	100	isocratic
45-48	0→100	100→0	re-equilibration
48-60	100	0	isocratic

Under the prescribed conditions, the retention time of venlafaxine is about 13 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D or impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix a quantity of the powdered tablets containing the equivalent of 50 mg of venlafaxine with 200 mL of a 0.2% v/v solution of *orthophosphoric acid* for 15 minutes with the aid of ultrasound and shake vigorously. Mix for a further 15 minutes with the aid of ultrasound, cool, add sufficient of a 0.2% v/v solution of *orthophosphoric acid* to produce 250 mL, mix and centrifuge. To 2 volumes of the supernatant liquid add sufficient of the mobile phase to produce 5 volumes.

(2) 0.009% w/v of *venlafaxine hydrochloride BPCRS*.

(3) 0.01% w/v of *venlafaxine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax C8 is suitable)

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a 1% v/v solution of *triethylamine*, previously adjusted to pH 3.0 with *orthophosphoric acid*.

Under the prescribed conditions, the retention time of venlafaxine is about 5 minutes, if necessary adjust the *acetonitrile* content of the mobile phase.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{27}NO_2$ in the tablets using the declared content of $C_{17}H_{27}NO_2$,HCl in *venlafaxine hydrochloride BPCRS*.

Each mg of $C_{17}H_{27}NO_2$,HCl is equivalent to 0.884 mg of $C_{17}H_{27}NO_2$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of venlafaxine.

IMPURITIES

The impurities limited by the requirements of this monograph include:

D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol (European Pharmacopoeia impurity D);

F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine (European Pharmacopoeia impurity F).

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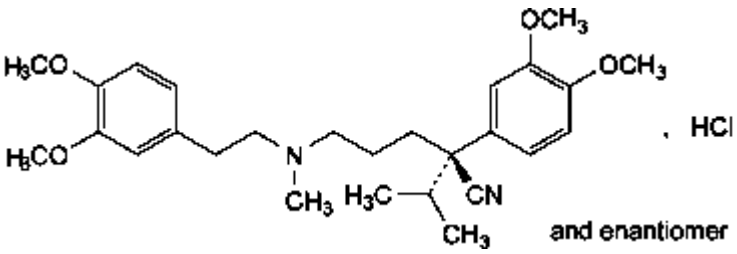
Verapamil Hydrochloride

General Notices

(Ph. Eur. monograph 0573)



$C_{27}H_{39}ClN_2O_4$ 491.1 *152-11-4*

Action and use

Calcium channel blocker.

Preparations

Verapamil Prolonged-release Capsules

Verapamil Prolonged-release Tablets

Verapamil Injection

Verapamil Oral Solution

Verapamil Tablets

Ph Eur

DEFINITION

(2*RS*)-2-(3,4-Dimethoxyphenyl)-5-[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]-2-(propan-2-yl)pentanenitrile hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

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White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in a 1.03 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 5.0 mL of this solution to 50.0 mL with a 1.03 g/L solution of *hydrochloric acid R*.

Spectral range 210-340 nm.

Absorption maxima 229 nm and 278 nm.

Shoulder 282 nm.

Absorbance ratio A_{278}/A_{229} = 0.35 to 0.39.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *verapamil hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *verapamil hydrochloride CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *papaverine hydrochloride CRS* in reference solution (a) and dilute to 5 mL with the same solution.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *diethylamine R*, *cyclohexane R* (15:85 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

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System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 28 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*); use *methanol R* instead of *water R* to wash the precipitate.

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* with gentle heating and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.0 for solution S.

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase B, mobile phase A (37:63 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *verapamil hydrochloride CRS*, 5 mg of *verapamil impurity I CRS* and 5 mg of *verapamil impurity M CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture. Dilute 1 mL of this solution to 10 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm).

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Mobile phase:

— *mobile phase A*: 6.97 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 7.20 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 22	63	37
22 - 27	63 → 35	37 → 65
27 - 45	35	65

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 278 nm.

Injection 10 µL.

Relative retention With reference to verapamil (retention time = about 15 min): impurity I = about 1.3; impurity M = about 2.4.

System suitability Reference solution (a):

— *resolution*: minimum 4.5 between the peaks due to verapamil and impurity I;

— impurity M elutes from the column.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous ethanol R* and add 5.0 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Measure the volume added between the 2 points of inflexion.

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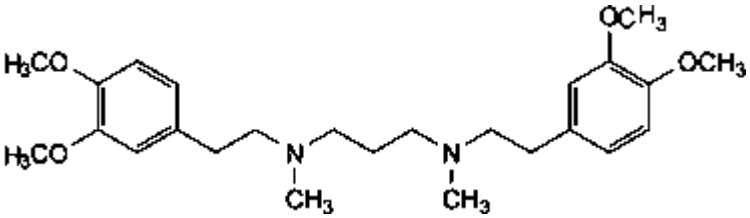
1 mL of *0.1 M sodium hydroxide* is equivalent to 49.11 mg of $C_{27}H_{39}ClN_2O_4$.

STORAGE

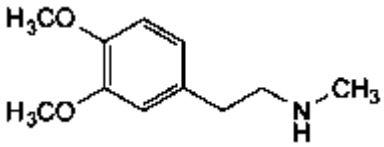
Protected from light.

IMPURITIES

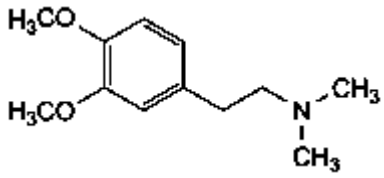
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P.



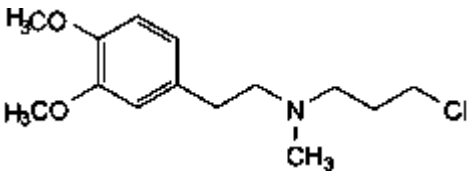
A. *N*^{1},*N*^{3}-bis[2-(3,4-dimethoxyphenyl)ethyl]-*N*^{1},*N*^{3}-dimethylpropane-1,3-diamine,



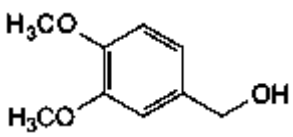
B. 2-(3,4-dimethoxyphenyl)-*N*-methylethan-1-amine,



C. 2-(3,4-dimethoxyphenyl)-*N*,*N*-dimethylethan-1-amine,



D. 3-chloro-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylpropan-1-amine,



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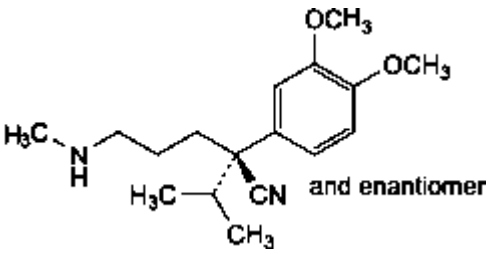
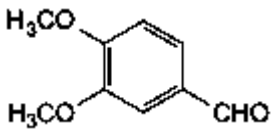
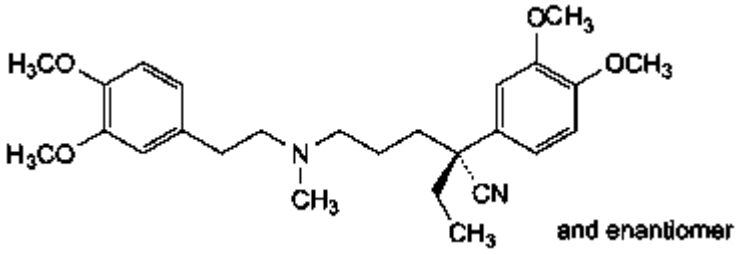
E. (3,4-dimethoxyphenyl)methanol,



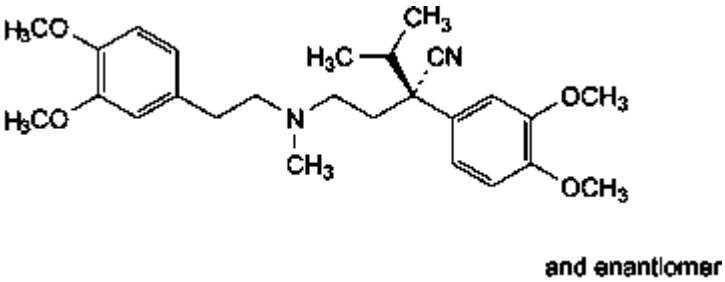
F. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-(methylamino)-2-(propan-2-yl)pentanenitrile,



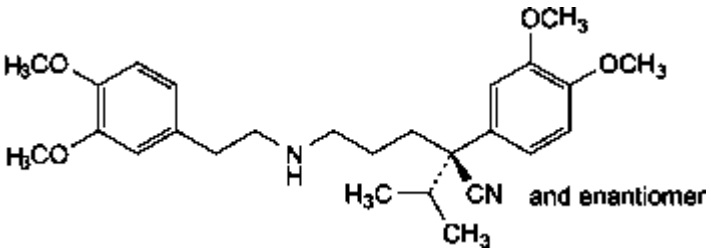
G. 3,4-dimethoxybenzaldehyde,



H. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]-2-ethylpentanenitrile,



I. (2*RS*)-2-(3,4-dimethoxyphenyl)-4-[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]-2-(propan-2-yl)butanenitrile,



J. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-[[2-(3,4-dimethoxy-phenyl)ethyl]amino]-2-(propan-2-yl)pentanenitrile (norverapamil),

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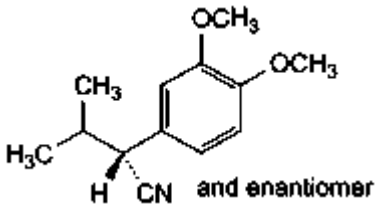
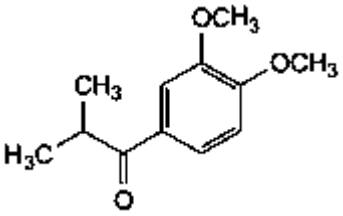
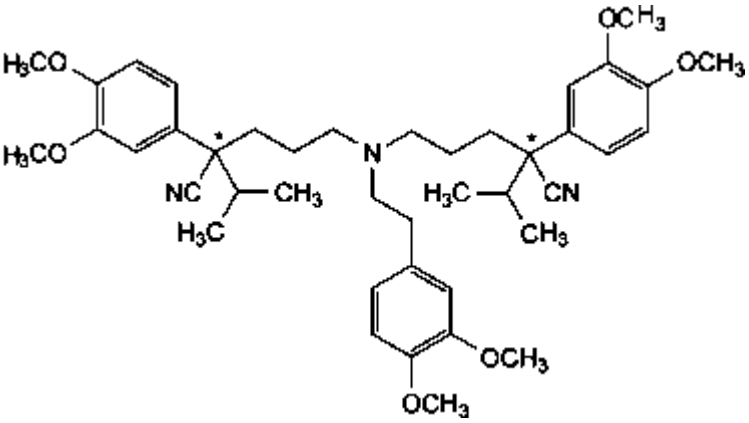


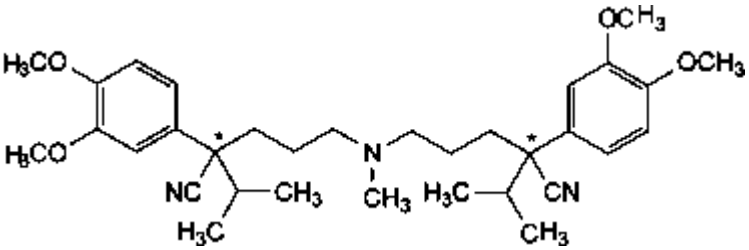
K. (2*RS*)-2-(3,4-dimethoxyphenyl)-3-methylbutanenitrile,



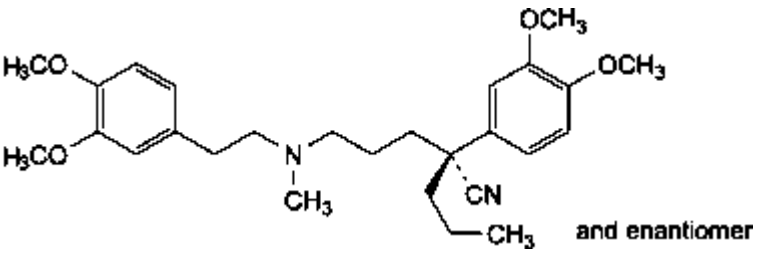
L. 1-(3,4-dimethoxyphenyl)-2-methylpropan-1-one,



M. 5,5′-[[2-(3,4-dimethoxyphenyl)ethyl]azanediyl]bis[(2Ξ)-2-(3,4-dimethoxyphenyl)-2-(propan-2-yl)pentanenitrile],



N. 5,5′-(methylazanediyl)bis[(2Ξ)-2-(3,4-dimethoxyphenyl)-2-(propan-2-yl)pentanenitrile],



O. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-[[2-(3,4-dimethoxy-phenyl)ethyl](methyl)amino]-2-propylpentanenitrile,

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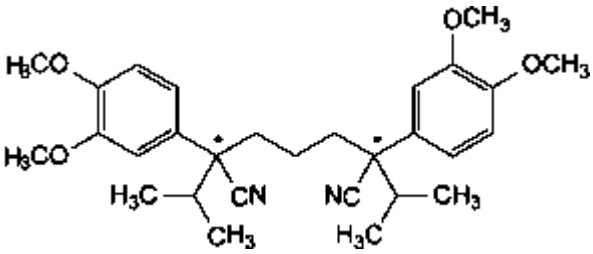

P. (2Ξ,6Ξ)-2,6-bis(3,4-dimethoxyphenyl)-2,6-di(propan-2-yl)heptane-1,7-dinitrile.

Ph Eur

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Verapamil Injection

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Verapamil Injection is a sterile solution of Verapamil Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of verapamil hydrochloride, $C_{27}H_{38}N_2O_4,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dilute a volume containing 10 mg of Verapamil Hydrochloride to 5 mL with 0.1M *hydrochloric acid*, extract with 5 mL of *ether*, discard the extract and make the aqueous layer just alkaline with 2M *potassium carbonate sesquihydrate*. Extract with 5 mL of *ether*, filter the ether layer through *anhydrous sodium sulfate* and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of verapamil (*RS 359*).

B. To a volume containing 5 mg of Verapamil Hydrochloride add 0.2 mL of a 5% w/v solution of *mercury*(II) *chloride*. A white precipitate is produced.

C. To a volume containing 5 mg of Verapamil Hydrochloride add 0.5 mL of 3M *sulfuric acid* and 0.2 mL of *dilute potassium permanganate solution*. A violet precipitate is produced which quickly dissolves to produce a very pale yellow solution.

TESTS

Acidity

pH, 4.5 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the injection diluted, if necessary, with mobile phase to contain 0.125% w/v of Verapamil Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of the resulting solution to 10 volumes with the same solvent.

(3) 0.005% w/v of *verapamil hydrochloride BPCRS* and 0.005% w/v of *verapamil impurity I EPCRS* in the mobile phase.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.85 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of verapamil.

MOBILE PHASE

1 volume of n-*heptylamine*, 4.7 volumes of *glacial acetic acid*, 58 volumes of *acetonitrile* and 137 volumes of 0.01M *sodium acetate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to verapamil and verapamil impurity I is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any such peaks is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

Disregard any peak with an area less than 0.5 times that of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Dilute a volume containing 5 mg of Verapamil Hydrochloride to 100 mL with 0.01M *hydrochloric acid*. Measure the *absorbance* of the resulting solution at the maximum at 278 nm, Appendix II B. Calculate the content of $C_{27}H_{38}N_2O_4$,HCl taking 118 as the value of A(1%, 1 cm) at the maximum at 278 nm.

STORAGE

Verapamil Injection should be protected from light.

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Verapamil Oral Solution

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Verapamil Oral Solution contains Verapamil Hydrochloride.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of verapamil hydrochloride, $C_{27}H_{38}N_2O_4,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Mix a volume of the oral solution containing 10 mg of Verapamil Hydrochloride with 5 mL of 0.1M *hydrochloric acid*, extract with 5 mL of *ether*, discard the extract and make the aqueous layer just alkaline with 2M *potassium carbonate sesquihydrate*. Extract with 5 mL of *ether*, filter the ether layer through *anhydrous sodium sulfate* and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of verapamil (*RS 359*).

B. In the test for Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to the peak due to verapamil in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the oral solution diluted, if necessary, with mobile phase to contain 0.16% w/v of Verapamil Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of the resulting solution to 5 volumes with the same solvent.

(3) 0.005% w/v of *verapamil hydrochloride BPCRS* and 0.005% w/v of *verapamil impurity I EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.85 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of verapamil.

MOBILE PHASE

1 volume of n-*heptylamine*, 4.7 volumes of *glacial acetic acid*, 58 volumes of *acetonitrile* and 137 volumes of 0.01M *sodium acetate*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to verapamil (retention time about 6 minutes) are: impurity I, about 0.9 and impurity M, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to verapamil and verapamil impurity I is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Use a weighed quantity of the oral solution diluted, if necessary, to contain 0.016% w/v of Verapamil Hydrochloride.

(2) 0.016% w/v of *verapamil hydrochloride BPCRS*.

(3) 0.005% w/v of *verapamil hydrochloride BPCRS* and 0.005% w/v of *verapamil impurity I EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to verapamil and verapamil impurity I is at least 2.0.

DETERMINATION OF CONTENT

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Determine the weight per mL of the oral solution, Appendix V G, and calculate the content of $C_{27}H_{38}N_2O_4$,HCl, weight in volume, using the declared content of $C_{27}H_{38}N_2O_4$,HCl in *verapamil hydrochloride BPCRS*.

STORAGE

Verapamil Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities D, E, F, G, I, J K and M listed under Verapamil Hydrochloride.

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Verapamil Prolonged-release Capsules

General Notices

Prolonged-release Verapamil Capsules

Verapamil Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Calcium channel blocker.

DEFINITION

Verapamil Prolonged-release Capsules contain Verapamil Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Verapamil Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of verapamil hydrochloride, $C_{27}H_{38}N_2O_4,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.1 g of Verapamil Hydrochloride with 25 mL of 0.1M *hydrochloric acid* for 10 minutes, filter, extract the filtrate with 25 mL of *ether*, discard the extract and make the aqueous solution alkaline with 2M *potassium carbonate sesquihydrate*. Extract with 25 mL of *ether*, filter the ether layer through *anhydrous sodium sulfate* and evaporate to dryness. The *infrared absorption spectrum* of a thin film of the oily residue, Appendix II A, is concordant with the *reference spectrum* of verapamil (*RS 359*).

TESTS

Related substances

Prepare a solution containing equal volumes of 0.01M *hydrochloric acid* and *methanol* (solvent A).

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

(1) To a quantity of the contents of the capsules containing 0.24 g of Verapamil Hydrochloride add 95 mL of solvent A, mix with the aid of ultrasound for 5 minutes, shaking occasionally, add sufficient solvent A to produce 100 mL and mix. Centrifuge 50 mL of the resulting solution; dilute the supernatant liquid with sufficient of solvent A to produce a solution containing 0.072% w/v of Verapamil Hydrochloride and filter through a 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 278 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for six times the retention time of verapamil (retention time = about 5.6 minutes).

MOBILE PHASE

3 volumes of *2-heptylamine*, 300 volumes of *acetonitrile* and 700 volumes of a solution containing 0.082% w/v of *anhydrous sodium acetate* and 3.3% v/v of *anhydrous acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of 20 capsules containing 0.12 g of Verapamil Hydrochloride in *methanol* and mix with the aid of ultrasound for 30 minutes, followed by shaking for 10 minutes. Add sufficient *methanol* to produce a solution containing 0.048% w/v of Verapamil Hydrochloride, mix and filter.

(2) 0.048% w/v of *verapamil hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µ-Bondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

3 volumes of a 0.164% w/v solution of *anhydrous sodium acetate* previously adjusted to pH 7.0 with a 5% v/v solution of *glacial acetic acid* and 7 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{38}N_2O_4$,HCl in the capsules using the declared content of $C_{27}H_{38}N_2O_4$,HCl in *verapamil hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities D, E, F, G, I, J and K listed under Verapamil Hydrochloride.

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Verapamil Prolonged-release Tablets

General Notices

Prolonged-release Verapamil Tablets

Verapamil Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Calcium channel blocker.

DEFINITION

Verapamil Prolonged-release Tablets contain Verapamil Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Verapamil Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of verapamil hydrochloride, $C_{27}H_{38}N_2O_4,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Verapamil Hydrochloride with 25 mL of 0.1M *hydrochloric acid* for 10 minutes, filter, extract the filtrate with 25 mL of *ether*, discard the extract and make the aqueous solution just alkaline with 2M *potassium carbonate sesquihydrate*. Extract with 25 mL of *ether*, filter the ether layer through *anhydrous sodium sulfate* and evaporate to dryness. The *infrared absorption spectrum* of a thin film of the oily residue, Appendix II A, is concordant with the *reference spectrum* of verapamil (*RS 359*).

B. Shake a quantity of the powdered tablets containing 0.24 g of Verapamil Hydrochloride with 6 mL of *methanol* for a few minutes, allow to settle and dilute 0.7 mL of the supernatant liquid to 2 mL with *water*. The resulting solution yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Related substances

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Prepare a solution containing equal volumes of 0.01M *hydrochloric acid* and *methanol* (solvent A).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

(1) To a quantity of the powdered tablets containing 0.24 g of Verapamil Hydrochloride add 95 mL of solvent A, mix with the aid of ultrasound for 5 minutes, shaking occasionally, add sufficient solvent A to produce 100 mL and mix. Centrifuge 50 mL of the resulting solution; dilute the supernatant liquid with sufficient of solvent A to produce a solution containing 0.072% w/v of Verapamil Hydrochloride and filter through a 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 278 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for six times the retention time of verapamil (retention time = about 5.6 minutes).

MOBILE PHASE

3 volumes of *2-heptylamine*, 300 volumes of *acetonitrile* and 700 volumes of a solution containing 0.082% w/v of *anhydrous sodium acetate* and 3.3% v/v of *anhydrous acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the powdered tablets containing 0.12 g of Verapamil Hydrochloride in *methanol* and mix with the aid of ultrasound for 30 minutes, followed by shaking for 10 minutes. Add sufficient *methanol* to produce a solution containing 0.048% w/v of Verapamil Hydrochloride, mix and filter.

(2) 0.048% w/v of *verapamil hydrochloride BPCRS* in *methanol*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µ-Bondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

3 volumes of a 0.164% w/v solution of *anhydrous sodium acetate* previously adjusted to pH 7.0 with a 5% v/v solution of *glacial acetic acid* and 7 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{38}N_2O_4$,HCl in the tablets using the declared content of $C_{27}H_{38}N_2O_4$,HCl in *verapamil hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities D, E, F, G, I, J and K listed under Verapamil Hydrochloride.

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Verapamil Tablets

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Verapamil Tablets contain Verapamil Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of verapamil hydrochloride, $C_{27}H_{38}N_2O_4,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Verapamil Hydrochloride with 25 mL of 0.1M *hydrochloric acid*, filter, extract the filtrate with 25 mL of *ether*, discard the extract and make the aqueous solution just alkaline with 2M *potassium carbonate sesquihydrate*. Extract with 25 mL of *ether*, filter the ether layer through *anhydrous sodium sulfate* and evaporate to dryness. The *infrared absorption spectrum* of a thin film of the oily residue, Appendix II A, is concordant with the *reference spectrum* of verapamil (*RS 359*).

B. Shake a quantity of the powdered tablets containing 0.1 g of Verapamil Hydrochloride with 10 mL of *dichloromethane*, filter, evaporate the filtrate to dryness and dissolve the residue in 10 mL of *water*. To 2 mL of the resulting solution add 0.2 mL of a 5% w/v solution of *mercury*(II) *chloride*. A white precipitate is produced.

C. To 2 mL of the solution obtained in test B add 0.5 mL of 3M *sulfuric acid* and 0.2 mL of *dilute potassium permanganate solution*. A violet precipitate is produced which quickly dissolves to produce a very pale yellow solution.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.24 g of Verapamil Hydrochloride with 90 mL of mobile phase, add sufficient of the mobile phase to produce 100 mL, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of the resulting solution to 10 volumes with the same solvent.

(3) 0.005% w/v of *verapamil hydrochloride BPCRS* and 0.005% w/v of *verapamil impurity I EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.85 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of verapamil.

MOBILE PHASE

1 volume of n-*heptylamine*, 4.7 volumes of *glacial acetic acid*, 58 volumes of *acetonitrile* and 137 volumes of 0.01M *sodium acetate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to verapamil and verapamil impurity I is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any such peaks is not greater than 3 times the principal peak in the chromatogram obtained with solution (2) (0.3%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of Verapamil Hydrochloride with 150 mL of 0.1M *hydrochloric acid* for 10 minutes, add sufficient 0.1M *hydrochloric acid* to produce 200 mL and filter. Dilute 10 mL of the filtrate to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 278 nm, Appendix II B. Calculate the content of $C_{27}H_{38}N_2O_4$,HCl taking 118 as the value of A(1%, 1 cm) at the maximum at 278 nm.

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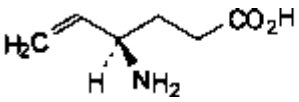
Vigabatrin

General Notices

(Ph. Eur. monograph 2305)



and enantiomer

$C_6H_{11}NO_2$ 129.2 *60643-86-9*

Action and use

Antiepileptic.

Preparations

Vigabatrin Oral Powder

Vigabatrin Tablets

Ph Eur

DEFINITION

(4*RS*)-4-Aminohex-5-enoic acid.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, slightly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *vigabatrin CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in *water R*, using sonication if necessary, and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 7.5 mg of *vigabatrin impurity A CRS* and 7.5 mg of *vigabatrin impurity B CRS* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with *water R*.

Reference solution (c) Dissolve 5.0 mg of *vigabatrin impurity E CRS* and 10.0 mg of *vigabatrin impurity D CRS* in *water R* and dilute to 50.0 mL with the same solvent. To 2.0 mL of the solution add 1.0 mL of reference solution (a) and dilute to 20.0 mL with *water R*.

Reference solution (d) Dilute 2 mL of reference solution (b) to 10 mL with *water R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core phenylhexylsilyl silica gel for chromatography R* (2.7 µm);

— *temperature*: 45 °C.

Mobile phase Dissolve 2.1 g of *perfluoroheptanoic acid R* in a mixture of 195 mL of *methanol R2* and 805 mL of *water for chromatography R*.

Flow rate 1.0 mL/min.

Post-column solution *methanol R2*.

Post-column flow rate 0.8 mL/min.

Detection Charged aerosol detector (gas source: nitrogen at 35 psi) and, for impurities A and B, spectrophotometer at 210 nm.

Autosampler Set at 15 °C.

Injection 30 µL of the test solution and reference solutions (b), (c) and (d).

Run time 3 times the retention time of vigabatrin.

Identification of impurities Use the chromatogram obtained with the spectrophotometer and with reference solution (b) to identify the peaks due to impurities A and B; use the chromatogram obtained with the charged aerosol detector and with reference solution (c) to identify the peaks due to impurities D and E.

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Relative retention With reference to vigabatrin (retention time = about 11 min): impurity A = about 0.3; impurity E = about 0.5; impurity D = about 0.6; impurity B = about 2.3.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities E and D in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 15 for the peak due to vigabatrin in the chromatogram obtained with reference solution (c); minimum 10 for the peak due to impurity B in the chromatogram obtained with reference solution (d);

— *symmetry factor*: minimum 0.6 for the peaks due to impurity D and vigabatrin in the chromatogram obtained with reference solution (c); minimum 0.6 for the peaks due to impurities A and B in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— for impurities A and B, use the concentration of each impurity in reference solution (b);

— for impurity D, use the concentration of impurity D in reference solution (c);

— for impurities other than A, B and D, use the concentration of vigabatrin in reference solution (c).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *impurities A, B (spectrophotometer at 210 nm)*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.03 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 90 mg in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 12.92 mg of $C_6H_{11}NO_2$.

IMPURITIES

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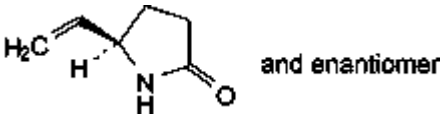
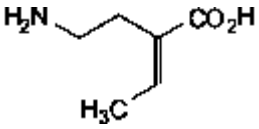
Specified impurities *A, B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E.*



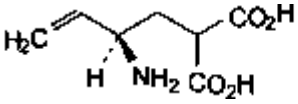
and enantiomer

A. (5*RS*)-5-ethenylpyrrolidin-2-one,



B. (2*E*)-2-(2-aminoethyl)but-2-enoic acid,

D. 4-aminobutanoic acid (GABA),



and enantiomer

E. 2-[(2*RS*)-2-aminobut-3-en-1-yl]propanedioic acid.

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Vigabatrin Oral Powder

General Notices

Action and use

Antiepileptic.

DEFINITION

Vigabatrin Oral Powder contains Vigabatrin.

The oral powder complies with the requirements stated under Oral Powders and with the following requirements.

Content of vigabatrin, $C_6H_{11}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of vigabatrin (*RS 360*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

5-Vinyl-2-pyrrolidone

In the Assay, the area of any peak corresponding to 5-vinyl-2-pyrrolidone in the chromatogram obtained with solution (1) is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve a quantity of the mixed contents of 20 sachets containing 0.2 g of Vigabatrin in sufficient of the mobile phase to produce 100 mL. Solution (2) contains 0.2% w/v of *vigabatrin BPCRS* in the mobile phase. Solution (3) contains 0.001% w/v of *5-vinyl-2-pyrrolidone BPCRS*. Solution (4) contains 0.002% w/v of *5-vinyl-2-pyrrolidone BPCRS*, 0.2% w/v of *povidone* and 0.2% w/v of *vigabatrin BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with cation exchange resin (10 µm) (Whatman Partisil SCX is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a mixture of 4 volumes of *acetonitrile*, 40 volumes of *methanol* and 1000 volumes of a 0.34% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 2.8 with *orthophosphoric acid* and (c) a detection wavelength of 210 nm.

Inject 20 µL of solution (4). When the chromatogram is recorded under the prescribed conditions, the retention times are povidone, about 4 minutes, 5-vinyl-2-pyrrolidone, about 5 minutes and vigabatrin, about 8 minutes. The test is not valid unless the *resolution factor* between

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the peaks corresponding to 5-vinyl-2-pyrrolidone and vigabatrin is at least 1.5 and the *resolution factor* between the peaks corresponding to povidone and 5-vinyl-2-pyrrolidone is at least 1.5.

Inject separately 20 µL of solutions (1) and (2). Calculate the content of $C_6H_{11}NO_2$ in one sachet from the areas of the peaks and using the declared content of $C_6H_{11}NO_2$ in *vigabatrin BPCRS*.

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Vigabatrin Tablets

General Notices

Action and use

Antiepileptic.

DEFINITION

Vigabatrin Tablets contain Vigabatrin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of vigabatrin, $C_6H_{11}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 0.5 g of Vigabatrin add 10 mL of *water*, shake and filter through a 0.7 µm filter (Whatman GF/F is suitable). To 0.2 mL of the filtrate add 5 mL of *acetone* and allow the solvent to evaporate in a current of nitrogen. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of vigabatrin (*RS 360*).

TESTS

5-Vinyl-2-pyrrolidone

In the Assay, the area of any peak corresponding to 5-vinyl-2-pyrrolidone in the chromatogram obtained with solution (1) is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, injecting 20 µL of each of the following solutions. For solution (1) add 800 mL of the mobile phase to 10 whole tablets, stir vigorously until all of the tablets are uniformLy dispersed into fine particles, add sufficient of the mobile phase to produce 1000 mL, mix well and filter through a 0.2 µm nylon-66 filter. Dilute 10 mL of the filtrate to 50 mL with the mobile phase. Solution (2) contains 0.10% w/v of *vigabatrin BPCRS* in the mobile phase. Solution (3) contains 0.0005% w/v of *5-vinyl-2-pyrrolidone BPCRS* in the mobile phase. Solution (4) contains 0.0005% w/v of *5-vinyl-2-pyrrolidone BPCRS*, 0.1% w/v of *povidone* and 0.1% w/v of *vigabatrin BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with cation exchange resin (10 µm) (Whatman Partisil SCX is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute, a mixture of 4 volumes of

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acetonitrile, 40 volumes of *methanol* and 1000 volumes of a 0.34% w/v solution of *potassium dihydrogen orthophosphate*, adjusting the pH to 2.8 with *orthophosphoric acid* and (c) a detection wavelength of 210 nm.

In the chromatogram obtained with solution (4), the retention times are about 4 minutes for povidone, about 5 minutes for 5-vinyl-2-pyrrolidone and about 8 minutes for vigabatrin. The test is not valid unless the *resolution factor* between the peaks corresponding to 5-vinyl-2-pyrrolidone and vigabatrin in the chromatogram obtained with solution (4) is at least 1.5 and the *resolution factor* between the peaks corresponding to povidone and 5-vinyl-2-pyrrolidone is at least 1.5.

Calculate the percentage content of $C_6H_{11}NO_2$ in the tablets from the areas of the peaks for vigabatrin in the chromatograms obtained with solutions (1) and (2) and from the declared content of $C_6H_{11}NO_2$ in *vigabatrin BPCRS*.

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Vinblastine Injection

General Notices

Vinblastine Sulphate Powder for Injection

Vinblastine Sulphate Solution for Injection

Action and use

Vinca alkaloid cytotoxic.

DEFINITION

Vinblastine Injection is a sterile solution of Vinblastine Sulfate in Water for Injections. It is supplied as a ready-to-use solution or it is prepared by dissolving Vinblastine Sulfate Powder for Injection in accordance with the manufacturer's instructions.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Vinblastine Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

VINBLASTINE SULFATE POWDER FOR INJECTION

DEFINITION

Vinblastine Sulfate Powder for Injection is a sterile material prepared from Vinblastine Sulfate. It may contain excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of vinblastine sulfate, $C_{46}H_{58}N_4O_9,H_2SO_4$

92.5 to 107.5% of the stated amount of anhydrous vinblastine sulfate.

IDENTIFICATION

A. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (3).

B. To 1 mg of the powder being examined, add 0.2 mL of a freshly prepared 1% w/v solution of *vanillin* in *hydrochloric acid*. A pink colour is produced in about 1 minute (distinction from vincristine sulfate).

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C. Yield the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

pH of a solution containing the equivalent of 0.15% w/v of anhydrous vinblastine sulfate, 3.5 to 5.0, Appendix V L.

Clarity of solution

Dissolve the contents of a sealed container in 10 mL of *carbon dioxide-free water*. The resulting solution is *clear*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Keep the solutions in ice before use.

(1) Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing the equivalent of 0.1% w/v of anhydrous vinblastine sulfate.
(2) 0.1% w/v each of *vinblastine sulfate EPCRS* and *vincristine sulfate EPCRS* in *water*.
(3) 0.1% w/v of *vinblastine sulfate EPCRS* in *water*.
(4) Dilute 1 volume of solution (1) to 50 volumes with *water*.
(5) Dilute 1 volume of solution (4) to 20 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Zorbax C8 is suitable). Place a guard column packed with a suitable silica gel placed between the pump and the injection device.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 262 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of the peak due to vinblastine.

MOBILE PHASE

12 volumes of *acetonitrile*, 38 volumes of a 1.5% v/v solution of *diethylamine* adjusted to pH 7.5 with *orthophosphoric acid* and 50 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times of vincristine sulfate and vinblastine sulfate are about 12.5 and 17.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2) the *resolution* between the peaks due to vinblastine and vincristine is at least 4.0.

LIMITS

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In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (4) (5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 16 hours, lose not more than 17.0% of their weight. Use 0.5 g.

Uniformity of content

The content of anhydrous vinblastine sulfate in each of 10 individual containers as determined in the Assay is not less than 90.0% and not more than 110.0% of the average except that in one container the content may be not less than 80.0% and not more than 120.0% of the average.

ASSAY

Dissolve the contents of a sealed container in a suitable volume of *methanol* and dilute with sufficient *methanol* to produce a solution containing 0.004% w/v of anhydrous vinblastine sulfate. Measure the *absorbance* of the resulting solution at the maximum at 267 nm, Appendix II B. Calculate the content of $C_{46}H_{58}N_4O_9,H_2SO_4$ in the sealed container taking 185 as the value of A(1%, 1 cm) at the maximum at 267 nm. Repeat the procedure with a further nine sealed containers. Calculate the average content of $C_{46}H_{58}N_4O_9,H_2SO_4$ per container from the 10 individual results thus obtained.

LABELLING

The label of the sealed container states (1) the weight of anhydrous vinblastine sulfate contained in it; (2) when reconstituted, that the preparation is for intravenous use only, it is fatal if given by other routes.

VINBLASTINE SULFATE SOLUTION FOR INJECTION

DEFINITION

Vinblastine Sulfate Solution for Injection is a sterile solution containing Vinblastine Sulfate. It may contain excipients. It is supplied as a ready-to-use solution.

The contents of the sealed container comply with the requirements for Parenteral Preparations and with the following requirements.

Content of vinblastine sulfate, $C_{46}H_{58}N_4O_9,H_2SO_4$

92.5 to 107.5% of the stated amount of anhydrous vinblastine sulfate.

IDENTIFICATION

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A. In the test for Related substances the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (3).

B. To a quantity of the injection containing 1 mg of Vinblastine Sulfate add 0.2 mL of a freshly prepared 1% w/v solution of *vanillin* in *hydrochloric acid*. A pink colour is produced in about 1 minute (distinction from vincristine sulfate).

C. Yield the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

The pH of the injection is 3.5 to 5.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Keep the solutions in ice before use.

(1) Dilute the injection with *water*, if necessary, to produce a solution containing the equivalent of 0.1% w/v of anhydrous vinblastine sulfate.

(2) 0.1% w/v each of *vinblastine sulfate EPCRS* and *vincristine sulfate EPCRS* in *water*.

(3) 0.1% w/v of *vinblastine sulfate EPCRS* in *water*.

(4) Dilute 1 volume of solution (1) to 50 volumes with *water*.

(5) Dilute 1 volume of solution (4) to 20 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Zorbax C8 is suitable). Place a guard column packed with a suitable silica gel placed between the pump and the injection device.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 262 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of the peak due to vinblastine.

MOBILE PHASE

12 volumes of *acetonitrile*, 38 volumes of a 1.5% v/v solution of *diethylamine* adjusted to pH 7.5 with *orthophosphoric acid* and 50 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times of vincristine sulfate and vinblastine sulfate are about 12.5 and 17.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2) the *resolution* between the peaks due to vinblastine and vincristine is at least 4.0.

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LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (4) (5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Dilute a quantity of the injection with *methanol* to produce a solution containing 0.004% w/v of anhydrous vinblastine sulfate. Measure the *absorbance* of the resulting solution at the maximum at 267 nm, Appendix II B using *methanol (96%)* in the reference cell. Calculate the content of $C_{46}H_{58}N_4O_9,H_2SO_4$ in the injection using a 0.004% w/v solution of *vinblastine sulfate EPCRS* in *methanol (96%)* and the declared content of *vinblastine sulfate EPCRS*.

LABELLING

The label of the sealed container states (1) the concentration of anhydrous vinblastine sulfate and volume contained in it; (2) that the preparation is for intravenous use only, it is fatal if given by other routes.

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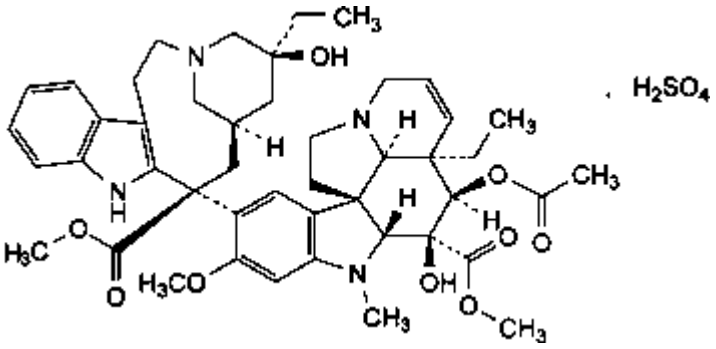
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Vinblastine Sulfate

General Notices

Vinblastine Sulphate

(Ph. Eur. monograph 0748)



$C_{46}H_{60}N_4O_{13}S$ 909 *143-67-9*

Action and use

Vinca alkaloid cytotoxic.

Preparation

Vinblastine Injection

Ph Eur

DEFINITION

Vinblastine sulfate contains not less than 95.0 per cent and not more than the equivalent of 104.0 per cent of methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(5*S*,7*R*,9*S*)5-ethyl-5-hydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate sulfate, calculated with reference to the dried substance.

CHARACTERS

A white or slightly yellowish, crystalline powder, very hygroscopic, freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

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A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the *Ph. Eur. reference spectrum of vinblastine sulfate*.

B. Examine the chromatograms obtained in the assay. The principal peak in the chromatogram obtained with the test solution is similar in position and approximate size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 50.0 mg in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method I*).

pH (2.2.3)

Dilute 3 mL of solution S to 10 mL with *carbon dioxide-free water R*. The pH of this solution is 3.5 to 5.0.

Related substances

Examine the chromatograms obtained in the assay. In the chromatogram obtained with the test solution, the area of any peak apart from the principal peak is not greater than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent) and the sum of the areas of any such peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (5.0 per cent). Disregard any peak with an area less than that of the peak in the chromatogram obtained with reference solution (d).

Loss on drying

Not more than 15.0 per cent, determined on 3 mg by thermogravimetry (2.2.34). Heat to 200 °C at a rate of 5 °C/min, under a stream of *nitrogen for chromatography R*, at a flow rate of 40 mL/min.

ASSAY

Examine by liquid chromatography (2.2.29).

Keep the solutions in iced water before use.

Test solution Dilute 1.0 mL of solution S (see Tests) to 5.0 mL with *water R*.

Reference solution (a) Dissolve the contents of a vial of *vinblastine sulfate CRS* in 5.0 mL of *water R* to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Dissolve 1.0 mg of *vincristine sulfate CRS* in 1.0 mL of reference solution (a).

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 50.0 mL with *water R*.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 20.0 mL with *water R*.

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The chromatographic procedure may be carried out using:

— a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *octylsilyl silica gel for chromatography R* (5 µm). Place between the injector and the column a precolumn packed with suitable silica gel,

— as mobile phase at a flow rate of 1.0 mL/min a mixture of 38 volumes of a 1.5 per cent *V/V* solution of *diethylamine R* adjusted to pH 7.5 with *phosphoric acid R*, 12 volumes of *acetonitrile R* and 50 volumes of *methanol R*,

— as detector a spectrophotometer set at 262 nm,

— a loop injector.

Inject 10 µL of each solution and record the chromatograms for 3 times the retention time of the peak due to vinblastine. The assay is not valid unless: in the chromatogram obtained with reference solution (b) the resolution between the peaks due to vincristine and vinblastine is not less than 4; the peak in the chromatogram obtained with reference solution (d) has a signal-to-noise ratio not less than 5. Calculate the percentage content of $C_{46}H_{60}N_4O_{13}S$ from the area of the principal peak in each of the chromatograms obtained with the test solution and reference solution (a) and from the declared content of *vinblastine sulfate CRS*.

STORAGE

Store in an airtight, glass container, protected from light, at a temperature not exceeding -20 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident glass container.

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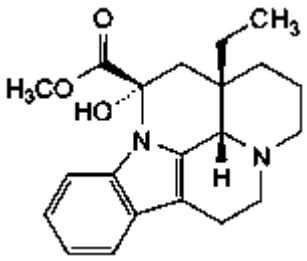
Vincamine

General Notices

(Ph. Eur. monograph 1800)



$C_{21}H_{26}N_2O_3$ 354.5 *1617-90-9*

Action and use

Vasodilator.

Ph Eur

DEFINITION

Methyl 14-hydroxyvincane-14β-carboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, slightly soluble in anhydrous ethanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *vincamine CRS*.

TESTS

Specific optical rotation (*2.2.7*)

+ 44.3 to + 49.0 (dried substance).

Dissolve 0.1 g in *dimethylformamide R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use. Dissolve the samples using sonication, while avoiding any overheating.*

Test solution Dissolve 50.0 mg of the substance to be examined in 10 mL of *tetrahydrofuran R* and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *vincamine for system suitability CRS* (containing impurities A, B and C) in 1 mL of *tetrahydrofuran R* and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (5 µm).

Mobile phase *tetrahydrofuran R*, *acetonitrile R*, 15.4 g/L solution of *ammonium acetate R* (17:18:65 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL.

Run time 3.5 times the retention time of vincamine.

Identification of impurities Use the chromatogram supplied with *vincamine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to vincamine (retention time = about 10 min): impurity A = about 0.8; impurity B = about 0.9; impurity C = about 1.35.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity B and vincamine.

Calculation of percentage contents:

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— for each impurity, use the concentration of vincamine in reference solution (a).

Limits:

— *impurities A, C*: for each impurity, maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

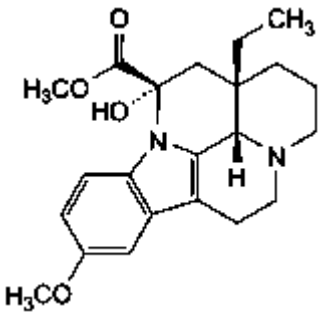
Dissolve 0.300 g in 30 mL of a mixture of 1 volume of *acetic anhydride R* and 5 volumes of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 35.45 mg of $C_{21}H_{26}N_2O_3$.

IMPURITIES

Specified impurities A, C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D.



A. methyl 14-hydroxy-10-methoxyvincane-14β-carboxylate (10-methoxyvincamine),

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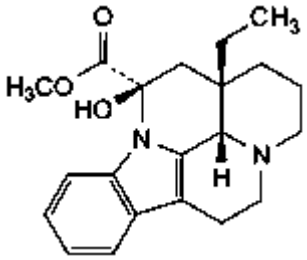
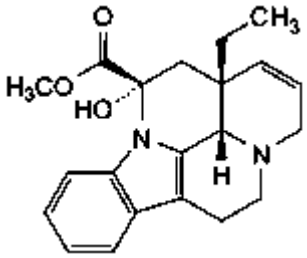
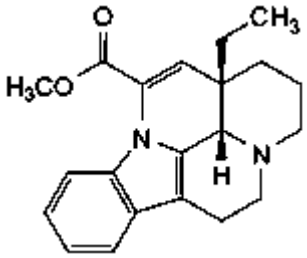


B. methyl 14-hydroxyvincane-14α-carboxylate (14-*epi*-vincamine),



C. methyl 14-hydroxy-17,18-didehydrovincane-14β-carboxylate (17,18-didehydrovincamine),



D. methyl 14,15-didehydrovincane-14-carboxylate (apovincamine).

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Vincristine Injection

General Notices

Action and use

Vinca alkaloid cytotoxic.

DEFINITION

Vincristine Injection is a sterile solution of Vincristine Sulfate in a suitable vehicle.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of vincristine sulfate, $C_{46}H_{56}N_4O_{10},H_2SO_4$

90.0 to 107.5% of the stated amount of anhydrous vincristine sulfate.

IDENTIFICATION

A. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (4).

B. Shake a volume of the injection containing the equivalent of 1 mg of anhydrous vincristine sulfate with 3 mL of *chloroform*, filter and wash the filter with 2 mL of *chloroform*. Evaporate the combined chloroform solutions to dryness at 40°. Add 0.2 mL of a freshly prepared 1% w/v solution of *vanillin* in *hydrochloric acid* to the residue. An orange colour is produced in about 1 minute (distinction from vinblastine sulfate).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a volume of the injection, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.10% w/v of anhydrous vincristine sulfate.

(2) Dilute 1 volume of solution (1) to 50 volumes.

(3) 0.10% w/v each of *vincristine sulfate EPCRS* and *vinblastine sulfate EPCRS*.

(4) 0.10% w/v of *vincristine sulfate EPCRS*.

(5) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Zorbax C8 is suitable) and a guard column packed with a suitable silica gel.

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(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 297 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of vincristine.

MOBILE PHASE

30 volumes of a 1.5% v/v solution of *diethylamine* adjusted to pH 7.5 with *orthophosphoric acid* and 70 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to vincristine and vinblastine is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Dissolve a volume of the injection, if necessary, in a suitable volume of *methanol* to produce a solution containing the equivalent of 0.005% w/v of anhydrous vincristine sulfate. Measure the *absorbance* of the resulting solution at the maximum at 297 nm, Appendix II B. Calculate the content of $C_{46}H_{56}N_4O_{10},H_2SO_4$ in the sealed container taking 177 as the value of A(1%, 1 cm) at the maximum at 297 nm. Repeat the procedure with a further nine containers. Calculate the average content of $C_{46}H_{56}N_4O_{10},H_2SO_4$ per container from the 10 individual results thus obtained.

STORAGE

Vincristine Injection should be stored strictly in accordance with the manufacturer’s instructions.

LABELLING

The label states:

the preparation is for intravenous use only, it may be fatal if given by other routes;

the quantity of active ingredient in terms of the equivalent amount of anhydrous vincristine sulfate.

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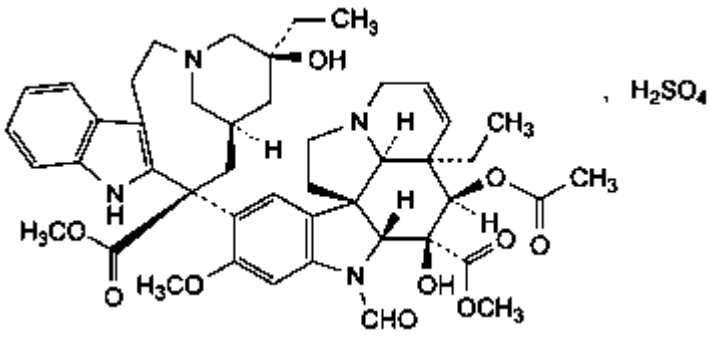
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Vincristine Sulfate

General Notices

Vincristine Sulphate

(Ph. Eur. monograph 0749)



$C_{46}H_{58}N_4O_{14}S$ 923 *2068-78-2*

Action and use

Vinca alkaloid cytotoxic.

Preparation

Vincristine Injection

Ph Eur

DEFINITION

Methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(5*S*,7*R*,9*S*)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-6-formyl-5-hydroxy-8-methoxy-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate sulfate.

Content

95.0 per cent to 104.0 per cent (dried substance).

CHARACTERS

Appearance

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White or slightly yellowish, crystalline powder, very hygroscopic.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of vincristine sulfate*.

TESTS

Solution S

Dissolve 50.0 mg in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent. *Keep the solution in iced water to carry out the test for related substances.*

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method I*).

pH (2.2.3)

3.5 to 4.5.

Dilute 2 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29). *Keep the solutions in iced water before use.*

Test solution Dilute 1.0 mL of solution S to 5.0 mL with *water R*.

Reference solution (a) Dissolve the contents of a vial of *vincristine sulfate CRS* in 5.0 mL of *water R* to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Dissolve 1.0 mg of *vinblastine sulfate CRS* in 1.0 mL of reference solution (a).

Reference solution (c) Dilute 1.0 mL of the test solution to 50.0 mL with *water R*.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 20.0 mL with *water R*.

Precolumn:

— *stationary phase*: *octylsilyl silica gel for chromatography R*.

Column:

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— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.5 per cent *V/V* solution of *diethylamine R* adjusted to pH 7.5 with *phosphoric acid R*,

— *mobile phase B*: *methanol R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	38	62
12 - 27	38 → 8	62 → 92

Flow rate 2 mL/min.

Detection Spectrophotometer at 297 nm.

Injection 20 µL.

System suitability Reference solution (b):

— *resolution*: minimum 4 between the peaks due to vincristine and vinblastine.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent),

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (5.0 per cent),

— *disregard limit*: area of the peak in the chromatogram obtained with reference solution (d) (0.1 per cent).

Loss on drying

Maximum 12.0 per cent, determined on 3 mg by thermogravimetry (2.2.34). Heat the substance to be examined to 200 °C increasing the temperature by 5 °C/min, under a current of *nitrogen for chromatography R*, at a flow rate of 40 mL/min.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances, with the following modifications.

Mobile phase Mix 30 volumes of a 1.5 per cent *V/V* solution of *diethylamine R* adjusted to pH 7.5 with *phosphoric acid R* and 70 volumes of *methanol R*.

Flow rate 1.0 mL/min.

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Calculate the percentage content of $C_{46}H_{58}N_4O_{14}S$ using the chromatogram obtained with reference solution (a) and the declared content of *vincristine sulfate CRS*.

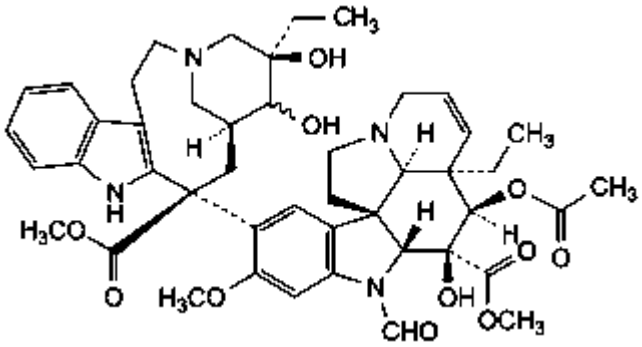
STORAGE

In an airtight, glass container, protected from light, at a temperature not exceeding -20 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident glass container.

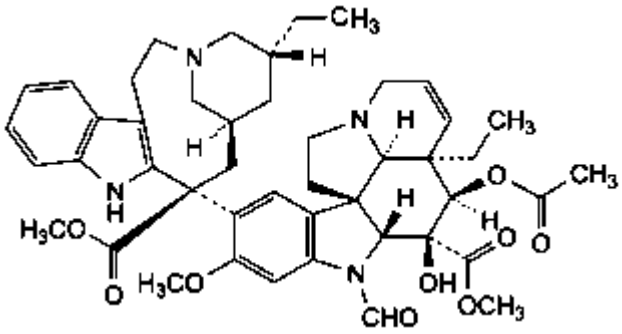
IMPURITIES

Specified impurities *A, B, C, D, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, G.*



A. methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(5*R*,7*S*,9*S*)-5-ethyl-5,6-dihydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methanoazacycloundecino[5,4-b]indol-9-yl]-6-formyl-5-hydroxy-8-methoxy-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (3′-hydroxy-VCR),



B. methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(5*R*,7*S*,9*S*)-5-ethyl-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-6-formyl-5-hydroxy-8-methoxy-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (4′-deoxyvincristine),

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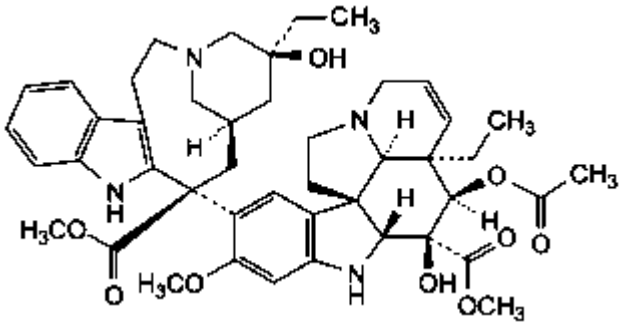
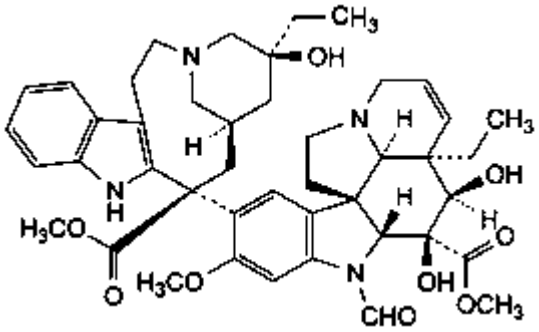
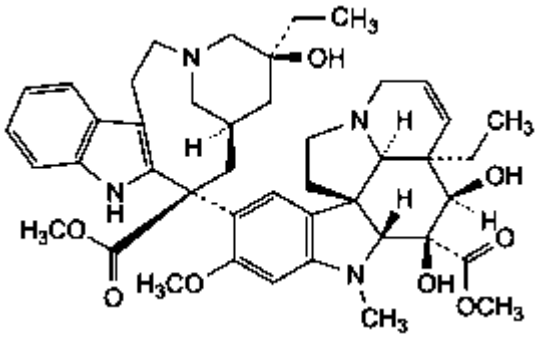


C. methyl (3a*R*,4*R*,5*S*,5a*R*,10b*S*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(5*S*,7*R*,9*S*)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-5-hydroxy-8-methoxy-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (*N*-desmethylvinblastine),



D. methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-3a-ethyl-9-[(5*S*,7*R*,9*S*)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-6-formyl-4,5-dihydroxy-8-methoxy-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (deacetylvincristine),



E. methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-3a-ethyl-9-[(5*S*,7*R*,9*S*)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methanoazacycloundecino[5,4-*b*]indol-9-yl]-4,5-dihydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (deacetylvinblastine),

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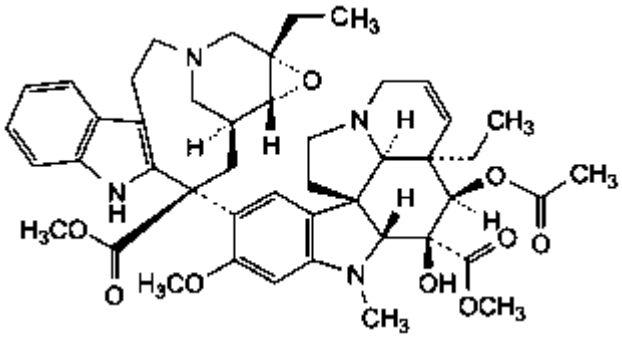
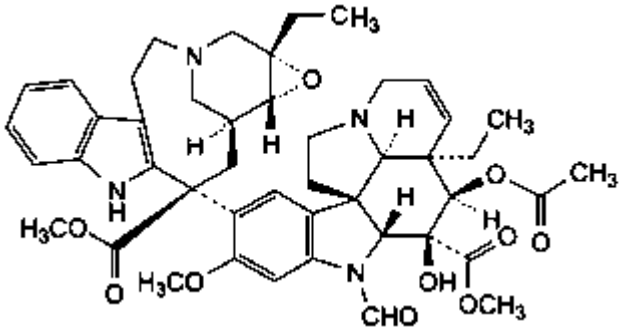
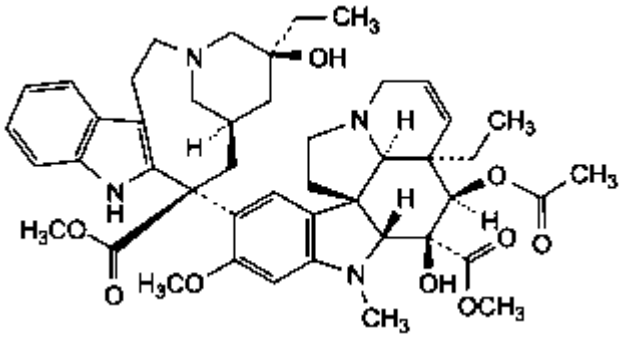


F. methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(1a*S*,11*S*,13*S*,13a*R*)-1a-ethyl-11-(methoxycarbonyl)-1a,4,5,10,11,12,13,13a-octahydro-2*H*-3,13-methano-oxireno[9,10]azacycloundecino[5,4-*b*]indol-11-yl]-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (leurosine),



G. methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(1a*S*,11*S*,13*S*,13a*R*)-1a-ethyl-11-(methoxycarbonyl)-1a,4,5,10,11,12,13,13a-octahydro-2*H*-3,13-methano-oxireno[9,10]azacycloundecino[5,4-*b*]indol-11-yl]-6-formyl-5-hydroxy-8-methoxy-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (formylleurosine),



H. vinblastine.

Ph Eur

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Vindesine Injection

General Notices

Vindesine Sulphate for Injection

Action and use

Vinca alkaloid cytotoxic.

DEFINITION

Vindesine Injection is a sterile solution of Vindesine Sulfate in a suitable liquid. It is prepared by dissolving Vindesine Sulfate for Injection in the requisite volume of a suitable diluent in accordance with the manufacturer's instructions.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Vindesine Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

VINDESINE SULFATE FOR INJECTION

DEFINITION

Vindesine Sulfate for Injection is a sterile material consisting of a mixture of one part by weight of Vindesine Sulfate and five parts by weight of a suitable carrier with or without other excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of vindesine sulfate, $C_{43}H_{55}N_5O_7,H_2SO_4$

90.0 to 105.0% of the stated amount of anhydrous vindesine sulfate.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dissolve a quantity of the contents of the injection in sufficient *methanol* to produce a solution containing the equivalent of 0.20% w/v of anhydrous vindesine sulfate.

(2) 0.20% w/v of *vindesine sulfate EPCRS*.

(3) 0.20% w/v each of *vinblastine sulfate EPCRS*, *vincristine sulfate EPCRS* and *vindesine sulfate EPCRS*.

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CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *diethylamine*, 5 volumes of *methanol* and 90 volumes of *chloroform*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Clarity of solution

Dissolve the contents of a sealed container in 10 mL of *carbon dioxide-free water*. The solution is *clear*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*. Keep the solutions in ice before use.

(1) To a quantity of injection add sufficient water to produce a solution expected to contain 0.10% w/v of anhydrous Vindesine Sulfate.

(2) Dilute 1 volume of solution (1) to 50 volumes.

(3) Dissolve 1 mg of *desacetylvinblastine EPCRS* in *water*, add 1 mL of solution (1) and dilute to 50 mL.

(4) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Jones Apex ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 200 µL of each solution.

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(g) Maintain the final concentration of the mobile phase until the total run time is twice the retention time of the principal peak in the chromatogram obtained with solution (1).

MOBILE PHASE

Mobile phase A A 1.5% v/v solution of *diethylamine* adjusted to pH 7.4 with *orthophosphoric acid*.

Mobile phase B *methanol*.

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)	Comment
	49	51	Equilibration
0–40	49	51	Isocratic
40–49	49→30	51→70	Linear gradient
49–end	30	70	Isocratic

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the retention time of vindesine is less than 40 minutes;

the *symmetry factor* of the vindesine peak is not more than 2.0;

the *resolution factor* between the peaks due to vindesine and desacetylvinblastine is at least 2.0.

LIMITS

In the chromatogram obtained with the solution (1):

the area of any *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the sum of the areas of any such peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

The content of anhydrous vindesine sulfate in each of 10 individual containers as determined in the Assay is not less than 90.0% and not more than 110.0% of the average except that in one container the content may be not less than 80.0% and not more than 120.0% of the average.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Keep the solutions in ice before use.

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(1) Dissolve the contents of a sealed container in *water* and add sufficient *water* to produce a solution containing the equivalent of 0.05% w/v of anhydrous vindesine sulfate.

(2) Dissolve and dilute the entire contents of a vial of *vindesine sulfate EPCRS* with *water* to yield a concentration of approximately 0.05% w/v.

(3) Add 2 mL of solution (2) to 1 mg of *desacetylvinblastine EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Jones Apex ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

38 volumes of a 1.5% v/v solution of *diethylamine*, previously adjusted to pH 7.4 with *orthophosphoric acid*, and 62 volumes of *methanol*.

SYSTEM SUITABILITY

The assay is not valid unless:

the *resolution factor* between the peaks corresponding to vindesine sulfate and desacetylvinblastine sulfate is greater than 1.5;

the *symmetry factor* of the vindesine peak is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the content of vindesine sulfate, $C_{43}H_{55}N_5O_7,H_2SO_4$, in the container using the declared content of $C_{43}H_{55}N_5O_7,H_2SO_4$ in *vindesine sulfate EPCRS*. Repeat the procedure with a further nine containers. Calculate the average content of $C_{43}H_{55}N_5O_7,H_2SO_4$ per container from the 10 individual results obtained.

STORAGE

Vindesine Sulfate for Injection should be stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Vindesine Sulfate.

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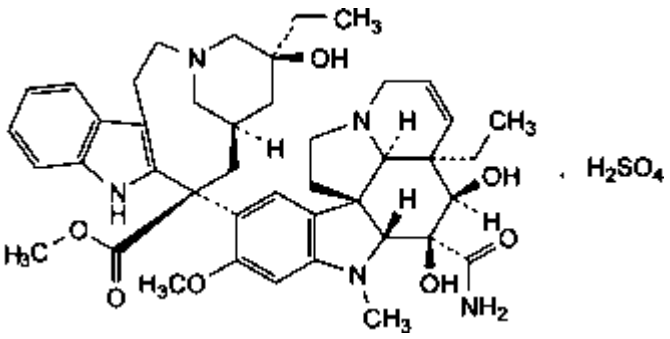
Vindesine Sulfate

General Notices

Vindesine Sulphate

(Ph. Eur. monograph 1276)



$C_{43}H_{57}N_5O_{11}S$ 852 *59917-39-4*

Action and use

Vinca alkaloid cytotoxic.

Preparation

Vindesine Injection

Ph Eur

DEFINITION

3-(Carbamoyl)-O^4-deacetyl-3-de(methoxycarbonyl)vincaleukoblastine sulfate.

Content

96.0 per cent to 103.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, amorphous, hygroscopic substance.

Solubility

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Freely soluble in water and in methanol, practically insoluble in cyclohexane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of vindesine sulfate*.

TESTS

Solution S

Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method I*).

pH (2.2.3)

3.5 to 5.5 for solution S.

Related substances

Liquid chromatography (2.2.29). *Keep the solutions in iced water before use*.

Test solution Dissolve 10.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 1.0 mg of *desacetylvinblastine CRS* in *water R*, add 1.0 mL of the test solution and dilute to 50.0 mL with *water R*.

Reference solution (c) In order to prepare impurity A *in situ*, dissolve 0.2 g of the substance to be examined in *dilute hydrogen peroxide solution R* and dilute to 20.0 mL with the same solvent. Dilute 2.0 mL of the solution to 10.0 mL with *water R*. Inject the solution within 1 h of preparation.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.5 per cent *V/V* solution of *diethylamine R* adjusted to pH 7.4 with *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	49	51
40 - 49	49 → 30	51 → 70
49 - 60	30	70

Flow rate 2 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 200 µL.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to vindesine (retention time = about 25 min): impurity A = about 0.2.

System suitability Reference solution (b):

— the retention time of vindesine is less than 40 min;

— *resolution*: minimum 2.0 between the peaks due to vindesine and desacetylvinblastine;

— *symmetry factor*: maximum 2.0 for the peak due to vindesine.

Limits:

— *impurity A*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.32)

Maximum 5.0 per cent, determined on 50.0 mg using the evaporation technique at 150 °C; weigh the sample in an inert atmosphere and carry out a blank test.

ASSAY

Liquid chromatography (2.2.29). *Keep the solutions in iced water before use*.

Test solution Dissolve 5.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

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Reference solution (a) Dissolve and dilute the entire contents of a vial of *vindesine sulfate CRS* with *water R* to yield a concentration of approximately 0.50 mg/mL.

Reference solution (b) Add 1.0 mg of *desacetylvinblastine CRS* to 2.0 mL of reference solution (a).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 38 volumes of a 1.5 per cent *V/V* solution of *diethylamine R*, previously adjusted to pH 7.4 with *phosphoric acid R*, and 62 volumes of *methanol R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to vindesine and desacetylvinblastine;

— *symmetry factor*: maximum 2.0 for the peak due to vindesine;

— *repeatability*: maximum relative standard deviation of 1.5 per cent for the peak due to vindesine after 5 injections.

Calculate the percentage content of $C_{43}H_{57}N_5O_{11}S$ taking into account the assigned content of *vindesine sulfate CRS*.

STORAGE

In an airtight, high-density polyethylene container with a high-density polyethylene cap, at a temperature of -50 °C or below. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C.*

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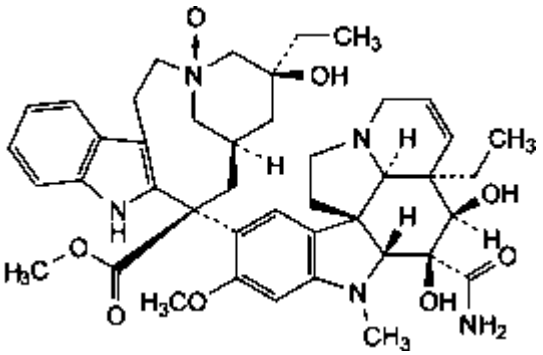
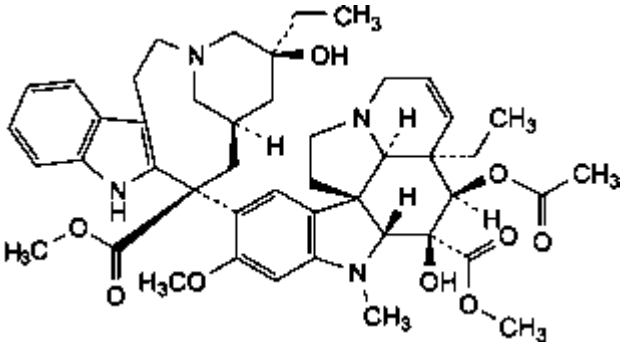
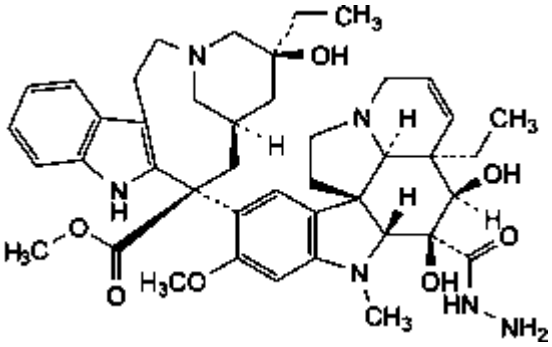


A. 3-(carbamoyl)-O^4-deacetyl-3-de(methoxycarbonyl)vincaleukoblastine $N^{6'}$-oxide (vindesine N^3-oxide),



B. vincaleukoblastine (vinblastine),



C. O^4-deacetyl-23-demethoxy-23-hydrazinylvincaleukoblastine (deacetylvinblastine hydrazide).

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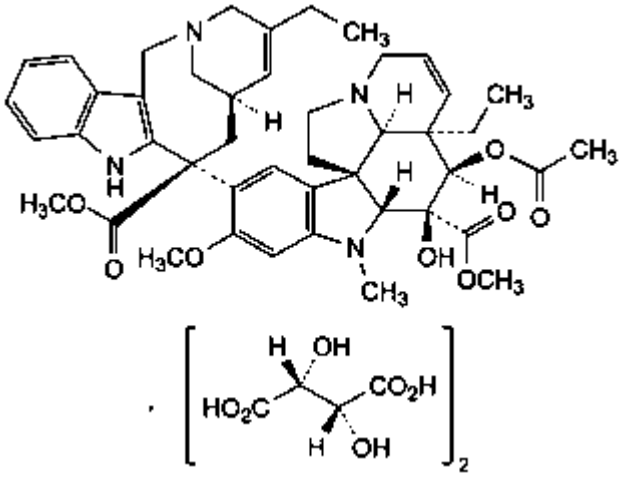
Vinorelbine Tartrate

General Notices

(Ph. Eur. monograph 2107)



$C_{53}H_{66}N_4O_{20}$ 1079 *125317-39-7*

Action and use

Vinca alkaloid cytotoxic.

Ph Eur

DEFINITION

4′-Deoxy-3′,4′-didehydro-8′-norvincaleukoblastine dihydrogen bis[(2*R*,3*R*)-2,3-dihydroxybutanedioate].

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Freely soluble in water and in methanol, practically insoluble in hexane.

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 10 mg in 5 mL of water R. Add 0.5 mL of sodium hydroxide solution R. Extract with 5 mL of methylene chloride R. Dry the organic layer over anhydrous sodium sulfate R, filter and reduce its volume to about 0.5 mL by evaporation and apply to a disc of potassium bromide R. Evaporate and record the spectrum.

Comparison vinorelbine tartrate CRS, treated as described above.

B. It gives reaction (b) of tartrates (2.3.1).

TESTS

Solution S

Dissolve a quantity equivalent to 0.140 g of the anhydrous substance in carbon dioxide-free water R and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 420 nm is not greater than 0.030.

pH (2.2.3)

3.3 to 3.8 for solution S.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Solvent mixture Mobile phase A, mobile phase B (45:55 *V/V*).

Test solution Dissolve 35.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 14 mg of vinorelbine tartrate CRS in water R and dilute to 10 mL with the same solvent. Expose this solution for 1 h to a xenon lamp apparatus at a wavelength of 310-880 nm, supplying a dose of 1600 kJ/m^2 at a fluence rate of 500 W/m^2 in order to generate impurity A.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 7 mg of vinorelbine for peak identification A CRS (containing impurity K) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution (d) Dissolve 7 mg of vinorelbine for peak identification B CRS (containing impurities C and I) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

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— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 14 mL of *diethylamine R* and 986 mL of *water for chromatography R* and adjust to pH 7.5 with *dilute phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*, *methanol R* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	45	55
5 - 45	45 → 20	55 → 80
45 - 50	20	80

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 267 nm.

Autosampler Set at 5 °C.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *vinorelbine for peak identification B CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities C and I; use the chromatogram supplied with *vinorelbine for peak identification A CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity K.

Relative retention With reference to vinorelbine (retention time = about 20 min): impurity C = about 0.65; impurity K = about 0.8; impurity A = about 0.9; impurity I = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity A and vinorelbine.

Limits:

— *impurity A*: maximum 0.3 per cent;

— *impurities C, I, K*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

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— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent (principal peak in the chromatogram obtained with reference solution (b)).

Boron

Maximum 50 ppm.

Test solution Dissolve 0.10 g of the substance to be examined in 2 mL of *water R*. Slowly add 10.0 mL of *sulfuric acid R* while cooling in iced water. Stir and allow to warm to room temperature. Add 10.0 mL of a 0.5 g/L solution of *carminic acid R* in *sulfuric acid R*.

Reference solution Dilute 2.5 mL of a 0.572 g/L solution of *boric acid R* to 100.0 mL with *water R*. To 2.0 mL of this solution slowly add 10.0 mL of *sulfuric acid R* while cooling in iced water. Stir and allow to warm to room temperature. Add 10.0 mL of a 0.5 g/L solution of *carminic acid R* in *sulfuric acid R*.

Blank solution To 2.0 mL of *water R* slowly add 10.0 mL of *sulfuric acid R* while cooling in iced water. Stir and allow to warm to room temperature. Add 10.0 mL of a 0.5 g/L solution of *carminic acid R* in *sulfuric acid R*.

After 45 min, measure the absorbance (*2.2.25*) of the test solution and the reference solution, between 560 nm and 650 nm, using the blank solution as compensation liquid. The maximum absorbance value of the test solution is not greater than that of the reference solution.

Fluorides

Maximum 50 ppm.

Potentiometry (*2.2.36, Method I*) using a fluoride-selective indicator electrode and a silver-silver chloride reference electrode.

Test solution Dissolve 0.19 g of the substance to be examined in 20 mL of *water R*. Add 5.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50 mL with *water R*.

Reference solutions To 0.6 mL, 0.8 mL, 1.0 mL, 1.2 mL and 1.4 mL of *fluoride standard solution (10 ppm F) R*, add 5.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50 mL with *water R*.

Introduce the electrodes into the reference solutions and allow to stand for 5 min. Determine the potential difference between the electrodes after 1 min of stabilisation. Using semi-logarithmic paper plot the potential difference obtained for each reference solution as a function of concentration of fluoride. Using exactly the same conditions, determine the potential difference obtained with the test solution and calculate the content of fluoride.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.250 g.

ASSAY

Dissolve 0.350 g in 40 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 53.96 mg of $C_{53}H_{66}N_4O_{20}$.

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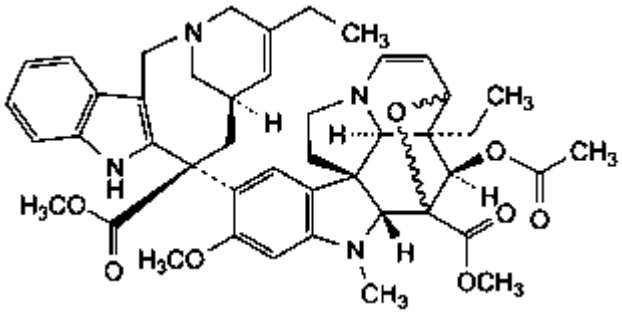
STORAGE

Under an inert gas, protected from light, at a temperature not exceeding -15 °C.

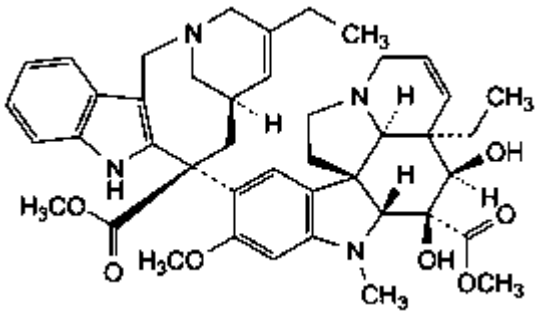
IMPURITIES

Specified impurities *A, C, I, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E, F, G, H, J.*

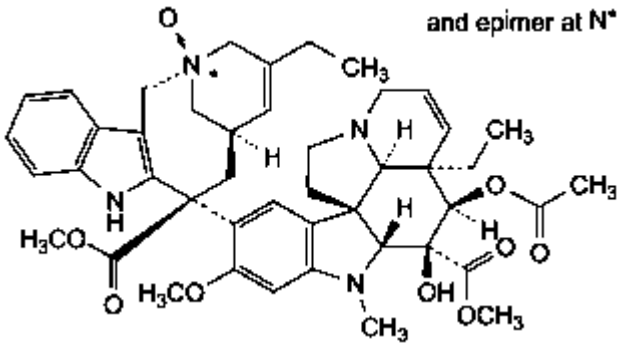


A. 3,4′-dideoxy-3,6ξ-epoxy-3′,4′,7,8-tetradehydro-6,7-dihydro-8′-nor-3ξ-vincaleukoblastine,



B. O^4-deacetyl-4′-deoxy-3′,4′-didehydro-8′-norvincaleukoblastine,

C. unknown structure,



D. (6′*RS*)-4′-deoxy-3′,4′-didehydro-8′-norvincaleukoblastine 6′-oxide,

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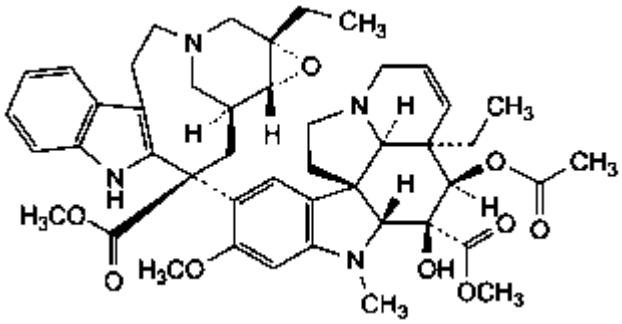
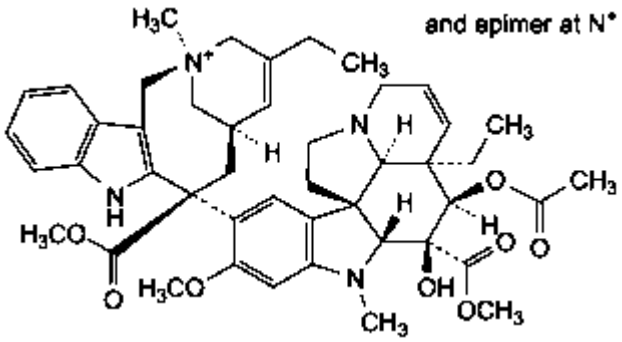
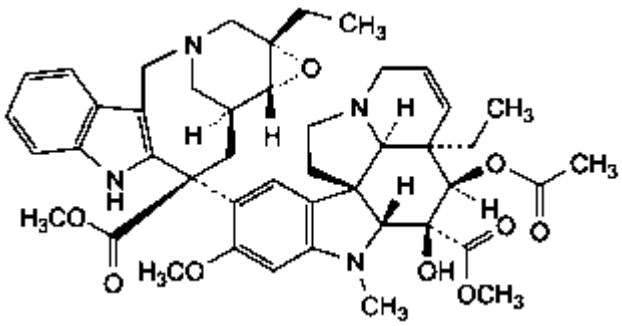


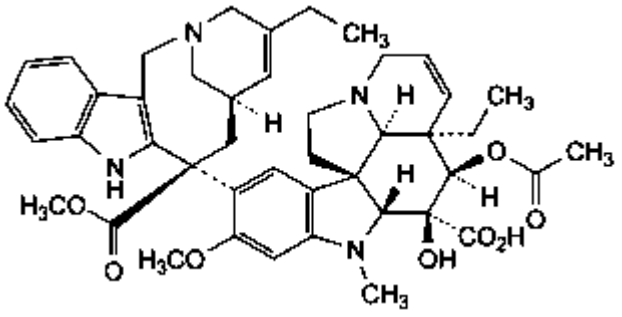
E. 4′-deoxy-3′α,4′α-epoxyvincaleukoblastine (leurosine),



F. (6′*RS*)-4′-deoxy-6′-methyl-3′,4′-didehydro-6′-azonia-8′-norvincaleukoblastine,



G. 4′-deoxy-3′α,4′α-epoxy-8′-norvincaleukoblastine,



H. 4′-deoxy-3′,4′-didehydro-8′,24-dinorvincaleukoblastine,

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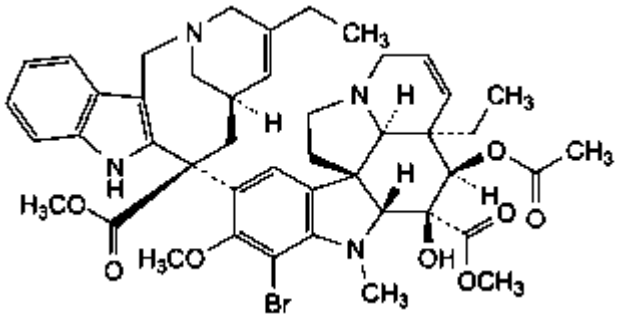
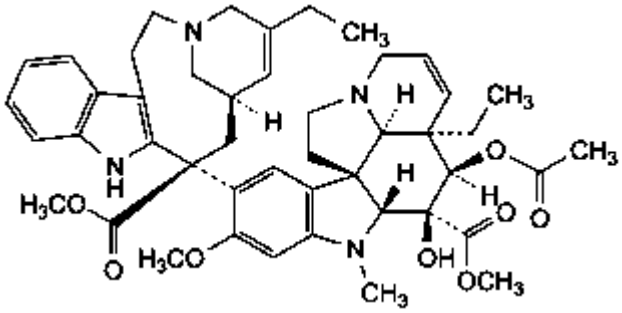
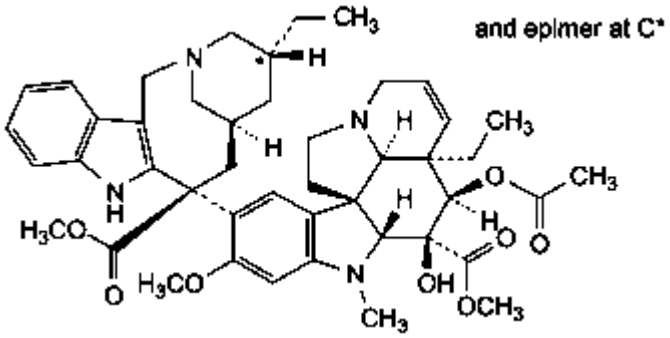


I. 17-bromo-4′-deoxy-3′,4′-didehydro-8′-norvincaleukoblastine,



J. 4′-deoxy-3′,4′-didehydrovincaleukoblastine,



K. 4′-deoxy-8′-nor-4′αβ-vincaleukoblastine.

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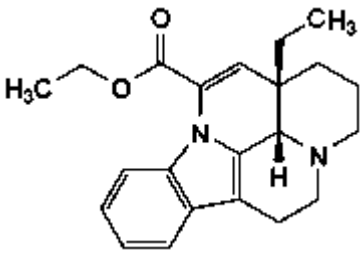
Vinpocetine

General Notices

(Ph. Eur. monograph 2139)



$C_{22}H_{26}N_2O_2$ 350.5 *42971-09-5*

Action and use

Vasodilator.

Ph Eur

DEFINITION

Ethyl (13a*S*,13b*S*)-13a-ethyl-2,3,5,6,13a,13b-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-12-carboxylate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, slightly soluble in anhydrous ethanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *vinpocetine CRS*.

TESTS

Specific optical rotation (*2.2.7*)

+ 127 to + 134 (dried substance).

Dissolve 0.25 g in *dimethylformamide R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *vinpocetine impurity B CRS*, 6.0 mg of *vinpocetine impurity A CRS*, 5.0 mg of *vinpocetine impurity C CRS* and 5.0 mg of *vinpocetine impurity D CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 15.4 g/L solution of *ammonium acetate R*, *acetonitrile R* (45:55 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 15 µL.

Run time 3 times the retention time of vinpocetine.

Relative retention With reference to vinpocetine (retention time = about 16 min): impurity A = about 0.4; impurity D = about 0.68; impurity B = about 0.75; impurity C = about 0.83.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurities D and B.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.6 per cent);

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— *impurities B, D*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity C*: not more than 0.6 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to vinpocetine in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 10 times the area of the peak due to vinpocetine in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the peak due to vinpocetine in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* in an oven at 100 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

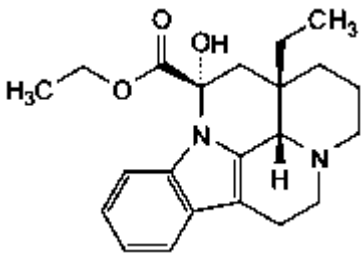
ASSAY

Dissolve 0.300 g in 50 mL of a mixture of equal volumes of *acetic anhydride R* and *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 35.05 mg of $C_{22}H_{26}N_2O_2$.

IMPURITIES

Specified impurities *A, B, C, D.*



A. ethyl (12*S*,13a*S*,13b*S*)-13a-ethyl-12-hydroxy-2,3,5,6,12,13,13a,13b-octahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-12-carboxylate (ethyl vincaminate),

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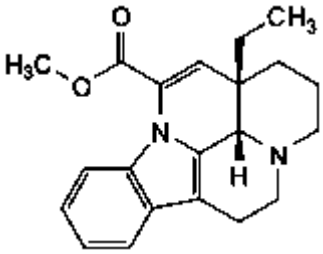
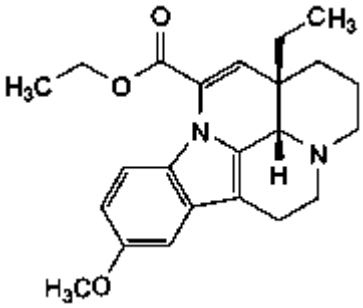
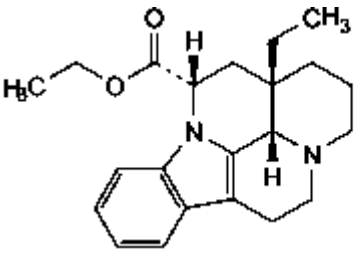


B. methyl (13a*S*,13b*S*)-13a-ethyl-2,3,5,6,13a,13b-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-12-carboxylate (apovincamine),



C. ethyl (13a*S*,13b*S*)-13a-ethyl-10-methoxy-2,3,5,6,13a,13b-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-12-carboxylate (methoxyvinpocetine),



D. ethyl (12*RS*,13a*RS*,13b*RS*)-13a-ethyl-2,3,5,6,12,13,13a,13b-octahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-12-carboxylate (dihydrovinpocetine).

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Virgin Almond Oil

General Notices

Almond Oil

(Ph. Eur. monograph 0261)

Preparation

Almond Oil Ear Drops

Ph Eur

DEFINITION

Fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* (Mill.) D.A.Webb var. *dulcis* or *Prunus dulcis* (Mill.) D.A.Webb var. *amara* (DC.) Buchheim or a mixture of both varieties.

CHARACTERS

Appearance

Yellow, clear liquid.

Solubility

Slightly soluble in ethanol (96 per cent), miscible with light petroleum.

Relative density

About 0.916.

It solidifies at about -18 °C.

IDENTIFICATION

First identification: A, C.

Second identification: A, B.

A. Absorbance (see Tests).

B. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

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C. Composition of fatty acids (see Tests).

TESTS

Specific absorbance (2.2.25)

Maximum 0.2, determined at the absorption maximum at 270 nm. The ratio of the absorbance measured at 232 nm to that measured at 270 nm is greater than 7.

To 0.100 g add *cyclohexane R* and dilute to 10.0 mL with the same solvent. Adapt the concentration of the solution so that the absorbance lies between 0.5 and 1.5, measured in a 1 cm cell.

Acid value (2.5.1)

Maximum 2.0, determined on 5.0 g.

Peroxide value (2.5.5, Method A)

Maximum 15.0.

Unsaponifiable matter (2.5.7)

Maximum 0.9 per cent, determined on 5.0 g.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{16}: maximum 0.1 per cent,

— *palmitic acid*: 4.0 per cent to 9.0 per cent,

— *palmitoleic acid*: maximum 0.8 per cent,

— *margaric acid*: maximum 0.2 per cent,

— *stearic acid*: maximum 3.0 per cent,

— *oleic acid*: 62.0 per cent to 86.0 per cent,

— *linoleic acid*: 20.0 per cent to 30.0 per cent,

— *linolenic acid*: maximum 0.4 per cent,

— *arachidic acid*: maximum 0.2 per cent,

— *eicosenoic acid*: maximum 0.3 per cent,

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— *behenic acid*: maximum 0.2 per cent,

— *erucic acid*: maximum 0.1 per cent.

Sterols (*2.4.23*)

Composition of sterol fraction of the oil:

— *cholesterol*: maximum 0.7 per cent,

— *campesterol*: maximum 4.0 per cent,

— *stigmasterol*: maximum 3.0 per cent,

— *β-sitosterol*: 73.0 per cent to 87.0 per cent,

— *Δ5-avenasterol*: minimum 10.0 per cent,

— *Δ7-stigmastenol*: maximum 3.0 per cent,

— *Δ7-avenasterol*: maximum 3.0 per cent,

— *brassicasterol*: maximum 0.3 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In a well-filled container, protected from light.

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Virgin Castor Oil

General Notices

(Ph. Eur. monograph 0051)

Action and use

Stimulant laxative; emollient.

Preparation

Zinc and Castor Oil Ointment

Ph Eur

DEFINITION

Fatty oil obtained by cold expression from the seeds of *Ricinus communis* L. A suitable antioxidant may be added.

PRODUCTION

During the expression step, the temperature of the oil must not exceed 50 °C.

CHARACTERS

Appearance

Clear at 40 °C, slightly yellow, viscous, hygroscopic liquid.

Solubility

Slightly soluble in light petroleum, miscible with ethanol (96 per cent) and with glacial acetic acid.

Relative density

About 0.958.

Refractive index

About 1.479.

IDENTIFICATION

First identification: B, C.

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Second identification: A, B.

A. A mixture of 2 mL of the substance to be examined and 8 mL of *ethanol (96 per cent) R* is clear (*2.2.1*).

B. Specific absorbance (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

Optical rotation (*2.2.7*)

+ 3.5° to + 6.0°.

Specific absorbance (*2.2.25*)

Maximum 0.7, determined at the absorption maximum at 270 nm.

To 1.00 g add *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent.

Acid value (*2.5.1*)

Maximum 1.5.

Dissolve 5.00 g in 25 mL of the prescribed mixture of solvents.

Hydroxyl value (*2.5.3, Method A*)

Minimum 160.

Peroxide value (*2.5.5, Method A*)

Maximum 10.0.

Unsaponifiable matter (*2.5.7*)

Maximum 0.8 per cent, determined on 5.0 g.

Composition of fatty acids

Gas chromatography (*2.4.22*) with the following modifications.

Use the mixture of calibrating substances in Table 2.4.22.-3.

Test solution Introduce 75 mg of the substance to be examined into a 10 mL centrifuge tube with a screw cap. Dissolve in 2 mL of *1,1-dimethylethyl methyl ether R1* with shaking and heat gently (50-60 °C). Add, while still warm, 1 mL of a 12 g/L solution of *sodium R* in *anhydrous methanol R*, prepared with the necessary precautions, and mix vigorously for at least 5 min. Add 5 mL of *distilled water R* and mix vigorously for about 30 s. Centrifuge for 15 min at 1500 *g*. Use the upper layer.

Reference solution Dissolve 50 mg of *methyl ricinoleate CRS* and 50 mg of *methyl stearate CRS* in 10.0 mL of *1,1-dimethylethyl methyl ether R1*.

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Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 0.9 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 55	215
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

System suitability:

— *symmetry factor*: 0.7 to 1.5 for the peak due to methyl stearate in the chromatogram obtained with the test solution.

Calculate the percentage content of each fatty acid by the normalisation procedure.

Correct the area of the peak due to methyl ricinoleate, by multiplying by a factor *R* calculated using the following expression:

$$\frac{m_1 \times A_2}{A_1 \times m_2}$$

m_1 = mass of methyl ricinoleate in the reference solution;

m_2 = mass of methyl stearate in the reference solution;

A_1 = area of the peak due to methyl ricinoleate in the chromatogram obtained with the reference solution;

A_2 = area of the peak due to methyl stearate in the chromatogram obtained with the reference solution.

Composition of the fatty-acid fraction of the oil:

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— *palmitic acid*: maximum 2.0 per cent;

— *stearic acid*: maximum 2.5 per cent;

— *oleic acid and isomer* : 2.5 per cent to 6.0 per cent;

— *linoleic acid* : 2.5 per cent to 7.0 per cent;

— *linolenic acid* : maximum 1.0 per cent;

— *eicosenoic acid* : maximum 1.0 per cent;

— *ricinoleic acid* : 85.0 per cent to 92.0 per cent;

— *any other fatty acid*: for each fatty acid, maximum 1.0 per cent.

Water (*2.5.32*)

Maximum 0.3 per cent, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light.

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Virgin Linseed Oil

General Notices

(Ph. Eur. monograph 1908)

Ph Eur

DEFINITION

Fatty oil obtained by cold expression from ripe seeds of *Linum usitatissimum* L. A suitable antioxidant may be added.

CHARACTERS

Appearance

Clear, yellow or brownish-yellow liquid, on exposure to air turning dark and gradually thickening. When cooled, it becomes a soft mass at about -20 °C.

Solubility

Very slightly soluble in ethanol (96 per cent), miscible with light petroleum.

Relative density

About 0.931.

Refractive index

About 1.480.

IDENTIFICATION

First identification: B, C.

Second identification: A, B.

A. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Iodine value (see Tests).

C. Composition of fatty acids (see Tests).

TESTS

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Acid value (2.5.1)

Maximum 4.5.

Iodine value (2.5.4)

160 to 200.

Peroxide value (2.5.5, Method A)

Maximum 15.0.

Saponification value (2.5.6)

188 to 195; carry out the saponification for 1 h.

Unsaponifiable matter (2.5.7)

Maximum 1.5 per cent, determined on 5.0 g.

Composition of fatty acids

Gas chromatography (2.4.22, Method C). Use the calibration mixture in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *fatty acids with a chain length less than* C_{16}: maximum 1.0 per cent,

— *palmitic acid*: 3.0 per cent to 8.0 per cent,

— *palmitoleic acid*: maximum 1.0 per cent,

— *stearic acid*: 2.0 per cent to 8.0 per cent,

— *oleic acid*: 11.0 per cent to 35.0 per cent,

— *linoleic acid*: 11.0 per cent to 24.0 per cent,

— *linolenic acid*: 35.0 per cent to 65.0 per cent,

— *arachidic acid*: maximum 1.0 per cent.

Cadmium

Maximum 0.5 ppm, determined as described in general method 2.4.27. *Heavy metals in herbal drugs and herbal drug preparations*.

Water (2.5.32)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

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In an airtight container, protected from light.

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Virgin Olive Oil

General Notices

Olive Oil

(Ph. Eur. monograph 0518)

Preparation

Olive Oil Ear Drops

Ph Eur

DEFINITION

Fatty oil obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea* L.

CHARACTERS

Appearance

Clear, transparent, yellow or greenish-yellow liquid.

Solubility

Practically insoluble in ethanol (96 per cent), miscible with light petroleum (bp: 50-70 °C).

When cooled, it begins to become cloudy at 10 °C and becomes a butter-like mass at about 0 °C.

Relative density

About 0.913.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1. For certain types of olive oil, the difference in the size of spots E and F is less pronounced than in the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

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TESTS

Absorbance (2.2.25)

Maximum 0.20 at 270 nm. The ratio of the absorbance at 232 nm to that at 270 nm is greater than 8.

To 1.00 g add *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Acid value (2.5.1)

Maximum 2.0, determined on 5.0 g.

Peroxide value (2.5.5, Method A)

Maximum 20.0.

Unsaponifiable matter

Maximum 1.5 per cent.

Place 5.0 g (*m* g) in a 150 mL flask fitted with a reflux condenser. Add 50 mL of *2 M alcoholic potassium hydroxide R* and heat on a water-bath for 1 h, shaking frequently. Add 50 mL of *water R* through the top of the condenser, shake, allow to cool and transfer the contents of the flask to a separating funnel. Rinse the flask with several portions totalling 50 mL of *light petroleum R1* and add the rinsings to the separating funnel. Shake vigorously for 1 min. Allow to separate and transfer the aqueous layer to a 2nd separating funnel. If an emulsion forms, add small quantities of *ethanol (96 per cent) R* or a concentrated solution of *potassium hydroxide R*. Shake the aqueous layer with 2 quantities, each of 50 mL, of *light petroleum R1*. Combine the light petroleum layers in a 3rd separating funnel and wash with 3 quantities, each of 50 mL, of *ethanol (50 per cent V/V) R*. Transfer the light petroleum layer to a tared 250 mL flask. Rinse the separating funnel with small quantities of *light petroleum R1* and add to the tared flask. Evaporate the light petroleum on a water-bath and dry the residue at 100-105 °C for 15 min, keeping the flask horizontal. Allow to cool in a desiccator and weigh (*a* g). Repeat the drying for successive periods of 15 min until the loss of mass between 2 successive weighings does not exceed 0.1 per cent. Dissolve the residue in 20 mL of *ethanol (96 per cent) R*, previously neutralised to 0.1 mL of *bromophenol blue solution R*. If necessary, titrate with *0.1 M hydrochloric acid* (*b* mL).

Calculate the percentage content of unsaponifiable matter using the following expression:

$$\frac{100\,(a - 0.032b)}{m}$$

If 0.032*b* is greater than 5 per cent of *a*, the test is not valid and must be repeated.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{16}: maximum 0.1 per cent;

— *palmitic acid*: 7.5 per cent to 20.0 per cent;

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— *palmitoleic acid*: maximum 3.5 per cent;

— *stearic acid*: 0.5 per cent to 5.0 per cent;

— *oleic acid and isomer*: 56.0 per cent to 85.0 per cent;

— *linoleic acid*: 3.5 per cent to 20.0 per cent;

— *linolenic acid*: maximum 1.2 per cent;

— *arachidic acid*: maximum 0.7 per cent;

— *eicosenoic acid*: maximum 0.4 per cent;

— *behenic acid*: maximum 0.2 per cent;

— *lignoceric acid*: maximum 0.2 per cent.

Sterols (*2.4.23, Method B*)

Composition of the sterol fraction of the oil:

— *cholesterol*: maximum 0.5 per cent;

— *campesterol*: maximum 4.0 per cent;

— *Δ7-stigmasterol*: maximum 0.5 per cent;

— *sum of contents of Δ5,23-stigmastadienol, clerosterol, β-sitosterol, sitostanol, Δ5-avenasterol and Δ5,24-stigmastadienol*: minimum 93.0 per cent.

The content of stigmasterol is not greater than that of campesterol.

Sesame oil

In a ground-glass-stoppered cylinder shake 10 mL for about 1 min with a mixture of 0.5 mL of a 0.35 per cent *V/V* solution of furfural R in *acetic anhydride R* and 4.5 mL of *acetic anhydride R*. Filter through a filter paper impregnated with *acetic anhydride R*. To the filtrate add 0.2 mL of *sulfuric acid R*. No bluish-green colour develops.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In a well-filled container, protected from light, at a temperature not exceeding 25 °C.

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Virgin Wheat-germ Oil

General Notices

(Ph. Eur. monograph 1480)

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DEFINITION

Fatty oil obtained from the germ of the grain of *Triticum aestivum* L. by cold expression or other suitable mechanical means.

PRODUCTION

The oil is prepared using materials and methods designed to ensure that the content of brassicasterol (2.4.23) in the sterol fraction of the oil is not greater than 0.3 per cent.

CHARACTERS

Appearance

Clear, light yellow or golden-yellow liquid.

Solubility

Practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C).

Relative density

About 0.925.

Refractive index

About 1.475.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

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TESTS

Acid value (*2.5.1*)

Maximum 20.0.

Peroxide value (*2.5.5, Method A*)

Maximum 15.0.

Unsaponifiable matter (*2.5.7*)

Maximum 5.0 per cent, determined on 5.0 g.

Composition of fatty acids (*2.4.22, Method C*)

Composition of the fatty-acid fraction of the oil:

— *palmitic acid*: 14.0 per cent to 19.0 per cent;

— *stearic acid*: maximum 2.0 per cent;

— *oleic acid*: 12.0 per cent to 23.0 per cent;

— *linoleic acid*: 52.0 per cent to 59.0 per cent;

— *linolenic acid*: 3.0 per cent to 10.0 per cent;

— *eicosenoic acid*: maximum 2.0 per cent.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light.

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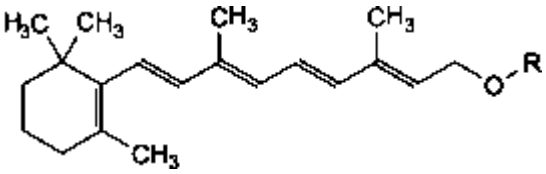
Vitamin A

General Notices

(Ph. Eur. monograph 0217)

In the British Pharmacopoeia, the term ‘Retinol’ is used within titles for preparations containing synthetic ester(s) and the term ‘Vitamin A’ within the title for the preparation containing material of natural origin.



Substance	R	Molecular formula	M_r
all-(*E*)-retinol	H	$C_{20}H_{30}O$	286.5
all-(*E*)-retinol acetate	$CO\text{-}CH_3$	$C_{22}H_{32}O_2$	328.5
all-(*E*)-retinol propionate	$CO\text{-}C_2H_5$	$C_{23}H_{34}O_2$	342.5
all-(*E*)-retinol palmitate	$CO\text{-}C_{15}H_{31}$	$C_{36}H_{60}O_2$	524.9

Preparation

Paediatric Vitamins A, C and D Oral Drops

Ph Eur

DEFINITION

Vitamin A Refers to a number of substances of very similar structure (including (*Z*)-isomers) found in animal tissues and possessing similar activity. The principal and biologically most active substance is all-(*E*)-retinol (all-(*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraen-1-ol; $C_{20}H_{30}O$). Vitamin A is generally used in the form of esters such as the acetate, propionate and palmitate.

Synthetic retinol ester Refers to an ester (acetate, propionate or palmitate) or a mixture of synthetic retinol esters.

The activity of vitamin A is expressed in retinol equivalents (R.E.). 1 mg R.E. corresponds to the activity of 1 mg of all-(*E*)-retinol. The activity of the other retinol esters is calculated stoichiometrically, so that 1 mg R.E. of vitamin A corresponds to the activity of:

— 1.147 mg of all-(*E*)-retinol acetate,

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— 1.195 mg of all-(*E*)-retinol propionate,

— 1.832 mg of all-(*E*)-retinol palmitate.

International Units (IU) are also used to express the activity of vitamin A. 1 IU of vitamin A is equivalent to the activity of 0.300 µg of all-(*E*)-retinol. The activity of the other retinol esters is calculated stoichiometrically, so that 1 IU of vitamin A is equivalent to the activity of:

— 0.344 µg of all-(*E*)-retinol acetate,

— 0.359 µg of all-(*E*)-retinol propionate,

— 0.550 µg of all-(*E*)-retinol palmitate,

1 mg of retinol equivalent is equivalent to 3333 IU.

CHARACTERS

Appearance

Retinol acetate: pale-yellow crystals (mp: about 60 °C). Once melted retinol acetate tends to yield a supercooled melt.

Retinol propionate: reddish-brown oily liquid.

Retinol palmitate: a fat-like, light yellow solid or a yellow oily liquid, if melted (mp: about 26 °C).

Solubility

All retinol esters are practically insoluble in water, soluble or partly soluble in anhydrous ethanol and miscible with organic solvents.

Vitamin A and its esters are very sensitive to the action of air, oxidising agents, acids, light and heat.

Carry out the assay and all tests as rapidly as possible, avoiding exposure to actinic light and air, oxidising agents, oxidation catalysts (e.g. copper, iron), acids and heat; use freshly prepared solutions.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

Test solution Prepare a solution containing about 3.3 IU of vitamin A per microlitre in *cyclohexane R* containing 1 g/L of *butylhydroxytoluene R*.

Reference solution Prepare a 10 mg/mL solution of *retinol esters CRS* (i.e. 3.3 IU of each ester per microlitre) in *cyclohexane R* containing 1 g/L of *butylhydroxytoluene R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 3 µL.

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Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution:

— the chromatogram shows the individual spots of the corresponding esters. The elution order from bottom to top is: retinol acetate, retinol propionate and retinol palmitate.

Results The composition of esters is confirmed by the correspondence of the principal spot or spots of the test solution with those obtained with the reference solution.

B. Related substances (see Tests).

TESTS

Retinol

Thin-layer chromatography (*2.2.27*).

Test solution Prepare a solution in *cyclohexane R*, stabilised with a solution containing 1 g/L of *butylhydroxytoluene R*, containing about 330 IU of vitamin A per microlitre.

Reference solution Shake 1 mL of the test solution with 20 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* for 2 min and dilute to 100 mL with *cyclohexane R*, stabilised with a solution containg 1 g/L of *butylhydroxytoluene R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 3 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution:

— in the chromatogram obtained no or only traces of the retinol esters are seen.

Limit Any spot corresponding to retinol in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (1.0 per cent).

Related substances

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Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution The solution described under Activity.

Absorption maximum At 325 nm to 327 nm.

Absorbance ratios:

— A_{300}/A_{326} = maximum 0.60;

— A_{350}/A_{326} = maximum 0.54;

— A_{370}/A_{326} = maximum 0.14.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ACTIVITY

The activity of the substance is determined in order to be taken into account for the production of concentrates.

Dissolve 25-100 mg, weighed with an accuracy of 0.1 per cent, in 5 mL of *pentane R* and dilute with *2-propanol R1* to a presumed concentration of 10 IU/mL to 15 IU/mL. Measure the absorbance (2.2.25) at the absorption maximum at 326 nm. Calculate the activity of vitamin A in International Units per gram from the expression:

$$\frac{A_{326} \times V \times 1900}{100 \times m}$$

A_{326}	=	absorbance at 326 nm,
m	=	mass of the substance to be examined, in grams,
V	=	total volume to which the substance to be examined is diluted to give 10 IU/mL to 15 IU/mL,
1900	=	factor to convert the specific absorbance of esters of retinol into International Units per gram.

STORAGE

In an airtight container, protected from light.

Once the container has been opened, its contents are to be used as soon as possible; any part of the contents not used at once should be protected by an atmosphere of inert gas.

LABELLING

The label states:

— the number of International Units per gram,

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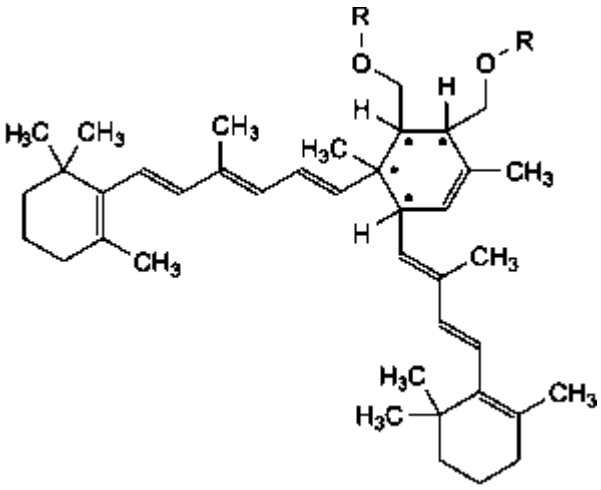
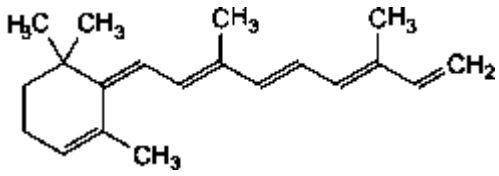
— the name of the ester or esters.

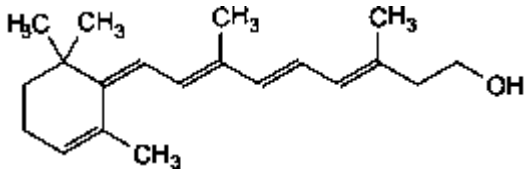
IMPURITIES



A. R = H, CO-CH_3: kitols (Diels-Alder dimers of vitamin A),



B. (3*E*,5*E*,7*E*)-3,7-dimethyl-9-[(1*Z*)-2,6,6-trimethylcyclohex-2-enylidene]nona-1,3,5,7-tetraene (anhydro-vitamin A),



C. (3*E*,5*E*,7*E*)-3,7-dimethyl-9-[(1*Z*)-2,6,6-trimethylcyclohex-2-enylidene]nona-3,5,7-trien-1-ol (*retro*-vitamin A),

D. oxidation products of vitamin A.

Ph Eur

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Vitamins B and C Injection

General Notices

DEFINITION

Vitamins B and C Injection is a sterile solution of Thiamine Hydrochloride, Pyridoxine Hydrochloride, Riboflavin Sodium Phosphate, Nicotinamide and Ascorbic Acid (as the sodium salt) in Water for Injections, containing Glucose for the intravenous injection or Benzyl Alcohol for the intramuscular injection.

Vitamins B and C Injection is prepared immediately before use by mixing the contents of two ampoules, (1) and (2). Ampoule (1) contains Thiamine Hydrochloride, Pyridoxine Hydrochloride, Riboflavin Sodium Phosphate and, where appropriate, Benzyl Alcohol. Ampoule (2) contains Nicotinamide and Ascorbic Acid and, where appropriate, Glucose. The air in ampoule (2) is replaced by nitrogen or other suitable inert gas.

The injection complies with the requirements stated under Parenteral Preparations and the contents of ampoules (1) and (2) comply with the following requirements, as appropriate.

Content of thiamine hydrochloride, $C_{12}H_{17}ClN_4OS,HCl$

92.0 to 106.0% of the stated amount.

Content of pyridoxine hydrochloride, $C_8H_{11}NO_3,HCl$

90.0 to 110.0% of the stated amount.

Content of riboflavin, $C_{17}H_{20}N_4O_6$

90.0 to 110.0% of the stated amount.

Content of nicotinamide, $C_6H_6N_2O$

95.0 to 105.0% of the stated amount.

Content of ascorbic acid, $C_6H_8O_6$

95.0 to 105.0% of the stated amount.

Content of glucose, $C_6H_{12}O_6$

Where appropriate, 90.0 to 110.0% of the stated amount.

IDENTIFICATION

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A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 60 volumes of *methanol* and 40 volumes of a solution containing 0.14% w/v of *potassium dihydrogen orthophosphate* and 0.5% w/v of *disodium edetate* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions in *water*. For solution (1) use a volume of the contents of ampoule (1) diluted, if necessary, with *water* to contain 0.2% w/v of Pyridoxine Hydrochloride. For solution (2) use a volume of the injection in ampoule (2) diluted, if necessary, with *water* to contain 2% w/v of Ascorbic Acid. Solutions (3) and (4) contain 1% w/v and 0.4% w/v respectively of *thiamine mononitrate BPCRS*. Solution (5) contains 0.2% w/v of *pyridoxine hydrochloride BPCRS*. Solution (6) contains 0.022% w/v of *riboflavin sodium phosphate BPCRS*. Solution (7) contains 0.64% w/v of *nicotinamide BPCRS*. Solution (8) contains 2% w/v of *ascorbic acid BPCRS*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light* (*254 nm and 365 nm*). The principal spots in the chromatogram obtained with solution (1) correspond to those in the chromatograms obtained with either solutions (3), (5) and (6) or solutions (4), (5) and (6). The principal spots in the chromatogram obtained with solution (2) correspond to those in the chromatograms obtained with solutions (7) and (8).

B. *For injections containing* *Glucose*, heat 1 mL of the contents of ampoule (2) with *cupri-tartaric solution R1*. A copious precipitate of copper(I) oxide is produced.

ASSAY

For thiamine hydrochloride, pyridoxine hydrochloride and nicotinamide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*. Solution (1) contains 0.01% w/v of *thiamine mononitrate BPCRS* and 0.002% w/v of *pyridoxine hydrochloride BPCRS*. Solution (2) contains 0.01% w/v of *thiamine mononitrate BPCRS* and 0.005% w/v of *pyridoxine hydrochloride BPCRS*. Solution (3) contains 0.016% w/v of *nicotinamide BPCRS*. For solution (4) dilute a suitable volume of the contents of ampoule (1) with *water* to contain 0.01% w/v of Thiamine Hydrochloride. For solution (5) dilute a suitable volume of the contents of ampoule (2) to contain 0.016% w/v of Nicotinamide.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute, 0.22% w/v of *sodium heptanesulfonate* in a mixture of 75 volumes of a 1.36% w/v solution of *potassium dihydrogen orthophosphate* and 25 volumes of *methanol*, the pH of the final mixture being adjusted to 3.0 with *orthophosphoric acid*, and (c) a detection wavelength of 280 nm.

Calculate the content of $C_{12}H_{17}ClN_4OS,HCl$ using the declared content of $C_{12}H_{17}N_5O_4S$ in *thiamine mononitrate BPCRS*. Each mg of $C_{12}H_{17}N_5O_4S$ is equivalent to 1.030 mg of $C_{12}H_{17}ClN_4OS,HCl$. Calculate the content of $C_8H_{11}NO_3,HCl$ using the declared content of $C_8H_{11}NO_3,HCl$ in *pyridoxine hydrochloride BPCRS*. Calculate the content of $C_6H_6N_2O$ using the declared content of $C_6H_6N_2O$ in *nicotinamide BPCRS*.

For riboflavin

Dilute a volume of the contents of ampoule (1) containing the equivalent of 4 mg of riboflavine with sufficient *phthalate buffer pH 4.0* to produce 200 mL and measure the *absorbance* of the resulting solution at the maximum at 446 nm, Appendix II B. Calculate the content of $C_{17}H_{20}N_4O_6$ taking 323 as the value of A(1%, 1 cm) at the maximum at 446 nm.

For ascorbic acid

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Dilute a volume of the contents of ampoule (2) with *water* to produce a solution containing 1% w/v of Ascorbic Acid. To 20 mL of the resulting solution add 5 mL of 1M *sulfuric acid* and 50 mL of *0.05M iodine VS* and titrate the excess iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Each mL of *0.05M iodine VS* is equivalent to 8.806 mg of $C_6H_8O_6$.

For glucose

For injections containing Glucose, dilute a volume of the contents of ampoule (2) containing 0.8 g of Glucose to 500 mL with *water* and dilute 2 mL of the resulting solution to 100 mL with *water*. Transfer 3 mL of this solution to a boiling tube previously cleaned with *chromic-sulfuric acid mixture* and rinsed with *water*. In two similar tubes place separately 3 mL of *glucose standard solution* and 3 mL of *water*. Add 6 mL of *anthrone reagent* in such a manner as to ensure rapid mixing, allow to stand for 10 minutes, cool quickly and measure the *absorbance*, Appendix II B, of the test solution and of the standard solution at the maximum at 625 nm using the solution prepared with *water* in the reference cell. Calculate the concentration of $C_6H_{12}O_6$ in the test solution.

STORAGE

Ampoules (1) and (2) for Vitamins B and C Injection should be protected from light.

LABELLING

For each ampoule the label states (1) the directions for the preparation of the injection; (2) whether the final injection is for intravenous or intramuscular use; (3) that the final injection is a high potency injection.

For ampoule (1) the label states the quantity of Riboflavin Sodium Phosphate in terms of the equivalent amount of riboflavin.

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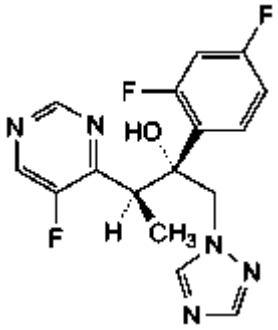
Voriconazole

General Notices

(Ph. Eur. monograph 2576)



$C_{16}H_{14}F_3N_5O$ 349.3 *137234-62-9*

Action and use

Antifungal.

Ph Eur

DEFINITION

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, freely soluble in acetone and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

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Comparison *voriconazole CRS*.

B. Enantiomeric purity (see Tests).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.5 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 20 mL with the same solution.

Enantiomeric purity

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in 2 mL of *acetonitrile R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *voriconazole impurity D CRS* in 2 mL of *acetonitrile R* and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 25 mg of the substance to be examined in 2 mL of *acetonitrile R*, add 1 mL of reference solution (a) and dilute to 50.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel BC for chiral chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 18 volumes of *acetonitrile R* and 82 volumes of a 0.77 g/L solution of *ammonium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 256 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 2.5 times the retention time of voriconazole.

Relative retention With reference to voriconazole (retention time = about 7 min): impurity D = about 1.5.

System suitability Reference solution (b):

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— *resolution*: minimum 4.0 between the peaks due to voriconazole and impurity D.

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent).

Impurity E

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 5.0 mL of *methanol R* and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *voriconazole impurity E CRS* in 50 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 17 mg of *sodium chloride R* in *water R* and dilute to 200.0 mL with the same solvent. Mix 1 mL of the solution, 1 mL of reference solution (a) and 25 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Reference solution (c) To 1.0 mL of reference solution (a) add 25 mL of *methanol R* and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm);

— *temperature*: 40 °C.

Mobile phase To 1500 mL of *water R* add 500 mL of *methanol R*, mix and degas; add about 175 µL of a 470 g/L solution of *sodium hydroxide R* and mix.

Flow rate 1.0 mL/min.

Detection Conductivity detector; use a self-regenerating anion suppressor.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of impurity E.

Relative retention With reference to impurity E (retention time = about 4 min): chloride = about 1.5.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurity E and chloride in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.7 for the peak due to impurity E in the chromatogram obtained with reference solution (c).

Limit:

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent).

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Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase, sonicating if necessary, and dilute to 100.0 mL with the mobile phase. Mix well to ensure complete dissolution.

Test solution (b) Dilute 5.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *voriconazole CRS* in the mobile phase, sonicating if necessary, and dilute to 100.0 mL with the mobile phase. Mix well to ensure complete dissolution. Dilute 5.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Suspend 0.100 g of the substance to be examined in 10 mL of a 40 g/L solution of *sodium hydroxide R* and dilute to 20 mL with the mobile phase; sonicate if necessary. Allow to stand for 30 min. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase (*in situ* degradation to obtain impurities A and C).

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase and mix. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase and mix well.

Reference solution (d) Dissolve 2 mg of *voriconazole impurity B CRS* in the mobile phase and dilute to 200 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm);

— *temperature*: 35 °C.

Mobile phase Mix 15 volumes of *acetonitrile R*, 30 volumes of *methanol R* and 55 volumes of a 1.90 g/L solution of *ammonium formate R* previously adjusted to pH 4.0 with *anhydrous formic acid R* while stirring continuously.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 256 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c) and (d).

Run time 3 times the retention time of voriconazole.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity B.

Relative retention With reference to voriconazole (retention time = about 8 min): impurity A = about 0.25; impurity C = about 0.3; impurity B = about 0.6.

System suitability Reference solution (b):

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— *resolution*: minimum 1.8 between the peaks due to impurities A and C.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity B = 2.1; impurity C = 0.7;

— *impurities A, B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *sum of impurities A, B, C, D, E and unspecified impurities*: maximum 0.5 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.4 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

Bacterial endotoxins (*2.6.14*)

Less than 0.2 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{16}H_{14}F_3N_5O$ from the declared content of *voriconazole CRS*.

STORAGE

If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Specified impurities *A, B, C, D, E.*

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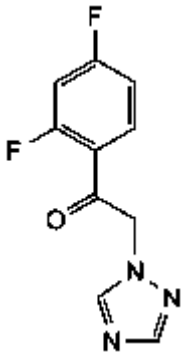
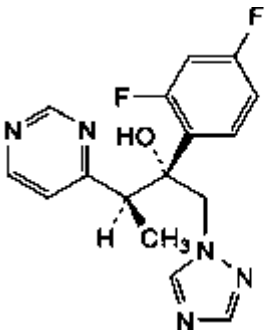


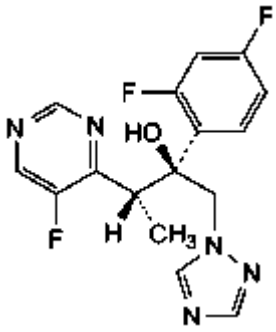
A. 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone,



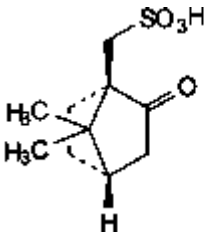
and enantiomer

B. (2*RS*,3*SR*)-2-(2,4-difluorophenyl)-3-pyrimidin-4-yl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol,

C. 4-ethyl-5-fluoropyrimidine,



D. (2*S*,3*R*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (voriconazole enantiomer),



and enantiomer

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E. [(1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methanesulfonic acid ((±)-10-camphorsulfonic acid).

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Warfarin Oral Suspension

General Notices

Action and use

Vitamin K epoxide reductase inhibitor; oral anticoagulant (coumarin).

DEFINITION

Warfarin Oral Suspension is a suspension of Warfarin Sodium in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of warfarin sodium, $C_{19}H_{15}NaO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.7 to 4.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the oral suspension containing 10 mg of Warfarin Sodium add 30 mL of *acetonitrile* and mix; add 50 mL of *water*, mix with the aid of ultrasound for 10 minutes and allow the solution to cool to room temperature. Add sufficient *water* to produce 100 mL, mix and filter through a 0.45-µm cellulose acetate filter (GD/X is suitable).
(2) Dissolve 10 mg of *4-hydroxycoumarin* (warfarin impurity B) in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.
(3) Dissolve 10 mg of *benzalacetone* (warfarin impurity C) in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.

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(4) Dissolve 10 mg of *(5RS)-3-(2-hydroxyphenyl)-5-phenylcyclohex-2-enone BPCRS* (warfarin impurity A) in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.

(5) Dissolve 80 mg of *benzoic acid* in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.

(6) Mix equal volumes of solution (2) and solution (5).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *phenylhexylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna Phenyl-Hexyl is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with *octadecylsilyl silica gel for chromatography*.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 283 nm.

(f) Inject 50 µL of each solution.

When the chromatograms are recorded under the prescribed conditions the retention time of warfarin is about 19 minutes.

MOBILE PHASE

1 volume of *acetic acid*, 50 volumes of *methanol* and 50 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the *resolution factor* between the peaks corresponding to 4-hydroxycoumarin and benzoic acid is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peaks corresponding to 4-hydroxycoumarin, benzalacetone and (5*RS*)-3-(2-hydroxyphenyl)-5-phenylcyclohex-2-enone are not greater than half the area of the principal peaks in the chromatograms obtained with solutions (2), (3) and (4) respectively (0.5% of each);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak corresponding to the peak in the chromatogram obtained with solution (5).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the oral suspension containing 10 mg of Warfarin Sodium add 30 mL of *acetonitrile* and mix; add 50 mL of *water*, mix with the aid of ultrasound for 10 minutes and allow the solution to cool to room temperature. Add sufficient *water* to produce 100 mL, mix and filter through a 0.45-µm cellulose acetate filter (GD/X is suitable).

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(2) Dissolve 0.1 g of *warfarin BPCRS* in 100 mL of a mixture of equal volumes of *acetonitrile* and *water*; dilute 10 volumes of this solution to 100 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *phenylhexylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna Phenyl-Hexyl is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with *octadecylsilyl silica gel for chromatography*.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 283 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

1 volume of *acetic acid*, 50 volumes of *methanol* and 50 volumes of *water*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{19}H_{15}NaO_4$, weight in volume, using the declared content of $C_{19}H_{16}O_4$ in *warfarin BPCRS*. Each mg of $C_{19}H_{16}O_4$ is equivalent to 1.071 mg of $C_{19}H_{15}NaO_4$.

STORAGE

Warfarin Oral Suspension should be protected from light.

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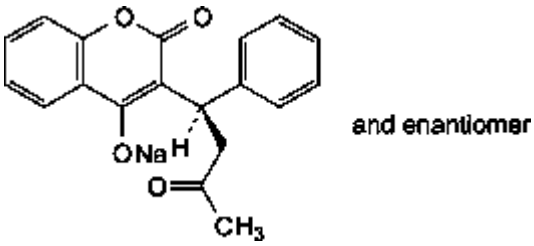
Warfarin Sodium

General Notices

(Ph. Eur. monograph 0698)



and enantiomer

$C_{19}H_{15}NaO_4$ 330.3 *129-06-6*

Action and use

Vitamin K epoxide reductase inhibitor; oral anticoagulant (coumarin).

Preparations

Warfarin Oral Suspension

Warfarin Tablets

Ph Eur

DEFINITION

Sodium 2-oxo-3-[(1*RS*)-3-oxo-1-phenylbutyl]-2*H*-1-benzopyran-4-olate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, amorphous powder.

Solubility

Very soluble in water and in ethanol (96 per cent), soluble in acetone, very slightly soluble in methylene chloride.

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *warfarin sodium CRS*.

B. Propan-2-ol (see Tests).

C. It gives reaction (b) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1.0 g in *water R* and dilute to 20 mL with the same solvent.

pH (2.2.3)

7.6 to 8.6.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, *water R* (25:75 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *4-hydroxycoumarin R* (impurity B) and 2 mg of benzalacetone R (impurity C) in 25 mL of *methanol R* and dilute to 100 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *glacial acetic acid R*, *acetonitrile R*, *water R* (1:25:75 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 260 nm.

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Injection 20 µL.

Run time Twice the retention time of warfarin.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and C.

Relative retention With reference to warfarin (retention time = about 9 min): impurity B = about 0.4; impurity C = about 0.6.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities B and C.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.5; impurity C = 0.4;

— *impurities B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Phenolic ketones

Dissolve 1.25 g in a 20 g/L solution of *sodium hydroxide R* and dilute to 10.0 mL with the same solvent. The absorbance (*2.2.25*) is maximum 0.20 measured at 385 nm within 15 min of preparing the solution.

Propan-2-ol (*2.4.24, System A*)

Maximum 0.5 per cent.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.750 g.

ASSAY

Dissolve 0.100 g in *0.01 M sodium hydroxide* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *0.01 M sodium hydroxide*. Dilute 10.0 mL of this solution to 100.0 mL with *0.01 M sodium hydroxide*. Measure the absorbance (*2.2.25*) at the absorption maximum at 308 nm.

Calculate the percentage content of $C_{19}H_{15}NaO_4$ taking the specific absorbance to be 431.

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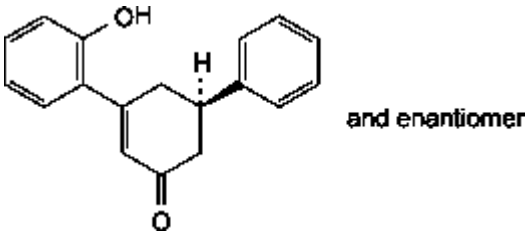
STORAGE

In an airtight container, protected from light.

IMPURITIES

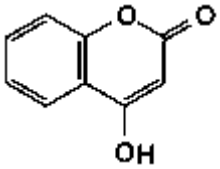
Specified impurities *B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*

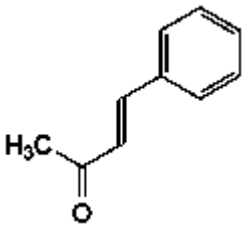


and enantiomer

A. (5*RS*)-3-(2-hydroxyphenyl)-5-phenylcyclohex-2-enone,



B. 4-hydroxy-2*H*-1-benzopyran-2-one (4-hydroxycoumarin),



C. (3*E*)-4-phenylbut-3-en-2-one (benzalacetone).

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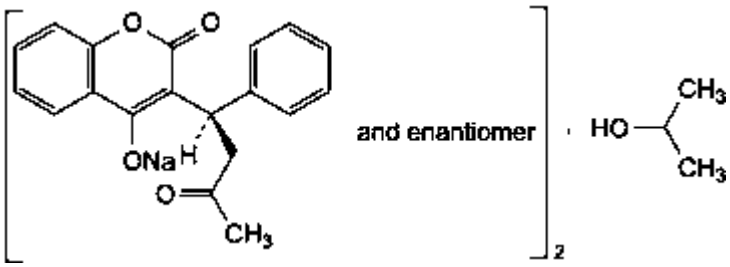
Warfarin Sodium Clathrate

General Notices

(Ph. Eur. monograph 0699)



Action and use

Vitamin K epoxide reductase inhibitor; oral anticoagulant (coumarin).

Preparation

Warfarin Tablets

Ph Eur

DEFINITION

Mixture, in the form of a clathrate, of warfarin sodium (sodium 2-oxo-3-[(1*RS*)-3-oxo-1-phenylbutyl]-2*H*-1-benzopyran-4-olate) and propan-2-ol in molecular proportions 2:1 (equivalent to about 92 per cent of warfarin sodium).

Content

— *warfarin sodium*: 98.0 per cent to 102.0 per cent (anhydrous and propan-2-ol-free substance);

— *propan-2-ol*: 8.0 per cent to 8.5 per cent.

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), soluble in acetone, very slightly soluble in methylene chloride.

IDENTIFICATION

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *warfarin sodium clathrate CRS*.

B. Propan-2-ol (see Tests).

C. It gives reaction (b) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1.0 g in *water R* and dilute to 20 mL with the same solvent.

pH (2.2.3)

7.6 to 8.6.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, *water R* (25:75 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *4-hydroxycoumarin R* (impurity B) and 2 mg of benzalacetone R (impurity C) in 25 mL of *methanol R* and dilute to 100 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *glacial acetic acid R*, *acetonitrile R*, *water R* (1:25:75 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 260 nm.

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Injection 20 µL.

Run time Twice the retention time of warfarin.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and C.

Relative retention With reference to warfarin (retention time = about 9 min): impurity B = about 0.4; impurity C = about 0.6.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities B and C.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.5; impurity C = 0.4;

— *impurities B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Phenolic ketones

Dissolve 1.25 g in a 20 g/L solution of *sodium hydroxide R* and dilute to 10.0 mL with the same solvent. The absorbance (*2.2.25*) is maximum 0.20 measured at 385 nm within 15 min of preparing the solution.

Propan-2-ol (*2.4.24, System A*)

8.0 per cent to 8.5 per cent.

Water (*2.5.12*)

Maximum 0.3 per cent, determined on 2.500 g.

ASSAY

Dissolve 0.100 g in *0.01 M sodium hydroxide* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *0.01 M sodium hydroxide*. Dilute 10.0 mL of this solution to 100.0 mL with *0.01 M sodium hydroxide*. Measure the absorbance (*2.2.25*) at the absorption maximum at 308 nm.

Calculate the percentage content of warfarin sodium ($C_{19}H_{15}NaO_4$) taking the specific absorbance to be 431.

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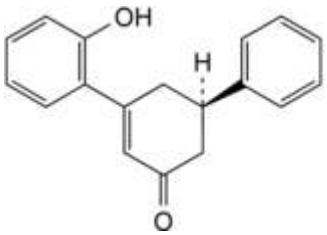
STORAGE

In an airtight container, protected from light.

IMPURITIES

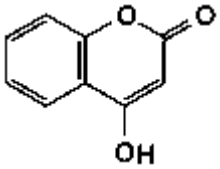
Specified impurities B, C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.

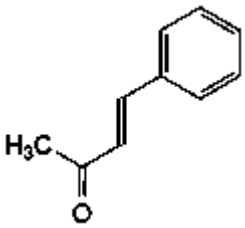


and enantiomer

A. (5*RS*)-3-(2-hydroxyphenyl)-5-phenylcyclohex-2-enone,



B. 4-hydroxy-2*H*-1-benzopyran-2-one (4-hydroxycoumarin),



C. (3*E*)-4-phenylbut-3-en-2-one (benzalacetone).

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Warfarin Tablets

General Notices

Warfarin Tablets prepared from Warfarin Sodium are not necessarily interchangeable with Warfarin Tablets prepared from Warfarin Sodium Clathrate.

Action and use

Vitamin K epoxide reductase inhibitor; oral anticoagulant (coumarin).

DEFINITION

Warfarin Tablets contain Warfarin Sodium or Warfarin Sodium Clathrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of warfarin sodium, $C_{19}H_{15}NaO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing the equivalent of 0.1 g of warfarin sodium with 30 mL of *water*, add 0.1 mL of *2M hydrochloric acid*, filter, wash the precipitate with *water* and dry. Warm the residue gently with 3 mL of *ethanol* (*96%*), filter and add the filtrate to 25 mL of *water* containing 0.1 mL of *2M hydrochloric acid*. Filter, wash the precipitate with *water* and dry it at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of warfarin (*RS 361*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of a 0.68% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 6.8 by the addition of 1M *sodium hydroxide*, at a temperature of 37°, as the medium.

(c) For tablets containing 2 mg or less of warfarin sodium, place three tablets in the basket for each test; for tablets containing more than 2 mg of warfarin sodium, place a single tablet in the basket for each test.

PROCEDURE

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After 45 minutes, withdraw a 10-mL sample of the medium. Measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maxima at 307 nm and 360 nm, Appendix II B, using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the difference between the two readings (ΔA). Calculate the total content of warfarin sodium, $C_{19}H_{15}NaO_4$, in the medium from the absorbances obtained and taking 428 as the value of ΔA(1%, 1 cm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mixture of *methanol (25%)*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 10 mg of warfarin sodium in 8 mL. Mix with the aid of ultrasound, dilute to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 10 volumes.
(3) 0.002% w/v each of *4-hydroxycoumarin* (impurity B) and (E)-*4-phenylbut-3-en-2-one* (impurity C).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Waters Spherisorb CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 283 nm.
(f) Inject 50 µL of each solution
(g) For solution (1) allow the chromatography to proceed for twice the retention time of warfarin.

MOBILE PHASE

1 volume of *glacial acetic acid*, 15 volumes of *acetonitrile* and 85 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to warfarin (retention time about 9 minutes) are: impurity B, about 0.4 and impurity C, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity C is at least 2.0.

LIMITS

Identify any peaks corresponding to impurity B and impurity C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity B by a correction factor of 0.5 and impurity C by a correction factor of 0.4.

In the chromatogram obtained with solution (1):

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the area of any peak corresponding to impurity B and impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of warfarin sodium comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Shake one tablet with 10 mL of 0.01M *sodium hydroxide* for 15 minutes, add 10 mL of a 2% v/v solution of *glacial acetic acid* in *acetonitrile*, centrifuge for 10 minutes. Dilute the clear supernatant liquid, if necessary, with the mobile phase to produce a solution containing 0.0025% w/v of warfarin.
Dilute 1 volume of a 0.010% w/v solution of *warfarin BPCRS* in 0.01M *sodium hydroxide* to 4 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable),
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 283 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 45 volumes of *water*, and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{15}NaO_4$ in each tablet using the declared content of $C_{19}H_{16}O_4$ in *warfarin BPCRS*. Each mg of $C_{19}H_{16}O_4$ is equivalent to 1.071 mg of $C_{19}H_{15}NaO_4$.

ASSAY

For tablets containing 2 mg or less or 2% w/w or less of warfarin sodium

Use the average of the individual results obtained in the test for Uniformity of content.

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For tablets containing more than 2 mg and more than 2% w/w of warfarin sodium

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 5 mg of warfarin sodium with 50 mL of 0.01M *sodium hydroxide* for 15 minutes, add 50 mL of a 2% v/v solution of *glacial acetic acid* in *acetonitrile*, centrifuge for 10 minutes and use the clear supernatant liquid.

(2) Dilute 5 mL of a 0.010% w/v solution of *warfarin BPCRS* in 0.01M *sodium hydroxide* to 10 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{15}NaO_4$ in the tablets using the declared content of $C_{19}H_{16}O_4$ in *warfarin BPCRS*. Each mg of $C_{19}H_{16}O_4$ is equivalent to 1.071 mg of $C_{19}H_{15}NaO_4$.

STORAGE

Warfarin Tablets should be protected from light.

LABELLING

When the active ingredient is Warfarin Sodium Clathrate the quantity is stated in terms of the equivalent amount of warfarin sodium.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Warfarin Sodium.

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Water for Diluting Concentrated Haemodialysis Solutions

General Notices

(Haemodialysis Solutions, Concentrated, Water for Diluting, Ph. Eur. monograph 1167)

Ph Eur

The following monograph is given for information.

The analytical methods described and the limits proposed are intended to be used for validating the procedure for obtaining the water.

DEFINITION

Water for diluting concentrated haemodialysis solutions is obtained from potable water by distillation, by reverse osmosis, by ion exchange or by any other suitable method. The conditions of preparation, transfer and storage are designed to minimise the risk of chemical and microbial contamination.

When water obtained by one of the methods described above is not available, potable water may be used for home dialysis. Because the chemical composition of potable water varies considerably from one locality to another, consideration must be given to its chemical composition to enable adjustments to be made to the content of ions so that the concentrations in the diluted solution correspond to the intended use.

Attention has also to be paid to the possible presence of residues from water treatment (for example, chloramines) and volatile halogenated hydrocarbons.

For the surveillance of the quality of water for diluting concentrated haemodialysis solutions, the following methods may be used to determine the chemical composition and/or to detect the presence of possible contaminants together with suggested limits to be obtained.

CHARACTERS

Clear, colourless, liquid.

TESTS

Acidity or alkalinity

To 10 mL of the water to be examined, freshly boiled and cooled in a borosilicate glass flask, add 0.05 mL of *methyl red solution R*. The solution is not red. To 10 mL of the water to be examined add 0.1 mL of *bromothymol blue solution R1*. The solution is not blue.

Oxidisable substances

To 100 mL of the water to be examined add 10 mL of *dilute sulfuric acid R* and 0.1 mL of *0.02 M potassium permanganate* and boil for 5 min. The solution remains faintly pink.

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Total available chlorine

Maximum 0.1 ppm.

In a 125 mL test-tube (A), place successively 5 mL of *buffer solution pH 6.5 R*, 5 mL of *diethylphenylenediamine sulfate solution R* and 1 g of *potassium iodide R*. In a second 125 mL test-tube (B), place successively 5 mL of *buffer solution pH 6.5 R* and 5 mL of *diethylphenylenediamine sulfate solution R*. Add as simultaneously as possible to tube A 100 mL of the water to be examined and to tube B a reference solution prepared as follows: to 1 mL of a 10 mg/L solution of *potassium iodate R*, add 1 g of *potassium iodide R* and 1 mL of *dilute sulfuric acid R*; allow to stand for 1 min, add 1 mL of *dilute sodium hydroxide solution R* and dilute to 100 mL with *water R*. Any colour in the mixture obtained with the water to be examined is not more intense than that in the mixture obtained with the reference solution.

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dilute 1 mL of the water to be examined to 15 mL with *water R*.

Fluorides

Maximum 0.2 ppm.

Potentiometry (*2.2.36, Method I*): use as indicator electrode a fluoride-selective solid-membrane electrode and as reference electrode a silver-silver chloride electrode.

Test solution The water to be examined.

Reference solutions Dilute 2.0 mL, 4.0 mL and 10.0 mL of *fluoride standard solution (1 ppm F) R* respectively to 20.0 mL with *total-ionic-strength-adjustment buffer R1*.

Carry out the measurement of each solution.

Nitrates

Maximum 2 ppm.

Dilute 2 mL of the water to be examined to 100 mL with *nitrate-free water R*. Place 5 mL of the dilution in a test-tube immersed in iced water, add 0.4 mL of a 100 g/L solution of *potassium chloride R* and 0.1 mL of *diphenylamine solution R* and then, dropwise and with shaking, 5 mL of *sulfuric acid R*. Transfer the tube to a water-bath at 50 °C. Allow to stand for 15 min. Any blue colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using a mixture of 0.1 mL of *nitrate standard solution (2 ppm NO_3) R* and 4.9 mL of *nitrate-free water R*.

Sulfates (*2.4.13*)

Maximum 50 ppm.

Dilute 3 mL of the water to be examined to 15 mL with *distilled water R*.

Aluminium (*2.4.17*)

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Maximum 10 µg/L.

Prescribed solution To 400 mL of the water to be examined add 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Ammonium

Maximum 0.2 ppm.

To 20 mL of the water to be examined in a flat-bottomed and transparent tube, add 1 mL of *alkaline potassium tetraiodomercurate solution R*. Allow to stand for 5 min. The solution is not more intensely coloured than a standard prepared at the same time and in the same manner using a mixture of 4 mL of *ammonium standard solution (1 ppm NH_4) R* and 16 mL of *ammonium-free water R*. Examine the solutions along the vertical axis of the tube.

Calcium

Maximum 2 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution The water to be examined.

Reference solutions Prepare reference solutions (1 ppm to 5 ppm) using *calcium standard solution (400 ppm Ca) R*.

Source Calcium hollow-cathode lamp.

Wavelength 422.7 nm.

Atomisation device Oxidising air-acetylene flame.

Magnesium

Maximum 2 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 10 mL of the water to be examined to 100 mL with *distilled water R*.

Reference solutions Prepare reference solutions (0.1 ppm to 0.5 ppm) using *magnesium standard solution (100 ppm Mg) R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285.2 nm.

Atomisation device Oxidising air-acetylene flame.

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Mercury

Maximum 0.001 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Add 5 mL of *nitric acid R* per litre of the water to be examined. In a 50 mL borosilicate glass flask with a ground-glass-stopper, place 20 mL of the water to be examined and add 1 mL of *dilute nitric acid R* and shake. Add 0.3 mL of *bromine water R1*. Stopper the flask, shake and heat the stoppered flask at 45 °C for 4 h. Allow to cool. If the solution does not become yellow, add 0.3 mL of *bromine water R1* and re-heat at 45 °C for 4 h. Add 0.5 mL of a freshly prepared 10 g/L solution of *hydroxylamine hydrochloride R*. Shake. Allow to stand for 20 min.

Reference solutions Use freshly prepared reference solutions (0.0005 ppm to 0.002 ppm) obtained by diluting *mercury standard solution (1000 ppm Hg) R* with a 5 per cent *V/V* solution of *dilute nitric acid R* and treat as described for the test solution.

To a volume of solution suitable for the instrument to be used, add *stannous chloride solution R2* equal to 1/5 of this volume. Fit immediately the device for the entrainment of the mercury vapour. Wait 20 s and pass through the device a stream of *nitrogen R* as the carrier gas.

Source Mercury hollow-cathode tube or a discharge lamp.

Wavelength 253.7 nm.

Atomisation device Flameless system whereby the mercury can be entrained in the form of cold vapour.

Potassium

Maximum 2 ppm.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution (a) Dilute 50.0 mL of the water to be examined to 100 mL with *distilled water R*. Carry out a determination using this solution. If the potassium content is more than 0.75 mg/L, further dilute the water to be examined with *distilled water R*.

Test solution (b) Take 50.0 mL of the water to be examined or, if necessary, the water to be examined diluted as described in the preparation of test solution (a). Add 1.25 mL of *potassium standard solution (20 ppm K) R* and dilute to 100.0 mL with *distilled water R*.

Reference solutions Prepare reference solutions (0 ppm; 0.25 ppm; 0.50 ppm; 0.75 ppm; 1 ppm) using *potassium standard solution (20 ppm K) R*.

Wavelength 766.5 nm.

Calculate the potassium content of the water to be examined in parts per million from the expression:

$$\frac{p \times n_1 \times 0.5}{n_2 - n_1}$$

p = dilution factor used for the preparation of test solution (a);

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n_1 = measured value of test solution (a);

n_2 = measured value of test solution (b).

Sodium

Maximum 50 ppm.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution The water to be examined. If the sodium content is more than 10 mg/L, dilute with *distilled water R* to obtain a concentration suitable for the apparatus used.

Reference solutions Prepare reference solutions (0 ppm; 2.5 ppm; 5.0 ppm; 7.5 ppm; 10 ppm) using *sodium standard solution (200 ppm Na) R*.

Wavelength 589 nm.

Zinc

Maximum 0.1 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*): use sampling and analytical equipment free from zinc or not liable to yield zinc under the conditions of use.

Test solution The water to be examined.

Reference solutions Prepare reference solutions (0.05 ppm to 0.15 ppm) using *zinc standard solution (100 ppm Zn) R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Oxidising air-acetylene flame.

Heavy metals (*2.4.8*)

Maximum 0.1 ppm.

Heat 200 mL of the water to be examined in a glass evaporating dish on a water-bath until the volume is reduced to 20 mL. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Bacterial endotoxins (*2.6.14*)

Less than 0.25 IU/mL.

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This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Water for Injections

General Notices

(Ph. Eur. monograph 0169)

H_2O 18.02

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DEFINITION

Water for the preparation of medicines for parenteral administration when water is used as vehicle (water for injections in bulk) and for dissolving or diluting substances or preparations for parenteral administration (sterilised water for injections).

WATER FOR INJECTIONS IN BULK

PRODUCTION

Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water. It is produced either:

— by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets; or

— by a purification process that is equivalent to distillation. Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration, is suitable. Notice is given to the supervisory authority of the manufacturer before implementation.

For all methods of production, correct operation monitoring and maintenance of the system are essential. In order to ensure the appropriate quality of the water, validated procedures, in-process monitoring of the electrical conductivity, and regular monitoring of total organic carbon and microbial contamination are applied.

The first portion of water obtained when the system begins to function is discarded.

Water for injections in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Microbiological monitoring

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During production and subsequent storage, appropriate measures are taken to ensure that the microbial count is adequately controlled and monitored. Appropriate alert and action levels are set so as to detect adverse trends. Under normal conditions, an appropriate action level is a microbial count of 10 CFU per 100 mL when determined by filtration through a membrane with a nominal pore size not greater than 0.45 µm, using R2A agar, using at least 200 mL of water for injections in bulk and incubating at 30-35 °C for not less than 5 days. For aseptic processing, stricter alert levels may need to be applied.

R2A agar

Yeast extract	0.5 g
Proteose peptone	0.5 g
Casein hydrolysate	0.5 g
Glucose	0.5 g
Starch	0.5 g
Dipotassium hydrogen phosphate	0.3 g
Magnesium sulfate, anhydrous	0.024 g
Sodium pyruvate	0.3 g
Agar	15.0 g
Purified water	to 1000 mL

Adjust the pH so that after sterilisation it is 7.2 ± 0.2. Sterilise by heating in an autoclave at 121 °C for 15 min.

Growth promotion of R2A agar

— *Preparation of test strains*. Use standardised stable suspensions of test strains or prepare them as stated in Table 0169.-1. Seed lot culture maintenance techniques (seed-lot systems) are used so that the viable micro-organisms used for inoculation are not more than 5 passages removed from the original master seed-lot. Grow each of the bacterial strains separately as described in Table 0169.-1. Use buffered sodium chloride-peptone solution pH 7.0 or phosphate buffer solution pH 7.2 to make test suspensions. Use the suspensions within 2 h, or within 24 h if stored at 2-8 °C. As an alternative to preparing and then diluting a fresh suspension of vegetative cells of *Bacillus subtilis*, a stable spore suspension is prepared and then an appropriate volume of the spore suspension is used for test inoculation. The stable spore suspension may be maintained at 2-8 °C for a validated period of time.

— *Growth promotion*. Test each batch of ready-prepared medium and each batch of medium, prepared either from dehydrated medium or from the ingredients described. Inoculate plates of R2A agar separately with a small number (not more than 100 CFU) of the micro-organisms indicated in Table 0169.-1. Incubate under the conditions described in the table. Growth obtained must not differ by a factor greater than 2 from the calculated value for a standardised inoculum. For a freshly prepared inoculum, growth of the micro-organisms must be comparable to that obtained with a previously tested and approved batch of medium.

Table 0169.-1. – *Growth promotion of R2A agar*

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Micro-organism	Preparation of the test strain	Growth promotion
Pseudomonas aeruginosa such as: ATCC 9027 NCIMB 8626 CIP 82.118 NBRC 13275	Casein soyabean digest agar or casein soyabean digest broth 30-35 °C 18-24 h	R2A agar ≤ 100 CFU 30-35 °C ≤ 3 days
Bacillus subtilis such as: ATCC 6633 NCIMB 8054 CIP 52.62 NBRC 3134	Casein soyabean digest agar or casein soyabean digest broth 30-35 °C 18-24 h	R2A agar ≤ 100 CFU 30-35 °C ≤ 3 days

Total organic carbon (*2.2.44*)

Maximum 0.5 mg/L.

Conductivity

Determine the conductivity off-line or in-line under the following conditions.

EQUIPMENT

Conductivity cell:

— electrodes of a suitable material such as stainless steel;

— cell constant: the cell constant is generally certified by the supplier and is subsequently verified at suitable intervals using a certified reference solution with a conductivity less than 1500 $\mu S \cdot cm^{-1}$ or by comparison with a cell having a certified cell constant. The cell constant is confirmed if the value found is within 2 per cent of the certified value, otherwise re-calibration must be performed.

Conductometer Accuracy of 0.1 $\mu S \cdot cm^{-1}$ or better at the lowest range.

System calibration (conductivity cell and conductometer):

— against one or more suitable certified reference solutions;

— accuracy: within 3 per cent of the measured conductivity plus 0.1 $\mu S \cdot cm^{-1}$.

Conductometer calibration Calibration is carried out for each range of measurement to be used, after disconnection of the conductivity cell, using certified precision resistors or equivalent devices with an uncertainty not greater than 0.1 per cent of the certified value.

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If in-line conductivity cells cannot be dismantled, system calibration may be performed against a calibrated conductivity-measuring instrument with a conductivity cell placed close to the cell to be calibrated in the water flow.

Temperature measurement Tolerance ± 2 °C.

PROCEDURE

Stage 1

1. Measure the conductivity without temperature compensation, recording simultaneously the temperature. Temperature-compensated measurement may be performed after suitable validation.
2. Using Table 0169.-2, find the closest temperature value that is not greater than the measured temperature. The corresponding conductivity value is the limit at that temperature.
3. If the measured conductivity is not greater than the value in Table 0169.-2, the water to be examined meets the requirements of the test for conductivity. If the conductivity is higher than the value in Table 0169.-2, proceed with stage 2.

Table 0169.-2. – *Stage 1 Temperature and conductivity requirements (for non-temperature-compensated conductivity measurements)*

Temperature (°C)	Conductivity ($\mu S \cdot cm^{-1}$)
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5

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Temperature (°C)	Conductivity ($\mu S \cdot cm^{-1}$)
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

Stage 2

4. Transfer a sufficient amount of the water to be examined (100 mL or more) to a suitable container, and stir the test sample. Adjust the temperature, if necessary, and while maintaining it at 25 ± 1 °C, begin vigorously agitating the test sample while periodically observing the conductivity. When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than 0.1 $\mu S \cdot cm^{-1}$ per 5 min, note the conductivity.

5. If the conductivity is not greater than 2.1 $\mu S \cdot cm^{-1}$, the water to be examined meets the requirements of the test for conductivity. If the conductivity is greater than 2.1 $\mu S \cdot cm^{-1}$, proceed with stage 3.

Stage 3

6. Perform this test within approximately 5 min of the conductivity determination in step 5 under stage 2, while maintaining the sample temperature at 25 ± 1 °C. Add a freshly prepared saturated solution of *potassium chloride R* to the test sample (0.3 mL per 100 mL of the test sample), and determine the pH (*2.2.3*) to the nearest 0.1 pH unit.

7. Using Table 0169.-3, determine the conductivity limit at the measured pH value in step 6. If the measured conductivity in step 4 under stage 2 is not greater than the conductivity requirements for the pH determined, the water to be examined meets the requirements of the test for conductivity. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0-7.0, the water to be examined does not meet the requirements of the test for conductivity.

Table 0169.-3. – *Stage 3 pH and conductivity requirements (for atmosphere- and temperature-equilibrated samples)*

pH	Conductivity ($\mu S \cdot cm^{-1}$)
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3

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pH	Conductivity ($\mu S \cdot cm^{-1}$)
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

CHARACTERS

Appearance

Clear and colourless liquid.

TESTS

Nitrates

Maximum 0.2 ppm.

Place 5 mL in a test-tube immersed in iced water, add 0.4 mL of a 100 g/L solution of *potassium chloride R*, 0.1 mL of *diphenylamine solution R* and, dropwise with shaking, 5 mL of *nitrogen-free sulfuric acid R*. Transfer the tube to a water-bath at 50 °C. After 15 min, any

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blue colour in the solution is not more intense than that in a reference solution prepared at the same time in the same manner using a mixture of 4.5 mL of *nitrate-free water R* and 0.5 mL of *nitrate standard solution (2 ppm NO_3) R*.

Aluminium (*2.4.17*)

Maximum 10 ppb, if intended for use in the manufacture of dialysis solutions.

Prescribed solution To 400 mL of the water to be examined add 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *distilled water R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *distilled water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *distilled water R*.

Bacterial endotoxins (*2.6.14*)

Less than 0.25 IU/mL.

STERILISED WATER FOR INJECTIONS

DEFINITION

Water for injections in bulk that has been distributed into suitable containers, closed and sterilised by heat in conditions which ensure that the product still complies with the test for bacterial endotoxins. Sterilised water for injections is free from any added substances.

Examined in suitable conditions of visibility, it is clear and colourless.

Each container contains a sufficient quantity of water for injections to permit the nominal volume to be withdrawn.

TESTS

Conductivity

Maximum 25 $\mu S \cdot cm^{-1}$ for containers with a nominal volume of 10 mL or less; maximum 5 $\mu S \cdot cm^{-1}$ for containers with a nominal volume greater than 10 mL.

Use equipment and the calibration procedure as defined under Water for injections in bulk, maintaining the sample temperature at 25 ± 1 °C.

Oxidisable substances

For containers with a nominal volume less than 50 mL: heat 100 mL to boiling with 10 mL of *dilute sulfuric acid R*, add 0.4 mL of *0.02 M potassium permanganate* and boil for 5 min; the solution remains faintly pink.

For containers with a nominal volume equal to or greater than 50 mL: heat 100 mL to boiling with 10 mL of *dilute sulfuric acid R*, add 0.2 mL of *0.02 M potassium permanganate* and boil for 5 min; the solution remains faintly pink.

Aluminium (*2.4.17*)

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Maximum 10 ppb, if intended for use in the manufacture of dialysis solutions.

Prescribed solution To 400 mL of the water to be examined add 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *distilled water R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *distilled water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *distilled water R*.

Residue on evaporation

Maximum 4 mg (0.004 per cent) for containers with a nominal volume of 10 mL or less; maximum 3 mg (0.003 per cent) for containers with a nominal volume greater than 10 mL.

Evaporate 100 mL to dryness on a water-bath and dry in an oven at 100-105 °C.

Particulate contamination: sub-visible particles (*2.9.19*)

It complies with test A or test B, as appropriate.

Sterility (*2.6.1*)

It complies with the test for sterility.

Bacterial endotoxins (*2.6.14*)

Less than 0.25 IU/mL.

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Water for Preparation of Extracts

General Notices

(Ph. Eur. monograph 2249)

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DEFINITION

Water intended for the preparation of *Herbal drug extracts (0765)* complies with the sections Purified water in bulk or Purified water in containers in the monograph *Purified water (0008)*, or is water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC which is monitored according to the Production section described below.

PRODUCTION

When water intended for human consumption is used as water for preparation of extracts it is a clear, colourless liquid. It is stored (where necessary) and distributed under conditions designed to prevent growth of micro-organisms and to avoid other contamination.

For monitoring purposes, the following tests are carried out at regular intervals to demonstrate consistency in the quality of the water used for the preparation of extracts.

Conductivity (*2.2.38*)

Maximum 2500 $\mu S \cdot cm^{-1}$, measured at 20 °C.

Nitrate

Liquid chromatography (*2.2.29*).

Test solution The substance to be examined.

Reference solution Dissolve 0.163 g of *potassium nitrate R* and 0.149 g of *potassium bromide R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: anion-exchange resin R3.

Mobile phase Dissolve 0.265 g of *anhydrous sodium carbonate R* and 0.210 g of *sodium hydrogen carbonate R* in *water R* and dilute to 1000.0 mL with the same solvent.

Flow rate 1.2 mL/min.

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Detection Conductivity detector, using a self-regenerating anion suppressor.

Injection 25 µL.

Run time Twice the retention time of nitrate.

Relative retention With reference to nitrate (retention time = about 7 min): bromide = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to bromide and nitrate.

Limit:

— *nitrate*: maximum 50 ppm.

Microbiological monitoring

Appropriate measures are taken to ensure that the microbial count is adequately controlled and monitored. Appropriate alert and action levels are set so as to detect adverse trends.

Under normal conditions, an appropriate action level is a microbial count of 100 CFU/mL, determined by filtration through a membrane with a nominal pore size not greater than 0.45 µm, using casein soya bean digest agar and incubating at 30-35 °C for not less than 5 days.

The size of the sample is to be chosen in relation to the expected result.

Casein soya bean digest agar

Pancreatic digest of casein	15.0 g
Papaic digest of soya bean	5.0 g
Sodium chloride	5.0 g
Agar	15.0 g
Purified water	to 1000 mL

Adjust the pH so that after sterilisation it is 7.3 ± 0.2. Sterilise in an autoclave using a validated cycle.

Growth promotion of casein soya bean digest agar

— *Preparation of test strains*. Use standardised stable suspensions of test strains or prepare them as stated in Table 2249.-1. Seed lot culture maintenance techniques (seed-lot systems) are used so that the viable micro-organisms used for inoculation are not more than 5 passages removed from the original master seed-lot. Grow each of the bacterial strains separately as described in Table 2249.-1. Use buffered sodium chloride-peptone solution pH 7.0 or phosphate buffer solution pH 7.2 to make test suspensions. Use the suspensions within 2 h, or within 24 h if stored at 2-8 °C. As an alternative to preparing and then diluting a fresh suspension of vegetative cells of *Bacillus subtilis*, a stable spore suspension is prepared and then an appropriate volume of the spore suspension is used for test inoculation. The stable spore suspension may be maintained at 2-8 °C for a validated period of time.

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— *Growth promotion*. Test each batch of ready-prepared medium and each batch of medium, prepared either from dehydrated medium or from the ingredients described. Inoculate plates of casein soya bean digest agar separately with a small number (not more than 100 CFU) of the micro-organisms indicated in Table 2249.-1. Incubate under the conditions described in this table. Growth obtained must not differ by a factor greater than 2 from the calculated value for a standardised inoculum. For a freshly prepared inoculum, growth of the micro-organisms must be comparable to that obtained with a previously tested and approved batch of medium.

Table 2249.-1. – *Growth promotion of casein soya bean digest agar*

Micro-organism	**Preparation of the test strain**	**Growth promotion**
Pseudomonas aeruginosa such as: ATCC 9027 NCIMB 8626 CIP 82.118 NBRC 13275	Casein soya bean digest agar or casein soya bean digest broth 30-35 °C 18-24 h	Casein soya bean digest agar ≤ 100 CFU 30-35 °C ≤ 3 days
Bacillus subtilis such as: ATCC 6633 NCIMB 8054 CIP 52.62 NBRC 3134	Casein soya bean digest agar or casein soya bean digest broth 30-35 °C 18-24 h	Casein soya bean digest agar ≤ 100 CFU 30-35 °C ≤ 3 days

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Wheat Starch[1]

General Notices

(Ph. Eur. monograph 0359)

Action and use

Excipient.

When Starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch or, in tropical countries where these are not available, Tapioca Starch may be supplied or used.

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DEFINITION

Wheat starch is obtained from the caryopsis of *Triticum aestivum* L. (*T. vulgare* Vill.).

◊ PRODUCTION

The gluten content is monitored and stated on the label.◊

♦ CHARACTERS

Appearance

Very fine, white or almost white powder that creaks when pressed between the fingers.

Solubility

Practically insoluble in cold water and in ethanol (96 per cent).

Wheat starch does not contain starch granules of any other origin. It may contain a minute quantity, if any, of tissue fragments of the original plant.♦

IDENTIFICATION

A. Microscopic examination (*2.8.23*) using a 50 per cent *V/V* solution of *glycerol R*. It shows large and small granules, and, very rarely, intermediate sizes (Figure 0359.-1). The large granules, 10-60 µm in diameter, are discoid or, more rarely, reniform in surface view. The central hilum and striations are invisible or barely visible and the granules sometimes show cracks on the edges. In side view, the granules are elliptical and fusiform and the hilum appears as a slit along the main axis. The small granules, rounded or polyhedral, are 2-10 µm in diameter. Between orthogonally orientated polarising plates or prisms, the granules show a distinct black cross intersecting at the hilum.

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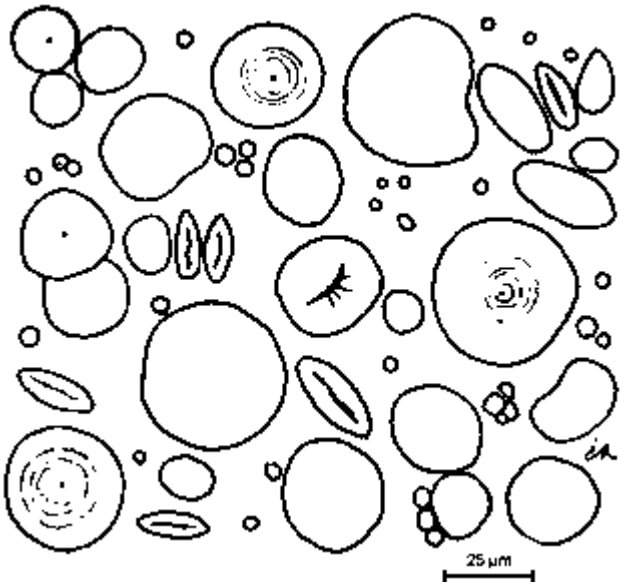

Figure 0359.-1. - *Illustration for identification test A of wheat starch*

B. Suspend 1 g in 50 mL of *water R*, boil for 1 min and cool. A thin, cloudy mucilage is formed.

C. To 1 mL of the mucilage obtained in identification test B add 0.05 mL of *iodine solution R1*. A dark blue colour is produced, which disappears on heating.

TESTS

pH (*2.2.3*)

4.5 to 7.0.

Shake 5.0 g with 25.0 mL of *carbon dioxide-free water R* for 60 s. Allow to stand for 15 min.

◊ Foreign matter

Examined under a microscope using a 50 per cent *V/V* solution of *glycerol R*, not more than traces of matter other than starch granules are present. No starch granules of any other origin are present.◊

Total protein

Maximum 0.3 per cent (corresponding to 0.048 per cent of nitrogen).

Determine the nitrogen content by sulfuric acid digestion as follows, and calculate the quantity of protein by multiplying by 6.25.

Carry out a blank determination by placing 4 g of a powdered mixture of 100 g of *dipotassium sulfate R*, 3 g of *copper sulfate pentahydrate R* and 3 g of *titanium dioxide R*, and 3 glass beads in a combustion flask. Wash any adhering particles from the neck of the flask with a fine jet of *water R*. Add 25 mL of *sulfuric acid R*, allowing it to run down the sides of the flask, and swirl to mix the contents. Close the mouth of the flask loosely, for example by means of a glass bulb with a short stem, to avoid excessive loss of sulfuric acid. Heat gradually at first, then increase the temperature until there is vigorous boiling with condensation of sulfuric acid in the neck of the flask; take precautions to prevent the upper part of the flask from becoming overheated. Continue heating until a clear solution is obtained and the inside wall of the flask is free from carbonaceous material. Cool, dissolve the solid material by cautiously adding 25 mL of *water R* to the

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mixture, cool again and place in a steam-distillation apparatus. Add a suitable volume of *strong sodium hydroxide solution R* to change the colour of the solution from bluish-green to brown or black, and distil immediately by passing steam through the mixture. Collect about 40 mL of distillate in 50.0 mL of *0.01 M hydrochloric acid*, adding enough *water R* if necessary to cover the tip of the condenser. Towards the end of the distillation, lower the receiver so that the tip of the condenser is above the surface of the acid and rinse the end of the condensing tube with a small quantity of *water R*. Take precautions to prevent any water on the outer surface of the condenser from reaching the contents of the receiver. Titrate the distillate with *0.025 M sodium hydroxide* (n_1 mL), using *methyl red mixed solution R* as indicator.

Repeat the test adding 3.0 g (m g) of the substance to be examined to the combustion flask, and using the same volume of *strong sodium hydroxide solution R*. Titrate the distillate as described for the blank determination with *0.025 M sodium hydroxide* (n_2 mL). Calculate the percentage content of nitrogen using the following expression:

$$\frac{0.03503\left(n_1 - n_2\right)}{m}$$

Oxidising substances (*2.5.30*)

Maximum 20 ppm, calculated as H_2O_2.

Sulfur dioxide (*2.5.29*)

Maximum 50 ppm.

Iron (*2.4.9*)

Maximum 10 ppm.

Shake 1.5 g with 15 mL of *dilute hydrochloric acid R*. Filter. The filtrate complies with the test.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 90 min.

Sulfated ash (*2.4.14*)

Maximum 0.6 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

◊ Absence of *Salmonella* (*2.6.13*).◊

◊ LABELLING

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The label states the gluten content.◊

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

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White Beeswax

General Notices

(Ph. Eur. monograph 0069)

Action and use

Excipient.

Ph Eur

DEFINITION

Wax obtained by bleaching yellow beeswax.

CHARACTERS

Appearance

White or yellowish-white pieces or plates, translucent when thin, with a fine-grained, matt and non-crystalline fracture; when warmed in the hand they become soft and malleable.

It has an odour similar to that of yellow beeswax, though fainter and never rancid. It is tasteless and does not stick to the teeth.

Solubility

Practically insoluble in water, partially soluble in hot ethanol (90 per cent *V/V*) and completely soluble in fatty and essential oils.

Relative density

About 0.960.

TESTS

Drop point (*2.2.17*)

61 °C to 66 °C.

Melt the beeswax by heating on a water-bath, pour onto a glass plate and allow to cool to a semi-solid mass. Fill the metal cup by inserting the wider end into the beeswax and repeating the procedure until beeswax extrudes from the narrow opening. Remove the excess with a spatula and insert the thermometer immediately. Remove the beeswax displaced. Allow to stand at room temperature for at least 12 h before determining the drop point.

Acid value

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17.0 to 24.0.

To 2.00 g (*m* g), in a 250 mL conical flask fitted with a reflux condenser, add 40 mL of *xylene R* and a few glass beads. Heat until the substance is dissolved. Add 20 mL of *ethanol (96 per cent) R* and 0.5 mL of *phenolphthalein solution R1* and titrate the hot solution with 0.5 M alcoholic potassium hydroxide until a red colour persists for at least 10 s (n_1 mL). Carry out a blank test (n_2 mL).

$$\text{Acid value} = \frac{28.05\left(n_1 - n_2\right)}{m}$$

Ester value (*2.5.2*)

70 to 80.

Saponification value

87 to 104.

To 2.00 g (*m* g), in a 250 mL conical flask fitted with a reflux condenser, add 30 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *xylene R* and a few glass beads. Heat until the substance is dissolved. Add 25.0 mL of 0.5 M alcoholic potassium hydroxide and heat under a reflux condenser for 3 h. Titrate the hot solution immediately with *0.5 M hydrochloric acid*, using 1 mL of *phenolphthalein solution R1* as indicator (n_1 mL). Reheat the solution to boiling several times during the course of the titration. Carry out a blank test (n_2 mL).

$$\text{Saponification value} = \frac{28.05\left(n_2 - n_1\right)}{m}$$

Ceresin, paraffins and certain other waxes

To 3.0 g, in a 100 mL round-bottomed flask, add 30 mL of a 40 g/L solution of *potassium hydroxide R* in *aldehyde-free alcohol R* and boil gently under a reflux condenser for 2 h. Remove the condenser and immediately insert a thermometer. Place the flask in a water-bath at 80 °C and allow to cool, swirling the solution continuously. No precipitate is formed until 65 °C, although the solution may be slightly opalescent. Beginning at 65 °C, the solution may become cloudy and precipitates may be formed. At 59 °C, the solution is cloudy.

Glycerol and other polyols

Maximum 0.5 per cent *m/m*, calculated as glycerol.

To 0.20 g add 10 mL of *alcoholic potassium hydroxide solution R* and heat on a water-bath under a reflux condenser for 30 min. Add 50 mL of *dilute sulfuric acid R*, cool and filter. Rinse the flask and the filter with *dilute sulfuric acid R*. Combine the filtrate and washings and dilute to 100.0 mL with *dilute sulfuric acid R*. Place 1.0 mL of the solution in a test-tube, add 0.5 mL of a 10.7 g/L solution of *sodium periodate R*, mix and allow to stand for 5 min. Add 1.0 mL of *decolorised fuchsin solution R* and mix. Any precipitate disappears. Place the tube in a beaker containing water at 40 °C. During cooling observe for 10-15 min. Any violet-blue colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 1.0 mL of a 10 mg/L solution of *glycerol R* in *dilute sulfuric acid R*.

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White Liniment

General Notices

White Cutaneous Emulsion

White Embrocation

DEFINITION

White Liniment is a *cutaneous emulsion*.

Oleic Acid	85 mL
Turpentine Oil	250 mL
Dilute Ammonia Solution	45 mL
Ammonium Chloride	12.5 g
Purified Water	625 mL

Extemporaneous preparation

The following directions apply.

Mix the Oleic Acid with the Turpentine Oil. Dilute the Dilute Ammonia Solution with 45 mL of the Purified Water, previously warmed, add to the oily solution and shake to form an emulsion. Separately dissolve the Ammonium Chloride in the remainder of the Purified Water, add to the emulsion and mix.

The liniment complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of volatile oil

24.5 to 27.5% v/w.

Refractive index

Of the oily liquid obtained in the Assay, 1.465 to 1.477, Appendix V E.

ASSAY

Acidify 100 g with 1M *sulfuric acid* using *methyl orange solution* as indicator, distil in steam and collect the distillate in a separating funnel; occasionally separate the aqueous portion of the distillate and return it to the flask. When all the volatile matter has been distilled, remove the aqueous portion of the distillate and measure the volume of the oily liquid.

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

White Soft Paraffin[1]

General Notices

White Petroleum Jelly

(Ph. Eur. monograph 1799)

Ph Eur

DEFINITION

Purified and wholly or nearly decolourised semi-solid mixture of hydrocarbons, obtained from petroleum. It may contain a suitable antioxidant.

◊ White soft paraffin described in this monograph is not suitable for oral use. ◊

♦ CHARACTERS

Appearance

White or almost white, translucent, soft unctuous mass, transparent in thin layers even after cooling to 0 °C.

Solubility

Practically insoluble in water, slightly soluble in methylene chloride, practically insoluble in ethanol (96 per cent) and in glycerol. ♦

IDENTIFICATION

First identification: A, B, D.

◊ *Second identification: A, C, D.* ◊

A. Drop point: between 35 °C and 70 °C; the value does not differ by more than 5 °C from the value stated on the label. Proceed as described in general method *2.2.17* with the following modifications: heat the substance to be examined at 100-105 °C for not more than 10 min, stirring to ensure uniformity. Warm the metal cup at 100-105 °C, remove it from the oven, place on a clean plate or ceramic tile and pour a sufficient quantity of the melted sample into the cup to fill it completely. Allow the filled cup to cool for 30 min on the plate or the ceramic tile at 25 ± 3 °C and place it in a water bath at 24-26 °C for a further 30-40 min. Level the surface of the sample with a single stroke of a knife or razor blade, avoiding compression of the sample. Determine the drop point using a starting temperature of at least 10 °C below the expected drop point and increasing the temperature at a rate of 1 °C/min.

B. Infrared absorption spectrophotometry (*2.2.24*).

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Preparation Spread a thin film of the substance to be examined.

Comparison *white soft paraffin CRS*, prepared in the same manner.

◊ C. Melt 2 g and when a homogeneous phase is obtained, add 2 mL of *water R* and 0.2 mL of *0.05 M iodine*. Shake. Allow to cool. The solid upper layer is violet-pink or brown. ◊

D. Appearance (see Tests).

TESTS

Appearance

Melt about 10 g on a water-bath and pour about 5 mL of the resulting liquid into a clear-glass, 15 mm × 150 mm test tube, maintaining the substance in a melted state: it is not more intensely coloured than 5 mL of a mixture of 1 volume of yellow primary solution and 9 volumes of a 10 g/L solution of *hydrochloric acid R* in a similar test tube (*2.2.2, Method II*). Compare the preparations in reflected light against a white background, holding the tubes directly against the background at such an angle that there is no interfering fluorescence.

Acidity or alkalinity

To 10 g add 20 mL of boiling *water R* and shake vigorously for 1 min. Allow to cool and decant. To 10 mL of the aqueous layer add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink or red.

UV absorbance limit for polycyclic aromatic hydrocarbons

Maximum 75 ppm (expressed as naphthalene equivalent).

Use reagents for ultraviolet absorption spectrophotometry. Dissolve 1.0 g in 50 mL of *hexane R* which has been previously shaken twice with 10 mL of *dimethyl sulfoxide R*. Transfer the solution to a 125 mL separating funnel with unlubricated ground-glass parts (stopper, stopcock). Add 20 mL of *dimethyl sulfoxide R*. Shake vigorously for 1 min and allow to stand until 2 clear layers are formed. Transfer the lower layer to a 2nd separating funnel. Repeat the extraction with a further 20 mL of *dimethyl sulfoxide R*. Shake the combined lower layers vigorously with 20 mL of *hexane R* for 1 min. Allow to stand until 2 clear layers are formed. Separate the lower layer and dilute to 50.0 mL with *dimethyl sulfoxide R*. Measure the absorbance (*2.2.25*) over the range 265 nm to 420 nm using a path length of 1 cm and the clear lower layer obtained by vigorously shaking 10 mL of *dimethyl sulfoxide R* with 25 mL of *hexane R* for 1 min as compensation liquid. Prepare a reference solution in *dimethyl sulfoxide R* containing 6.0 mg of *naphthalene R* per litre and measure the absorbance of the solution at the maximum at 278 nm using a path length of 1 cm and *dimethyl sulfoxide R* as compensation liquid. At no wavelength in the range 265 nm to 420 nm does the absorbance of the test solution exceed a quarter of that of the reference solution at 278 nm.

Sulfated ash (*2.4.14*)

Maximum 0.05 per cent, determined on 2.0 g.

♦ STORAGE

Protected from light. ♦

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♦ LABELLING

The label states the nominal drop point. ♦

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for white soft paraffin used as a basis in semi-solid preparations.

Consistency (*2.9.9*)

◊ 60 ◊ to 300.

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

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Wool Alcohols

General Notices

Wool Wax Alcohols

(Ph. Eur. monograph 0593)

Preparation

Wool Alcohols Ointment

Ph Eur

DEFINITION

Mixture of sterols and higher aliphatic alcohols from wool fat. A suitable antioxidant may be added.

Content

Minimum 30.0 per cent of cholesterol.

CHARACTERS

Appearance

Pale-yellow or brownish-yellow, brittle mass becoming plastic on heating.

Solubility

Practically insoluble in water, soluble in boiling anhydrous ethanol and in methylene chloride, slightly soluble in ethanol (90 per cent *V/V*).

IDENTIFICATION

Dissolve 50 mg in 5 mL of *methylene chloride R* and add 1 mL of *acetic anhydride R* and 0.1 mL of *sulfuric acid R*. Within a few seconds, a green colour develops.

TESTS

Appearance of solution

To 1.0 g add 10 mL of *light petroleum R1* and shake while warming in a water-bath. The substance dissolves completely. After cooling, the solution is clear (*2.2.1*).

Alkalinity

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Dissolve 2.0 g in 25 mL of hot *ethanol (90 per cent V/V) R* and add 0.5 mL of *phenolphthalein solution R1*. No red colour develops.

Melting point (*2.2.15*)

Minimum 56 °C.

Melt the substance to be examined by heating in a water-bath at a temperature which exceeds the expected melting point by not more than 10 °C; introduce the substance to be examined into the capillary tubes and allow to stand on ice for at least 2 h.

Water-absorption capacity

Place 0.6 g of the substance to be examined and 9.4 g of *white soft paraffin R* in a mortar and melt on a water-bath. Allow to cool and incorporate 20 mL of *water R*, added in portions. Within 24 h no water is released from the almost white, ointment-like emulsion.

Acid value (*2.5.1*)

Maximum 2.0.

If necessary, heat in a water-bath under a reflux condenser to dissolve the substance to be examined.

Hydroxyl value (*2.5.3, Method A*)

120 to 180.

Peroxide value (*2.5.5, Method A*)

Maximum 15.

Take from the substance to be examined wedge-shaped pieces whose base consists of part of the surface. Melt the pieces before carrying out the determination. Before adding 0.5 mL of *saturated potassium iodide solution R*, cool the solution obtained to room temperature.

Saponification value (*2.5.6*)

Maximum 12.0, determined on 10.00 g. Heat under reflux for 4 h.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 2.000 g by drying in an oven at 105 °C.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

ASSAY

Gas chromatography (*2.2.28*). *Homogenise the sample before use.*

Internal standard solution Dissolve 0.125 g of *pregnenolone isobutyrate CRS* in *heptane R* and dilute to 50.0 mL with the same solvent.

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Test solution Dissolve 75.0 mg of the substance to be examined in 10.0 mL of the internal standard solution and dilute to 25.0 mL with *heptane R*.

Reference solution Dissolve 25.0 mg of *cholesterol CRS* in 10.0 mL of the internal standard solution and dilute to 25.0 mL with *heptane R*.

Injection liner:

— *packing material*: quartz wool;

— *size*: *l* = 78.5 mm, Ø = 4.0 mm.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:50.

Temperature:

— *column*: 275 °C;

— *injection port*: 285 °C;

— *detector*: 300 °C.

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to pregnenolone isobutyrate (retention time = about 8 min): cholesterol = about 1.2.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to pregnenolone isobutyrate and cholesterol.

Calculate the percentage content of cholesterol in the substance to be examined taking into account the assigned content of *cholesterol CRS*.

STORAGE

In a well-filled container, protected from light.

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FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for wool alcohols used in water-emulsifying ointments and lipophilic creams.

Melting point

(see Tests).

Water-absorption capacity

(see Tests).

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Wool Alcohols Ointment

General Notices

DEFINITION

Wool Alcohols	60 g
Hard Paraffin	240 g
White Soft Paraffin or Yellow Soft Paraffin	100 g
Liquid Paraffin	600 g

In preparing Wool Alcohols Ointment, the proportions of Hard Paraffin, Soft Paraffin and Liquid Paraffin may be varied to produce Wool Alcohols Ointment having suitable properties.

When Wool Alcohols Ointment is used in a white ointment, it should be prepared with White Soft Paraffin; when used in a coloured ointment it should be prepared with Yellow Soft Paraffin.

Extemporaneous preparation

The following directions apply.

Melt together with the aid of gentle heat and stir until cold.

The ointment complies with the requirements stated under Topical Semi-solid Preparations.

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Wool Fat

General Notices

Anhydrous Lanolin

(Ph. Eur. monograph 0134)

Ph Eur

DEFINITION

Purified, anhydrous, waxy substance obtained from the wool of sheep (*Ovis aries*). A suitable antioxidant may be added.

CHARACTERS

Appearance

Yellow, unctuous substance. When melted, it is a clear or almost clear, yellow liquid. A solution in light petroleum is opalescent.

Solubility

Practically insoluble in water, slightly soluble in boiling anhydrous ethanol.

Characteristic odour.

IDENTIFICATION

A. In a test-tube, dissolve 0.5 g in 5 mL of *methylene chloride R* and add 1 mL of *acetic anhydride R* and 0.1 mL of *sulfuric acid R*. A green colour develops.

B. Dissolve 50 mg in 5 mL of *methylene chloride R*, add 5 mL of *sulfuric acid R* and shake. A red colour develops and an intense green fluorescence appears in the lower layer when examined in daylight, with illumination from behind the observer.

TESTS

Water-soluble acid or alkaline substances

Melt 5.0 g on a water-bath and shake vigorously for 2 min with 75 mL of *water R* previously heated to 90-95 °C. Allow to cool and filter through filter paper previously rinsed with *water R*. To 60 mL of the filtrate (which may not be clear) add 0.25 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.02 M hydrochloric acid* or 0.15 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Water-absorption capacity

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Place 10 g of molten wool fat in a mortar and allow to cool to room temperature. Weigh the mortar. Add *water R* in portions of 0.2-0.5 mL from a burette, stirring vigorously after each addition to incorporate the *water R*. Instead of a pestle, use a high-density polypropylene cylindrical rod (120 mm long and 10 mm in diameter, for example). The end-point is reached when visible droplets remain which cannot be incorporated. Weigh the mortar again and determine the amount of water absorbed by weight difference. Not less than 20 mL of *water R* is absorbed.

Acid value (*2.5.1*)

Maximum 1.0, determined on 5.0 g dissolved in 25 mL of the prescribed mixture of solvents.

Peroxide value (*2.5.5, Method A*)

Maximum 20.

Before adding 0.5 mL of *saturated potassium iodide solution R*, cool the solution obtained to room temperature.

Saponification value (*2.5.6*)

90 to 105, determined on 2.00 g while heating under reflux for 4 h.

Water-soluble oxidisable substances

To 10 mL of the filtrate obtained in the test for water-soluble acid or alkaline substances add 1 mL of *dilute sulfuric acid R* and 0.1 mL of *0.02 M potassium permanganate*. After 10 min, the solution is not completely decolourised.

Paraffins

Maximum 1.0 per cent.

The tap and cotton plugs used must be free from grease Prepare a column of anhydrous aluminium oxide 0.23 m long and 20 mm in diameter by adding a slurry of *anhydrous aluminium oxide R* and *light petroleum R1* to a glass tube fitted with a tap and containing *light petroleum R1* (before use, dehydrate the anhydrous aluminium oxide by heating it in an oven at 600 °C for 3 h). Allow to settle and reduce the depth of the layer of solvent above the column to about 40 mm. Dissolve 3.0 g of the substance to be examined in 50 mL of warm *light petroleum R1*, cool, pass the solution through the column at a flow rate of 3 mL/min and wash with 250 mL of *light petroleum R1*. Concentrate the combined eluate and washings to low bulk by distillation, evaporate to dryness on a water-bath and heat the residue at 105 °C for periods of 10 min until 2 successive weighings do not differ by more than 1 mg. The residue weighs a maximum of 30 mg.

Pesticide residues

Maximum 0.05 ppm for each organochlorine pesticide, 0.5 ppm for each other pesticide and 1 ppm for the sum of all the pesticides.

All glassware used is thoroughly washed using phosphate-free detergent as follows. The glassware is immersed in a bath of detergent solution (5 per cent in deionised water) and allowed to soak for 24 h. The detergent is washed off with copious amounts of acetone and hexane for pesticide analysis. It is important to keep glassware specifically for pesticide analyses, it must not be mixed up with glassware used for other applications. The glassware used must be free of chlorinated solvents, plastics and rubber materials, in particular phthalate plasticisers, oxygenated compounds and nitrogenated solvents such as acetonitrile. Use hexane, toluene and acetone for pesticide analysis. Use HPLC grade reagents for ethyl acetate, cyclohexane and water.

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The test consists of the isolation of pesticide residues by size-exclusion chromatography (2.2.30) followed by solid phase extraction and identification by gas chromatography coupled with an electron capture detector or a thermionic detector.

ISOLATION OF THE PESTICIDE RESIDUES

As detector, use a UV-visible spectrophotometer set at a wavelength of 254 nm to calibrate the chromatographic column for gel permeation.

Calibration is extremely important in gel permeation chromatography (GPC) to check that the pressure, solvent flow rate, solvent ratio, temperature and column conditions remain constant. The gel permeation column is to be calibrated at regular intervals using a standard mixture prepared as follows: into a 1000 mL volumetric flask, introduce 50.00 g of *maize oil R*, 0.20 g of *methoxychlor R* and 50.0 mg of *perylene R*. Dilute to 1000.0 mL with a mixture of equal volumes of *cyclohexane R* and *ethyl acetate R*.

To calibrate the column, set the mobile phase at a flow rate of 5 mL/min with a mixture of equal volumes of *cyclohexane R* and *ethyl acetate R*. Inject 5 mL of the standard mixture and record the resulting chromatogram. The retention times for the analytes must not vary by more than ± 5 per cent between calibrations. If the retention time shift is greater than ± 5 per cent, take corrective action. Excessive retention time shifts may be caused by:

— poor laboratory temperature control;

— the pump containing air; this can be verified by measuring the flow rate: collect 25 mL of column eluate in a volumetric flask and record the time (300 ± 5 s);

— a leak in the system.

Changes in pressure, in mobile phase flow rate or in column temperature conditions, as well as column contamination, can affect pesticide retention times and are to be monitored. If the flow rate or column pressure are outside desired bands the precolumn or column is to be replaced.

Test solution In a volumetric flask, dissolve 1 g of the substance to be examined, accurately weighed, in a mixture of 1 volume of *ethyl acetate R* and 7 volumes of *cyclohexane R*. Add 1 mL of an internal standard (2 ppm, either *isodrin R* or *ditalimphos R*) and dilute to 20 mL. *The internal standard solutions are used to establish that recoveries of the pesticides from the GPC purification stage, evaporation and solid phase extraction stage are at acceptable levels. Recovery levels of the internal standard solutions from the wool fat are determined by comparing the peak areas of the wool fat extracts with peak areas of solutions of the internal standards.*

Precolumn:

— *size*: *l* = 0.075 m, Ø = 21.2 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm).

Gel permeation column:

— *size*: *l* = 0.3 m, Ø = 21.2 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm).

Mobile phase *ethyl acetate R*, *cyclohexane R* (10:70 *V/V*).

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Flow rate 5 mL/min.

Detection Spectrophotometer at 254 nm.

Inject 5 mL of the test solution. Discard the first 95 mL (19 min) of eluate containing the substance to be examined. Collect the next 155 mL of eluate (31 min) containing any pesticide residues in an evaporating vessel.

Place the 155 mL of the eluate collected from the gel permeation chromatography column into an evaporating vessel. Place this vessel in an autoevaporator setting the water-bath temperature at 45 °C and the nitrogen pressure at 55 kPa. Evaporate the eluate down to 0.5 mL.

To prepare the solid phase extraction cartridges take some *magnesium silicate for pesticide residue analysis R* and heat it in a muffle furnace at 700 °C for 4 h to remove moisture and polychlorinated biphenyls. Subsequently allow the magnesium silicate to cool for 2 h and transfer it directly to an oven at 100-105 °C, and allow to stand for 30 min. Transfer the magnesium silicate to a stoppered glass jar and allow to equilibrate for 48 h. This material may be used for up to 2 weeks. After that period the magnesium silicate is to be reactivated, by heating at 600 °C for 2 h in a muffle furnace. Remove the magnesium silicate from the furnace, cool and store in a stoppered glass jar. The magnesium silicate is deactivated by adding 1 per cent of *water R*. After the water has been added, shake the magnesium silicate intermittently over 15 min just prior to use. The deactivated magnesium silicate is suitable for use for up to 1 week. It is essential that only deactivated magnesium silicate is used.

Take a 6 mL empty solid phase extraction cartridge and weigh into the cartridge 1 g of the deactivated magnesium silicate.

At this stage the GPC fraction still contains about 10 per cent of the substance to be examined, so further clean-up is necessary. A separate isolation procedure is carried out a) for organochlorine and synthetic pyrethroid pesticides and b) for organophosphorus pesticides. Place a preconditioned solid phase extraction cartridge containing l g of deactivated *magnesium silicate for pesticide residue analysis R* onto a vacuum manifold.

Condition the cartridge by adding 10 mL of *toluene R* and allowing the solvent to elute through the cartridge. Place the 0.5 mL of the solvent fraction from the evaporating vessel on the preconditioned cartridge. Elute the pesticide fractions from the cartridges using 20 mL of either of the 2 different solvent systems shown below:

a) for determination of the organochlorine and synthetic pyrethroid pesticides: *toluene R*; a very small amount of the substance to be examined is co-eluted;

b) for determination of the organophosphorus pesticides: a mixture of 2 volumes of *acetone R* and 98 volumes of *toluene R*; this solvent system is used to elute all the pesticides including the more polar organophosphorus pesticides; unfortunately, some of the substance to be examined is co-eluted with this solvent system, which can interfere with the electron capture detector.

Collect the eluate from the extraction cartridges in 25 mL glass vials. Quantitatively transfer the eluate to an evaporating vessel, washing the vial with 3 quantities, each of 10 mL, of *hexane R*.

Place the evaporating vessel on the autoevaporator and evaporate the solid phase extraction fractions down to 0.5 mL. The water-bath temperature is set at 45 °C and the nitrogen pressure is 55 kPa.

Examine the residues by gas chromatography (*2.2.28*) using electron capture and thermionic detectors as described below.

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Recovery Calculate the recovery correction factor (R_{cf}) of the internal standards (*ditalimphos R* or *isodrin R*) added to the test solution using the following expression:

$$\frac{A_2}{A_1} \times 100$$

A_1 = peak area of an internal standard 1 ppm in solution;

A_2 = peak area of internal standard extracted from the test solution.

5 mL of the 20 mL test solution containing 1 mL of 2 ppm internal standard concentrated to 0.5 mL is equivalent to 1 ppm of the internal standard in the solution.

If the recovery of the internal standards falls outside the range of 70 per cent to 110 per cent the test is not valid.

Reference solutions Prepare reference solutions of pesticides using the pesticides standards at a concentration of 0.5 ppm (see composition of reference solutions A to D in Table 0134.-1). Commercially available pesticides may be purchased. The individual standards have a concentration of 10 ppm.

Table 0134.-1. – *Composition of the reference solutions*

Reference solution A (0.5 ppm or 0.5 mg/L) (organochlorine and synthetic pyrethroid pesticides)	**Reference solution B (0.5 ppm or 0.5 mg/L) (organochlorine and synthetic pyrethroid pesticides)**
Cyhalothrin R	*Aldrin R*
Cypermethrin R	*o,p'-DDT R*
o,p'-DDE R	*o,p'-DDD R*
p,p'-DDE R	*p,p'-DDD R*
p,p'-DDT R	*Dieldrin R*
Deltamethrin R	*α-Endosulfan R*
Endrin R	*β-Endosulfan R*
Heptachlor R	*Fenvalerate R*
Heptachlor epoxide R	*α-Hexachlorocyclohexane R*
Hexachlorobenzene R	*β-Hexachlorocyclohexane R*
Lindane R	*δ-Hexachlorocyclohexane R*
Tecnazene R	*Methoxychlor R*
	Permethrin R

Reference solution C (0.5 ppm or 0.5 mg/L) (organophosphorus	**Reference solution D (0.5 ppm or 0.5 mg/L) (organophosphorus**

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Reference solution A (0.5 ppm or 0.5 mg/L) (organochlorine and synthetic pyrethroid pesticides)	Reference solution B (0.5 ppm or 0.5 mg/L) (organochlorine and synthetic pyrethroid pesticides)
Bromophos-ethyl R	*Bromophos R*
Carbophenothion R	*Chlorpyriphos R*
Chlorfenvinphos R	*Chlorpyriphos-methyl R*
Diazinon R	*Coumaphos R*
Dichlofenthion R	*Phosalone R*
Ethion R	*Pirimiphos-ethyl R*
Fenchlorphos R	*Tetrachlorvinphos R*
Malathion R	
Propetamphos R	

Reference solution E (electron capture detector calibration mixture)	Reference solution F (thermionic detector calibration mixture)
Aldrin R (0.01 mg/L)	*Chlorfenvinphos R* (0.05 mg/L)
Cypermethrin R (0.1 mg/L)	*Diazinon R* (0.05 mg/L)
o,p'-DDD R (0.01 mg/L)	*Ethion R* (0.05 mg/L)
Deltamethrin R (0.1 mg/L)	*Fenchlorphos R* (0.05 mg/L)
Endrin R (0.01 mg/L)	*Propetamphos R* (0.05 mg/L)
β-Hexachlorocyclohexane R (0.01 mg/L)	

Reference solution G (internal standard organo-phosphorus pesticide)	Reference solution H (internal standard organo-chlorine pesticide)
Ditalimphos R (2 ppm or 2.0 mg/L)	*Isodrin R* (2 ppm or 2.0 mg/L)
Ditalimphos R (1 ppm or 1.0 mg/L)	*Isodrin R* (1 ppm or 1.0 mg/L)

At the same time prepare solutions of pesticides equivalent to the limit of detection of the method (see recommended compositions in Table 0134.-1). These reference solutions are used to optimise the electron capture detector and thermionic detector to achieve the detection limits of the method (reference solutions E and F).

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To prepare the reference solutions at the different concentrations use a calibrated pipette and volumetric flasks. To prepare the internal standard solutions G and H use a four-place analytical balance, pipette and volumetric flasks.

IDENTIFICATION AND QUANTIFICATION OF THE PESTICIDE RESIDUES

To identify any pesticide residues compare the chromatograms obtained with chromatograms obtained with reference solutions A to D.

The identity of the pesticides can be confirmed by spiking samples or overlaying chromatograms using an integration package on a computer. The interpretation of pesticides in trace residue analyses is extremely complex. The detectors, particularly the electron capture detector, are prone to interference, both from the substance to be examined itself, and from solvents, reagents and apparatus used in the extraction. These peaks can easily be misinterpreted or quoted as a false positive. Confirmation of pesticides can be achieved by running samples and standards on different capillary columns (see chromatographic systems A or B described below). The peaks can be identified by using the information in Table 0134.-2.

A knowledge of the different responses the pesticides have with the 2 detectors is useful in identification of unknown peaks.

Table 0134.-2. – *Elution order of the pesticides on chromatographic systems A and B*

Chromatographic system A	**Chromatographic system B**
Tecnazene	Tecnazene
α-Hexachlorocyclohexane	Hexachlorobenzene
Hexachlorobenzene	α-Hexachlorocyclohexane
β-Hexachlorocyclohexane	Diazinon
Lindane	Lindane
Propetamphos	Propetamphos
δ-Hexachlorocyclohexane	Heptachlor
Diazinon	Dichlofenthion
Dichlofenthion	Aldrin
Chlorpyriphos-methyl	Chlorpyriphos-methyl
Heptachlor	Fenchlorphos
Fenchlorphos	β-Hexachlorocyclohexane
Aldrin	δ-Hexachlorocyclohexane
Malathion	Pirimiphos-ethyl
Chlorpyriphos	Chlorpyriphos
Bromophos	Bromophos
Pirimiphos-ethyl	Malathion
Heptachlor epoxide	Heptachlor epoxide
Chlorfenvinphos (*E*)	*o,p'*-DDE
Chlorfenvinphos (*Z*)	Chlorfenvinphos (*E*)
Bromophos-ethyl	α-Endosulfan
o,p'-DDE	Chlorfenvinphos (*Z*)
α-Endosulfan	Bromophos-ethyl

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Chromatographic system A	Chromatographic system B
Tetrachlorvinphos	*p,p′*-DDE
Dieldrin	Dieldrin
p,p′-DDE	Tetrachlorvinphos
o,p′-DDT	*o,p′*-DDT
Endrin	Endrin
β-Endosulfan	*o,p′*-DDD
o,p′-DDD	*p,p′*-DDD
p,p′-DDD	β-Endosulfan
Ethion	Ethion
Carbophenothion	*p,p′*-DDT
p,p′-DDT	Carbophenothion
Methoxychlor	Methoxychlor
Phosalone	Cyhalothrin
Cyhalothrin (2 isomers)	*cis*-Permethrin
cis-Permethrin	Phosalone
trans-Permethrin	*trans*-Permethrin
Coumaphos	Cypermethrin (4 isomers)
Cypermethrin (4 isomers)	Coumaphos
Fenvalerate (2 isomers)	Fenvalerate (2 isomers)
Deltamethrin	Deltamethrin

Once the pesticides have been identified, calculate the content of each pesticide using the following expression:

$$C_P = \frac{P_P \times D \times C_e}{P_e} \times \frac{100}{R_{cf}}$$

C_p = concentration of identified pesticide (ppm);

P_p = peak area of the individual pesticide in the test sample obtained;

C_e = concentration of the individual pesticide in the external standard (ppm);

P_e = peak area of the individual pesticide in the external standard;

D = dilution factor;

R_{cf} = recovery correction factor.

The dilution factor (D) can be defined as follows:

$$\frac{V_1}{m \times \frac{V_2}{V_3}}$$

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V_1 = volume of sample obtained after the 2nd evaporation stage;

m = sample weight;

V_2 = GPC injection volume;

V_3 = sample volumetric flask volume.

Chromatographic system A:

Precolumn:

— *material*: deactivated silica;

— *size*: *l* = 4.5 m, Ø = 0.53 mm.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.25 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 25 cm/s.

Pressure 180 kPa.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	75
	1 - 5	75 → 175
	5 - 30	175 → 275
	30 - 40	275 → 285
	40 - 55	285
Injection port		300
Detector		350

Detection Electron capture or thermionic specific detector.

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Injection 2 µL.

Chromatographic system B Which may be used for confirmation analysis:

Precolumn:

— *material*: deactivated silica;

— *size*: *l* = 4.5 m, Ø = 0.53 mm.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.25 mm;

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 25 cm/s.

Pressure 180 kPa.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	75
	1 - 5	75 → 175
	5 - 30	175 → 275
	30 - 40	275 → 285
	40 - 55	285
Injection port		300
Detector		350

Detection Electron capture or thermionic specific detector.

Injection 2 µL.

Chlorides

Maximum 150 ppm.

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Boil 1.0 g with 20 mL of *ethanol (90 per cent V/V) R* in a round-bottomed flask fitted with a reflux condenser for 5 min. Cool, add 40 mL of *water R* and 0.5 mL of *nitric acid R* and filter. To the filtrate add 0.15 mL of a 10 g/L solution of *silver nitrate R* in *ethanol (90 per cent V/V) R*. Allow to stand for 5 min protected from light. Any opalescence in the solution is not more intense than that in a standard prepared at the same time by adding 0.15 mL of a 10 g/L solution of *silver nitrate R* in *ethanol (90 per cent V/V) R* to a mixture of 0.2 mL of *0.02 M hydrochloric acid*, 20 mL of *ethanol (90 per cent V/V) R*, 40 mL of *water R* and 0.5 mL of *nitric acid R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (*2.4.14*)

Maximum 0.15 per cent.

Ignite 5.0 g and use the residue to determine the sulfated ash.

STORAGE

At a temperature not exceeding 25 °C.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for wool fat used in water-emulsifying ointments and lipophilic creams.

Water-absorption capacity

(see Tests).

Drop point (*2.2.17, Method A*)

To fill the metal cup, melt the wool fat on a water-bath, cool to about 50 °C, pour into the cup and allow to stand at 15-20 °C for 24 h. The drop point is typically 38 °C to 44 °C.

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Xanthan Gum

General Notices

(Ph. Eur. monograph 1277)

11138-66-2

Action and use

Excipient.

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DEFINITION

High-molecular-mass anionic polysaccharide produced by fermentation of carbohydrates with *Xanthomonas campestris*. It consists of a principal chain of β(1→4)-linked D-glucose units with trisaccharide side chains, on alternating anhydroglucose units, consisting of 1 glucuronic acid unit included between 2 mannose units. Most of the terminal units contain a pyruvate moiety and the mannose unit adjacent to the principal chain may be acetylated at C-6.

Xanthan gum has a relative molecular mass of approximately 1×10^6. It exists as the sodium, potassium or calcium salt.

Content

Minimum 1.5 per cent of pyruvate acetal groups ($C_3H_3O_2$; M_r 71.1) (dried substance).

CHARACTERS

Appearance

White or yellowish-white, free-flowing powder.

Solubility

Soluble in water giving a highly viscous solution, practically insoluble in organic solvents.

IDENTIFICATION

A. In a flask, suspend 1 g in 15 mL of *0.1 M hydrochloric acid*. Close the flask with a fermentation bulb containing *barium hydroxide solution R* and heat carefully for 5 min. The barium hydroxide solution shows a white turbidity.

B. To 300 mL of *water R*, previously heated to 80 °C and stirred rapidly with a mechanical stirrer in a 400 mL beaker, add, at the point of maximum agitation, a dry blend of 1.5 g of *carob bean gum R* and 1.5 g of the substance to be examined. Stir until the mixture forms a solution, and then continue stirring for 30 min or longer. Do not allow the water temperature to drop below 60 °C during stirring. Discontinue

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stirring and allow the mixture to stand for at least 2 h. A firm rubbery gel forms after the temperature drops below 40 °C but no such gel forms in a 1 per cent control solution of the sample prepared in the same manner but omitting the carob bean gum.

TESTS

pH (2.2.3)

6.0 to 8.0 for a 10.0 g/L solution in *carbon dioxide-free water R*.

2-Propanol

Gas chromatography (2.2.28).

Internal standard solution Dilute 0.50 g of *2-methyl-2-propanol R* to 500 mL with *water R*.

Test solution To 200 mL of *water R* in a 1000 mL round-bottomed flask, add 5.0 g of the substance to be examined and 1 mL of a 10 g/L emulsion of *dimeticone R* in *liquid paraffin R*, stopper the flask and shake for 1 h. Distil about 90.0 mL, mix the distillate with 4.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Reference solution Dilute a suitable quantity of *2-propanol R*, accurately weighed, with *water R* to obtain a solution having a known concentration of 2-propanol of about 1 mg/mL. To 4.0 mL of this solution add 4.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Column:

— *size*: *l* = 1.8 m, Ø = 4.0 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (149-177 µm).

Carrier gas *helium for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 165 °C;

— *injection port and detector*: 200 °C.

Detection Flame ionisation.

Injection 5 µL.

Relative retention With reference to 2-propanol: 2-methyl-2-propanol = about 1.5.

Limit:

— *2-propanol*: maximum 750 ppm.

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Loss on drying (2.2.32)

Maximum 15.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2.5 h.

Total ash (2.4.16)

6.5 per cent to 16.0 per cent.

ASSAY

Test solution Dissolve a quantity of the substance to be examined corresponding to 120.0 mg of the dried substance in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution Dissolve 45.0 mg of *pyruvic acid R* in *water R* and dilute to 500.0 mL with the same solvent.

Place 10.0 mL of the test solution in a 50 mL round-bottomed flask, add 20.0 mL of *0.1 M hydrochloric acid* and weigh. Boil on a water-bath under a reflux condenser for 3 h. Weigh and adjust to the initial mass with *water R*. In a separating funnel mix 2.0 mL of the solution with 1.0 mL of *dinitrophenylhydrazine-hydrochloric solution R*. Allow to stand for 5 min and add 5.0 mL of *ethyl acetate R*. Shake and allow the solids to settle. Collect the upper layer and shake with 3 quantities, each of 5.0 mL, of *sodium carbonate solution R*. Combine the aqueous layers and dilute to 50.0 mL with *sodium carbonate solution R*. Mix. Treat 10.0 mL of the reference solution at the same time and in the same manner as for the test solution.

Immediately measure the absorbance (2.2.25) of the 2 solutions at 375 nm, using *sodium carbonate solution R* as the compensation liquid.

The absorbance of the test solution is not less than that of the reference solution, which corresponds to a content of pyruvoyl groups of not less than 1.5 per cent.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for xanthan gum used as viscosity-increasing agent.

Viscosity

(2.2.10): typically minimum 600 mPa·s.

Add 3.0 g (dried substance) within 45-90 s into 250 mL of a 12 g/L solution of *potassium chloride R* in a 500 mL beaker stirring with a low-pitch propeller-type stirrer rotating at 800 r/min. When adding the substance take care that agglomerates are destroyed. Add an additional

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quantity of 44 mL of *water R*, to rinse any adhering residue from the walls of the beaker. Stir the preparation at 800 r/min for 2 h whilst maintaining the temperature at 24 ± 1 °C. Determine the viscosity within 15 min at 24 ± 1 °C using a rotating viscosimeter set at 60 r/min and equipped with a rotating spindle 1.78 mm high and 12.60 mm in diameter which is attached to a shaft 3.2 mm in diameter. The distance from the top of the cylinder to the lower tip of the shaft should be 25.60 mm and the immersion depth 50.0 mm.

The following characteristics may be relevant for xanthan gum used as matrix former in prolonged-release tablets.

Viscosity

See test above.

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

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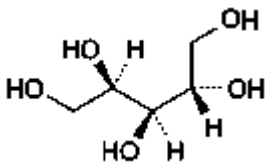
Xylitol

General Notices

(Ph. Eur. monograph 1381)



$C_5H_{12}O_5$ 152.1 *87-99-0*

Action and use

Sweetening agent.

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DEFINITION

Meso-xylitol.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

Very soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 92 °C to 96 °C.

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B. Infrared absorption spectrophotometry (2.2.24).

Preparation Mulls in liquid paraffin R.

Comparison xylitol CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in water R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of xylitol CRS in water R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 25 mg of mannitol R and 25 mg of xylitol R in water R and dilute to 10 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase water R, ethyl acetate R, propanol R (10:20:70 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with 4-aminobenzoic acid solution R, dry in a current of cold air until the acetone is removed, then heat at 100 °C for 15 min; allow to cool, spray with a 2 g/L solution of sodium periodate R, dry in a current of cold air, then heat at 100 °C for 15 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension IV (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, Method II).

Dissolve 2.5 g in water R and dilute to 50.0 mL with the same solvent.

Conductivity (2.2.38)

Maximum 20 µS·cm^{-1}.

Dissolve 20.0 g in carbon dioxide-free water R prepared from distilled water R and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

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Reducing sugars

Maximum 0.2 per cent, calculated as glucose equivalent.

Dissolve 5.0 g in 6 mL of *water R* with the aid of gentle heat. Cool and add 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and 94 volumes of *water R* and, when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Not less than 12.8 mL of *0.05 M sodium thiosulfate* is required.

Related substances

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 5 mg of *erythritol R* in *water R* and dilute to 25.0 mL with the same solvent.

Test solution (a) Dissolve 5.000 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *water R*.

Reference solution (a) Dissolve 5.0 mg each of *L-arabinitol CRS* (impurity A), *galactitol CRS* (impurity B), *mannitol CRS* (impurity C) and *sorbitol CRS* (impurity D) in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dissolve 50.0 mg of xylitol CRS in *water R* and dilute to 10.0 mL with the same solvent.

Pipette 1.0 mL of test solutions (a) and (b) and reference solutions (a) and (b) into 4 separate 100 mL round-bottomed flasks. Add 1.0 mL of the internal standard solution to each of the flasks containing test solution (a) or reference solution (a), and 5.0 mL of the internal standard solution to each of the flasks containing test solution (b) or reference solution (b). Evaporate each mixture to dryness in a water-bath at 60 °C by suitable means. Dissolve each dry residue in 1 mL of *anhydrous pyridine R*, add 1 mL of *acetic anhydride R* to each flask and boil each solution under reflux for 1 h to complete acetylation.

Column:

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (0.25 µm).

Carrier gas *nitrogen R*.

Flow rate 1 mL/min.

Split ratio 1:50 to 1:100.

Temperature:

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	Time (min)	Temperature (°C)
Column	0 - 1	170
	1 - 6	170 → 230
	6 - 30	230
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL of test solution (a) and reference solution (a) (solutions obtained after derivatisation).

Relative retention With reference to xylitol (retention time = about 15 min): internal standard = about 0.6; impurity A = about 0.9; impurity C = about 1.4; impurity B = about 1.45; impurity D = about 1.5.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities B and D.

Calculate the percentage content of each related substance in the substance to be examined using the following expression:

$$100 \times \frac{m_s}{m_u} \times \frac{R_u}{R_s}$$

m_s = mass of the particular component in 1 mL of reference solution (a), in milligrams;

m_u = mass of the substance to be examined in 1 mL of test solution (a), in milligrams;

R_s = ratio of the area of the peak due to the particular derivatised component to the area of the peak due to the derivatised internal standard in the chromatogram obtained with reference solution (a);

R_u = ratio of the area of the peak due to the particular derivatised component to the area of the peak due to the derivatised internal standard in the chromatogram obtained with test solution (a).

The sum of the percentage contents of the related substances in the chromatogram obtained with test solution (a) is not greater than 2.0 per cent. Disregard any peak with an area corresponding to a percentage content of 0.05 per cent or less.

Lead (*2.4.10*)

Maximum 0.5 ppm.

Dissolve the substance to be examined in 150.0 mL of the prescribed mixture of solvents.

Nickel (*2.4.15*)

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Maximum 1 ppm.

Dissolve the substance to be examined in 150.0 mL of the prescribed mixture of solvents.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g.

Bacterial endotoxins (*2.6.14*)

Less than 4 IU/g if the concentration is less than 100 g/L of xylitol and less than 2.5 IU/g if the concentration is 100 g/L or more of xylitol, when intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Gas chromatography (*2.2.28*) as described in the test for related substances with the following modifications.

Injection 1 µL of test solution (b) and reference solution (b) (solutions obtained after derivatisation).

Calculate the percentage content of $C_5H_{12}O_5$ using the following expression:

$$T \times \frac{m_t}{m_v} \times \frac{R_v}{R_t}$$

T	=	declared percentage content of xylitol CRS;
m_t	=	mass of xylitol CRS in 1 mL of reference solution (b), in milligrams;
m_v	=	mass of the substance to be examined in 1 mL of test solution (b), in milligrams;
R_t	=	ratio of the area of the peak due to derivatised xylitol to the area of the peak due to the derivatised internal standard in the chromatogram obtained with reference solution (b);
R_v	=	ratio of the area of the peak due to derivatised xylitol to the area of the peak due to the derivatised internal standard in the chromatogram obtained with test solution (b).

LABELLING

The label states:

— where applicable, the maximum concentration of bacterial endotoxins;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

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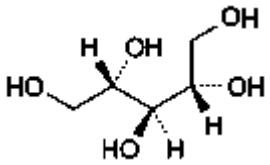
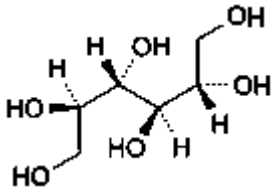
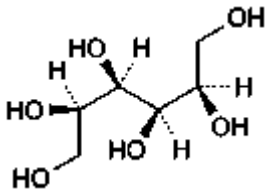


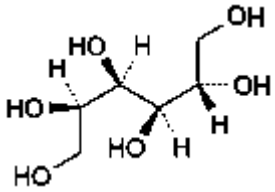
A. L-arabinitol,



B. *meso*-galactitol,



C. D-mannitol,



D. D-glucitol (D-sorbitol).

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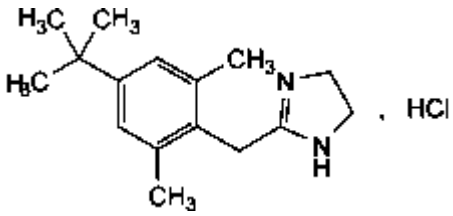
Xylometazoline Hydrochloride

General Notices

(Ph. Eur. monograph 1162)



$C_{16}H_{25}ClN_2$ 280.8 *1218-35-5*

Action and use

Alpha-adrenoceptor agonist.

Preparation

Xylometazoline Nasal Drops

Ph Eur

DEFINITION

2-[4-(1,1-Dimethylethyl)-2,6-dimethylbenzyl]-4,5-dihydro-1*H*-imidazole hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, in ethanol (96 per cent) and in methanol.

IDENTIFICATION

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First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *xylometazoline hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 20 mg of *xylometazoline hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methanol R* (5:100 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Chlorine treatment At the bottom of a chromatographic tank place a beaker containing a mixture of 1 volume of *hydrochloric acid R1*, 1 volume of *water R* and 2 volumes of a 15 g/L solution of *potassium permanganate R*. Close the tank and allow to stand for 15 min. Place the dried plate in the tank and reclose the tank. Leave the plate in contact with the chlorine vapour for 5 min. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed and an area of the coating below the points of application does not give a blue colour with a drop of *potassium iodide and starch solution R*.

Detection Spray with *potassium iodide and starch solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve about 0.5 mg in 1 mL of *methanol R*. Add 0.5 mL of a freshly prepared 50 g/L solution of *sodium nitroprusside R* and 0.5 mL of a 20 g/L solution of *sodium hydroxide R*. Allow to stand for 10 min and add 1 mL of an 80 g/L solution of *sodium hydrogen carbonate R*. A violet colour develops.

D. Dissolve 0.2 g in 1 mL of *water R*, add 2.5 mL of *ethanol (96 per cent) R* and 2 mL of *1 M sodium hydroxide*. Mix thoroughly and examine in ultraviolet light at 365 nm. The solution shows no fluorescence or at most the same fluorescence as a blank solution prepared in the same manner. The identification is not valid unless a solution prepared in the same manner using *naphazoline hydrochloride CRS* instead of the substance to be examined shows a distinct bluish fluorescence.

E. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

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The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 2.5 g in water R and dilute to 50.0 mL with the same solvent.

Acidity or alkalinity

Dissolve 0.25 g in carbon dioxide-free water R and dilute to 25 mL with the same solvent. Add 0.1 mL of methyl red solution R and 0.1 mL of 0.01 M hydrochloric acid. The solution is red. Not more than 0.2 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in water R and dilute to 50.0 mL with the same solvent. Allow to stand for 1 h before injection.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with water R. Dilute 2.0 mL of this solution to 100.0 mL with water R.

Reference solution (b) Dissolve 5.0 mg of xylometazoline impurity A CRS and 5 mg of the substance to be examined in water R and dilute to 50.0 mL with the same solvent. Dilute 10.0 mL of this solution to 50.0 mL with water R.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 50.0 mL with water R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R (5 µm).

Mobile phase:

— *mobile phase A*: 1.36 g/L solution of potassium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	70	30
5 - 20	70 → 15	30 → 85
20 - 35	15	85

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

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Injection 10 µL.

Relative retention With reference to xylometazoline (retention time = about 7.2 min): impurity A = about 0.79.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity A and xylometazoline.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 25 mL of *anhydrous acetic acid R* and add 10 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 28.08 mg of $C_{16}H_{25}ClN_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F.*

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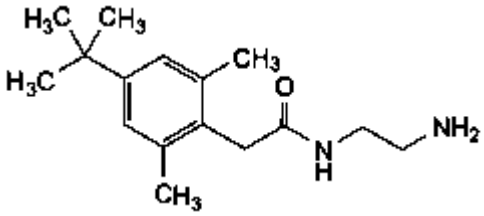
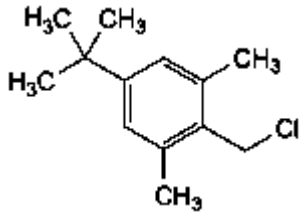
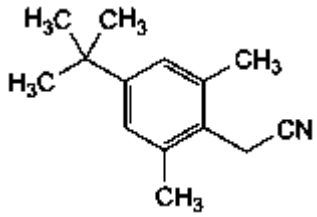


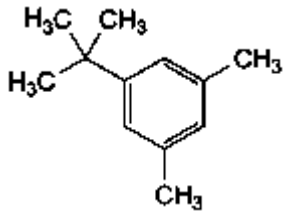
A. *N*-(2-aminoethyl)-2-[4-(1,1-dimethylethyl)-2,6-dimethylphenyl]acetamide,



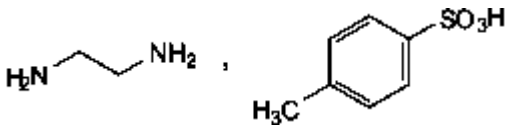
B. 2-(chloromethyl)-5-(1,1-dimethylethyl)-1,3-dimethylbenzene,



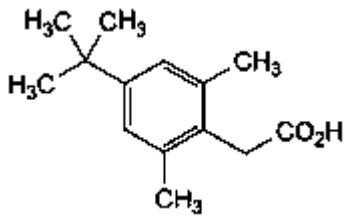
C. [4-(1,1-dimethylethyl)-2,6-dimethylphenyl]acetonitrile,



D. 1-(1,1-dimethylethyl)-3,5-dimethylbenzene,



E. ethane-1,2-diamine mono(4-methylbenzenesulfonate),



F. [4-(1,1-dimethylethyl)-2,6-dimethylphenyl]acetic acid.

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Xylometazoline Nasal Drops

General Notices

Action and use

Alpha-adrenoceptor agonist.

DEFINITION

Xylometazoline Nasal Drops are a solution of Xylometazoline Hydrochloride in Purified Water.

The nasal drops comply with the requirements stated under Nasal Preparations and with the following requirements.

Content of xylometazoline hydrochloride, $C_{16}H_{24}N_2$,HCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a volume of the nasal drops containing 50 mg of Xylometazoline Hydrochloride add 5 mL of 1M *sodium hydroxide*, extract with 10 mL of *dichloromethane IR*, evaporate to dryness and dissolve the residue in 0.5 mL of *dichloromethane IR*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of xylometazoline (*RS 362*).

B. To a volume containing 0.5 mg of Xylometazoline Hydrochloride add 0.2 mL of a 5% w/v solution of *sodium nitroprusside* and 0.1 mL of 5M *sodium hydroxide* and allow to stand for 10 minutes. Add 1 mL of a 10% w/v solution of *sodium hydrogen carbonate*. A violet colour is produced.

TESTS

Acidity

pH, 5.6 to 6.6, Appendix V L.

N-(2-Aminoethyl)-4-*tert*-butyl-2,6-xylylacetamide

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* HF_{254} as the coating substance and a mixture of 200 volumes of *methanol* and 3 volumes of 13.5M *ammonia* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) add a volume of the nasal drops containing 10 mg of Xylometazoline Hydrochloride to 30 mL of *water*, add 5 mL of 5M *sodium hydroxide*, mix, extract with three 20 mL quantities of *dichloromethane*, evaporate the combined extracts to dryness and dissolve the residue in 1 mL of *dichloromethane*. Solution (2) contains 0.03% w/v of *xylometazoline impurity A EPCRS* in *dichloromethane*. After removal of the plate, allow it to dry in air and spray with a solution prepared by dissolving 0.3 g of *ninhydrin* in a mixture of 100 mL of *butan-1-ol* and 3 mL of *glacial acetic acid*. Heat at 100° for 10 minutes, allow to cool, and spray with *dilute potassium iodobismuthate*

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solution. Any spot corresponding to xylometazoline impurity A [*N*-(2-aminoethyl)-4-*tert*-butyl-2,6-xylylacetamide] in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

To a volume of the nasal drops containing 10 mg of Xylometazoline Hydrochloride add 5 mL of *water*, 10 mL of *2M hydrochloric acid* and 10 mL of *dichloromethane* and shake for 1 minute. Discard the dichloromethane layer and repeat the extraction with two further 10 mL quantities of *dichloromethane*. Add to the aqueous extract 10 mL of 5M *sodium hydroxide* and 10 mL of *dichloromethane*, shake for 1 minute and allow to separate. Filter the dichloromethane extract through glass wool and repeat the extraction with four further 10 mL quantities of *dichloromethane*. Evaporate the combined dichloromethane extracts almost to dryness on a water bath, removing the final traces of solvent in a current of air, and dissolve the residue in 10 mL of 0.01M *hydrochloric acid*. To 2 mL of this solution add 3 mL of *water*, 2.5 mL of 1M *sodium hydroxide* and 2.5 mL of a 5% w/v solution of *sodium nitroprusside*, mix and allow to stand protected from light for 10 minutes. Add 10 mL of a freshly prepared 8.3% w/v solution of *sodium hydrogen carbonate*, dilute to 100 mL with *water*, allow to stand protected from light for 10 minutes and measure the *absorbance* of the resulting solution at the maximum at 560 nm, Appendix II B, using in the reference cell a solution prepared by treating 5 mL of *water* and 2.5 mL of 1M *sodium hydroxide* in the same manner, beginning at the words ‘and 2.5 mL of a 5% w/v solution of *sodium nitroprusside* ...’. Repeat the operation using a 0.1% w/v solution of *xylometazoline hydrochloride BPCRS*, diluted if necessary with *water*, in place of the nasal drops. Calculate the content of $C_{16}H_{24}N_2$,HCl in the nasal drops from the absorbances obtained using the declared content of $C_{16}H_{24}N_2$,HCl in *xylometazoline hydrochloride BPCRS*.

STORAGE

Xylometazoline Nasal Drops should be protected from light.

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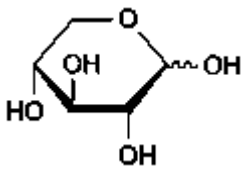
Xylose

General Notices

(Ph. Eur. monograph 1278)



$C_5H_{10}O_5$ 150.1 *58-86-6*

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DEFINITION

D-Xylopyranose.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless needles.

Solubility

Freely soluble in water, soluble in hot ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *xylose CRS*.

B. Thin-layer chromatography (2.2.27).

Solvent mixture *water R*, *methanol R* (2:3 *V/V*).

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Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *xylose CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *fructose R*, 10 mg of *glucose R* and 10 mg of *xylose R* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *methanol R*, *anhydrous acetic acid R*, *ethylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately since a slight excess of water produces cloudiness.

Application 2 µL; thoroughly dry the points of application.

Development Over a path of 15 cm.

Drying In a current of warm air.

Detection Spray with a 5 g/L solution of *thymol R* in a mixture of 5 volumes of *sulfuric acid R* and 95 volumes of *ethanol (96 per cent) R*. Heat in an oven at 130 °C for 10 min.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.1 g in 10 mL of *water R*. Add 3 mL of *cupri-tartaric solution R* and heat. An orange or red precipitate is formed.

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 50 mL of solution S add 0.3 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*)

+ 18.5 to + 19.5 (dried substance).

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Dissolve 10.0 g in 80 mL of *water R*, add 1 mL of *dilute ammonia R2* and dilute to 100.0 mL with *water R*. Allow to stand for 30 min.

Chlorides (*2.4.4*)

Maximum 330 ppm.

Dilute 1.5 mL of solution S to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C at a pressure not exceeding 0.7 kPa.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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Yellow Beeswax

General Notices

(Ph. Eur. monograph 0070)

Action and use

Excipient.

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DEFINITION

Wax obtained by melting the walls of the honeycomb made by the honey-bee, *Apis mellifera* L., with hot water and removing foreign matter.

CHARACTERS

Appearance

Yellow or light brown pieces or plates with a fine-grained, matt and non-crystalline fracture; when warmed in the hand they become soft and malleable.

It has a faint odour, characteristic of honey. It is tasteless and does not stick to the teeth.

Solubility

Practically insoluble in water, partially soluble in hot ethanol (90 per cent *V/V*) and completely soluble in fatty and essential oils.

Relative density

About 0.960.

TESTS

Drop point (*2.2.17*)

61 °C to 66 °C.

Melt the beeswax by heating on a water-bath, pour onto a glass plate and allow to cool to a semi-solid mass. Fill the metal cup by inserting the wider end into the beeswax and repeating the procedure until beeswax extrudes from the narrow opening. Remove the excess with a spatula and insert the thermometer immediately. Remove the beeswax displaced. Allow to stand at room temperature for at least 12 h before determining the drop point.

Acid value

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17.0 to 22.0.

To 2.00 g (*m* g), in a 250 mL conical flask fitted with a reflux condenser, add 40 mL of *xylene R* and a few glass beads. Heat until the substance is dissolved. Add 20 mL of *ethanol (96 per cent) R* and 0.5 mL of *phenolphthalein solution R1* and titrate the hot solution with 0.5 M alcoholic potassium hydroxide until a red colour persists for at least 10 s (n_1 mL). Carry out a blank test (n_2 mL).

$$\text{Acid value} = \frac{28.05\left(n_1 - n_2\right)}{m}$$

Ester value (*2.5.2*)

70 to 80.

Saponification value

87 to 102.

To 2.00 g (*m* g), in a 250 mL conical flask fitted with a reflux condenser, add 30 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *xylene R* and a few glass beads. Heat until the substance is dissolved. Add 25.0 mL of 0.5 M alcoholic potassium hydroxide and heat under a reflux condenser for 3 h. Titrate the hot solution immediately with *0.5 M hydrochloric acid*, using 1 mL of *phenolphthalein solution R1* as indicator (n_1 mL). Reheat the solution to boiling several times during the course of the titration. Carry out a blank test (n_2 mL).

$$\text{Saponification value} = \frac{28.05\left(n_2 - n_1\right)}{m}$$

Ceresin, paraffins and certain other waxes

To 3.0 g, in a 100 mL round-bottomed flask, add 30 mL of a 40 g/L solution of *potassium hydroxide R* in *aldehyde-free alcohol R* and boil gently under a reflux condenser for 2 h. Remove the condenser and immediately insert a thermometer. Place the flask in a water-bath at 80 °C and allow to cool, swirling the solution continuously. No precipitate is formed until 65 °C, although the solution may be slightly opalescent. Beginning at 65 °C, the solution may become cloudy and precipitates may be formed. At 59 °C, the solution is cloudy.

Glycerol and other polyols

Maximum 0.5 per cent *m/m*, calculated as glycerol.

To 0.20 g add 10 mL of *alcoholic potassium hydroxide solution R* and heat on a water-bath under a reflux condenser for 30 min. Add 50 mL of *dilute sulfuric acid R*, cool and filter. Rinse the flask and the filter with *dilute sulfuric acid R*. Combine the filtrate and washings and dilute to 100.0 mL with *dilute sulfuric acid R*. Place 1.0 mL of the solution in a test-tube, add 0.5 mL of a 10.7 g/L solution of *sodium periodate R*, mix and allow to stand for 5 min. Add 1.0 mL of *decolorised fuchsin solution R* and mix. Any precipitate disappears. Place the tube in a beaker containing water at 40 °C. During cooling observe for 10-15 min. Any violet-blue colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 1.0 mL of a 10 mg/L solution of *glycerol R* in *dilute sulfuric acid R*.

Ph Eur

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This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Yellow Soft Paraffin[1]

General Notices

Yellow Petroleum Jelly

(Ph. Eur. monograph 1554)

Action and use

Excipient.

Ph Eur

DEFINITION

Purified semi-solid mixture of hydrocarbons, obtained from petroleum. It may contain a suitable antioxidant. ◊ Yellow soft paraffin described in this monograph is not suitable for oral use. ◊

♦ CHARACTERS

Appearance

Yellowish or light amber, unctuous mass, slightly fluorescent in daylight even when melted, transparent in thin layers.

Solubility

Practically insoluble in water, slightly soluble in methylene chloride, practically insoluble in ethanol (96 per cent) and in glycerol. ♦

IDENTIFICATION

First identification: A, B, D.

◊ *Second identification: A, C, D.* ◊

A. Drop point: between 35 °C and 70 °C; the value does not differ by more than 5 °C from the value stated on the label. Proceed as described in general method *2.2.17* with the following modifications: heat the substance to be examined at 100-105 °C for not more than 10 min, stirring to ensure uniformity. Warm the metal cup at 100-105 °C, remove it from the oven, place on a clean plate or ceramic tile and pour a sufficient quantity of the melted sample into the cup to fill it completely. Allow the filled cup to cool for 30 min on the plate or ceramic tile at 25 ± 3 °C and place it in a water-bath at 24-26 °C for a further 30-40 min. Level the surface of the sample with a single stroke of a

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knife or razor blade, avoiding compression of the sample. Determine the drop point using a starting temperature of at least 10 °C below the expected drop point and increasing the temperature at a rate of 1 °C/min.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Spread a thin film of the substance to be examined.

Comparison *yellow soft paraffin CRS*, prepared in the same manner.

◊ C. Melt 2 g and when a homogeneous phase is obtained, add 2 mL of *water R* and 0.2 mL of *0.05 M iodine*. Shake. Allow to cool. The solid upper layer is violet-pink or brown. ◊

D. Appearance (see Tests).

TESTS

Appearance

Melt about 10 g on a water-bath and pour about 5 mL of the resulting liquid into a clear-glass, 15 mm × 150 mm test tube, maintaining the substance in a melted state: it is more intensely coloured than 5 mL of a mixture of 1 volume of yellow primary solution and 9 volumes of a 10 g/L solution of *hydrochloric acid R* in a similar test tube and it is not more intensely coloured than a mixture of 3.8 mL of yellow primary solution and 1.2 mL of red primary solution in a similar test tube (*2.2.2, Method II*). Compare the preparations in reflected light against a white background, holding the tubes directly against the background at such an angle that there is no interfering fluorescence.

Acidity or alkalinity

To 10 g add 20 mL of boiling *water R* and shake vigorously for 1 min. Allow to cool and decant. To 10 mL of the aqueous layer add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink or red.

UV absorbance limit for polycyclic aromatic hydrocarbons

Maximum 75 ppm (expressed as naphthalene equivalent).

Use reagents for ultraviolet absorption spectrophotometry. Dissolve 1.0 g in 50 mL of *hexane R* which has been previously shaken twice with 10 mL of *dimethyl sulfoxide R*. Transfer the solution to a 125 mL separating funnel with unlubricated ground-glass parts (stopper, stopcock). Add 20 mL of *dimethyl sulfoxide R*. Shake vigorously for 1 min and allow to stand until 2 clear layers are formed. Transfer the lower layer to a 2nd separating funnel. Repeat the extraction with a further 20 mL of *dimethyl sulfoxide R*. Shake the combined lower layers vigorously with 20 mL of *hexane R* for 1 min. Allow to stand until 2 clear layers are formed. Separate the lower layer and dilute to 50.0 mL with *dimethyl sulfoxide R*. Measure the absorbance (*2.2.25*) between 265 nm and 420 nm using a path length of 1 cm and using the clear lower layer obtained by vigorously shaking 10 mL of *dimethyl sulfoxide R* with 25 mL of *hexane R* for 1 min as compensation liquid. Prepare a reference solution in *dimethyl sulfoxide R* containing 6.0 mg of *naphthalene R* per litre and measure the absorbance of the solution at the maximum at 278 nm using a path length of 1 cm and *dimethyl sulfoxide R* as the compensation liquid. At no wavelength in the range of 265 nm to 420 nm does the absorbance of the test solution exceed a quarter of that of the reference solution at 278 nm.

Sulfated ash (*2.4.14*)

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Maximum 0.05 per cent, determined on 2.0 g.

♦ STORAGE

Protected from light. ♦

♦ LABELLING

The label states the nominal drop point. ♦

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for yellow soft paraffin used as a basis in semi-solid preparations.

Consistency (*2.9.9*)

100 to 300.

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1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

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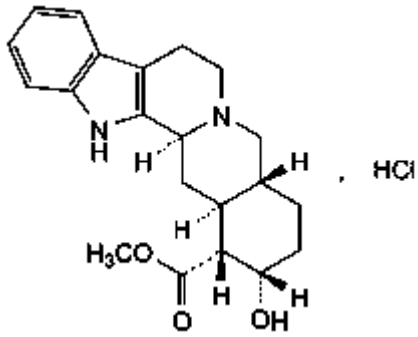
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Yohimbine Hydrochloride

General Notices

(Ph. Eur. monograph 2172)



$C_{21}H_{27}ClN_2O_3$ 390.9 *65-19-0*

Action and use

Alpha2-adrenoceptor antagonist.

Ph Eur

DEFINITION

Methyl 17α-hydroxyyohimban-16α-carboxylate hydrochloride.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *yohimbine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.500 g in *carbon dioxide-free water R* with heating, allow to cool to room temperature and dilute to 50.0 mL with the same solvent.

pH (2.2.3)

3.5 to 5.5 for solution S.

Specific optical rotation (2.2.7)

+ 101.0 to + 105.0 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from light.*

Test solution Dissolve 10.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *yohimbine for system suitability CRS* (containing impurities A, F and G) in *methanol R* and dilute to 25 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with *methanol R*.

Reference solution (d) Dissolve 5.0 mg of *yohimbine hydrochloride CRS* in *methanol R* and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (4 µm);

— *temperature*: 40 °C.

Mobile phase Mix 50 mL of a 9.08 g/L solution of *potassium dihydrogen phosphate R*, 100 mL of an 11.88 g/L solution of *disodium hydrogen phosphate dihydrate R*, 285 mL of *acetonitrile for chromatography R*, 4.0 g of *sodium laurilsulfate R* and 355 mL of *water for chromatography R*.

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 229 nm.

Injection 10 µL of the test solution and of reference solutions (a) (b) and (c).

Run time 3 times the retention time of yohimbine.

Identification of impurities Use the chromatogram supplied with *yohimbine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, F and G.

Relative retention With reference to yohimbine (retention time = about 7 min): impurity F = about 0.65; impurity G = about 0.70; impurity A = about 0.75.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.3, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A; minimum 1.3, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

Limits:

— *sum of impurities A and G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity F*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.4 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (d).

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Calculate the percentage content of $C_{21}H_{27}ClN_2O_3$ taking into account the assigned content of *yohimbine hydrochloride CRS*.

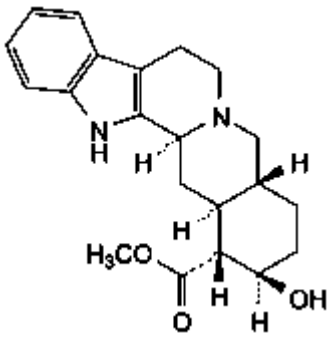
STORAGE

In an airtight container, protected from light.

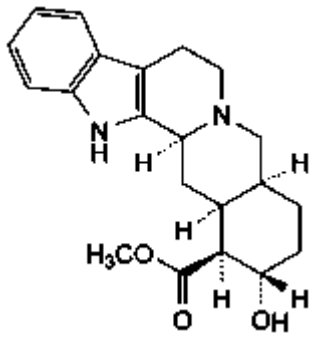
IMPURITIES

Specified impurities *A, F, G*.

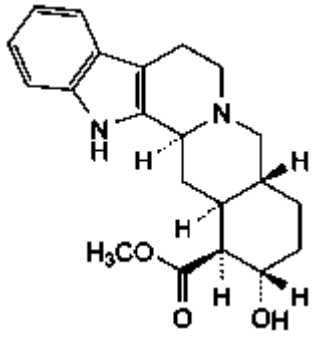
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E*.



A. methyl 17β-hydroxyyohimban-16α-carboxylate (β-yohimbine),



B. methyl 17α-hydroxy-20α-yohimban-16β-carboxylate (α-yohimbine),



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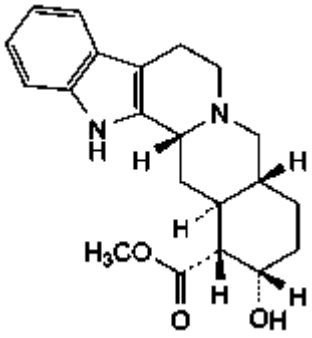
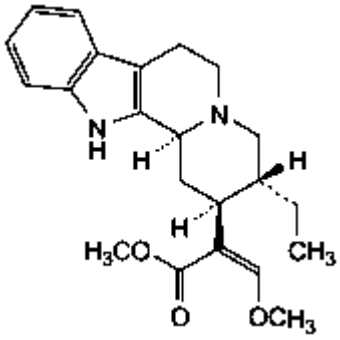
C. methyl 17α-hydroxyyohimban-16β-carboxylate (corynantheine),



D. methyl 17α-hydroxy-3β-yohimban-16α-carboxylate (pseudo-yohimbine),



E. methyl (2*Z*)-2-[(2*S*,3*R*,12b*S*)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl]-3-methoxyprop-2-enoate,

F. unknown structure,

G. unknown structure.

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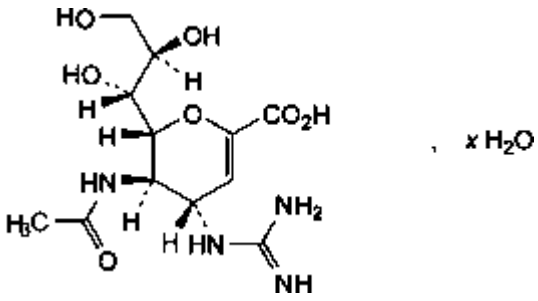
Zanamivir Hydrate

General Notices

(Ph. Eur. monograph 2611)



$C_{12}H_{20}N_4O_7,xH_2O$ 332.3 (anhydrous substance) *551942-41-7*

Action and use

Neuraminidase inhibitor; treatment and prophylaxis of influenza.

Preparation

Zanamivir Inhalation Powder, pre-metered

Ph Eur

DEFINITION

(2*R*,3*R*,4*S*)-3-Acetamido-4-carbamimidamido-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid hydrate.

Content

97.0 per cent to 102.0 per cent (dried substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

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IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *zanamivir hydrate CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 36.0 to + 38.5 (dried substance).

Dissolve 0.250 g in 25.0 mL of *water R*; sonicate until dissolution is complete.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 23.0 mg of the substance to be examined in 20 mL of *water R* and dilute to 50.0 mL with *acetonitrile R1*.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 23.0 mg of *zanamivir for assay CRS* in 20 mL of *water R* and dilute to 50.0 mL with *acetonitrile R1*. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *zanamivir for system suitability CRS* (containing impurities A, B, C and E) in 6 mL of *water R* and dilute to 10 mL with *acetonitrile R1*.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 3.0 mg of *zanamivir impurity F CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (e) Dilute 1.0 mL of reference solution (d) to 100.0 mL with the mobile phase. Dilute 3.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amino alkyl vinyl polymer for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase 0.7 g/L solution of *sulfuric acid R* previously adjusted to pH 5.5 with *dilute ammonia R3*, *acetonitrile R1* (40:60 *V/V*).

Flow rate 1.5 mL/min.

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Detection Spectrophotometer at 234 nm.

Preconditioning of the column Prior to first use, rinse with a 0.7 g/L solution of *ammonium sulfate R* at 1.5 mL/min at 30 °C for about 1 h; prior to each use, rinse with the mobile phase for at least 8 h.

Injection 20 µL of test solution (a) and reference solutions (b), (c) and (e).

Run time 3 times the retention time of zanamivir.

Identification of impurities Use the chromatogram supplied with *zanamivir for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and E; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity F.

Relative retention With reference to zanamivir (retention time = about 9 min): impurity F = about 0.3; impurity B = about 0.6; impurity C = about 0.75; impurity E = about 0.8; impurity A = about 2.6.

System suitability:

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (e);

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— for impurity F, use the concentration of impurity F in reference solution (e);

— for impurities other than F, use the concentration of zanamivir hydrate in reference solution (c).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity B*: maximum 0.3 per cent;

— *impurity C*: maximum 0.2 per cent;

— *impurity F*: maximum 0.01 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.2 per cent;

— *reporting threshold*: 0.05 per cent, except for impurity F.

Loss on drying (*2.2.32*)

4.0 per cent to 9.0 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C.

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Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{12}H_{20}N_4O_7$ taking into account the assigned content of *zanamivir for assay CRS*.

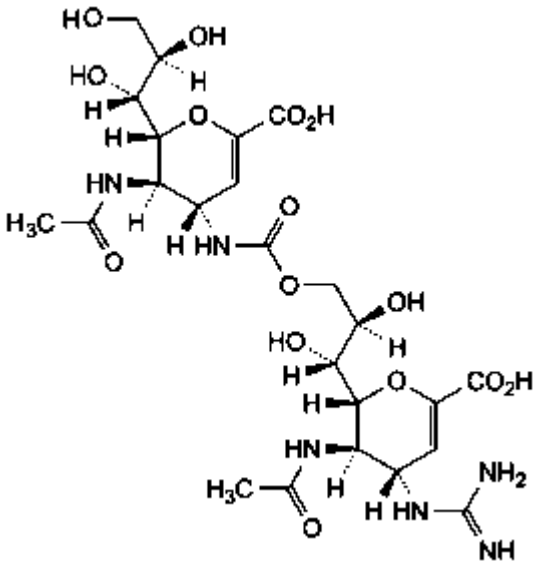
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B, C, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, H.*



A. (2*R*,3*R*,4*S*)-3-acetamido-2-[(1*R*,2*R*)-3-[[[(2*R*,3*R*,4*S*)-3-acetamido-6-carboxy-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-4-yl]carbamoyl]oxy]-1,2-dihydroxypropyl]-4-carbamimidamido-3,4-dihydro-2*H*-pyran-6-carboxylic acid,

B. unknown structure,

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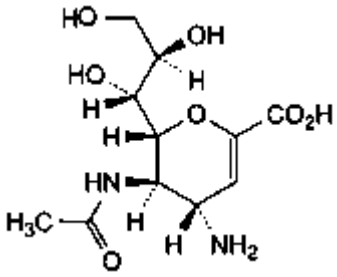
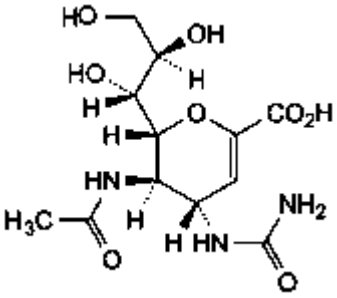
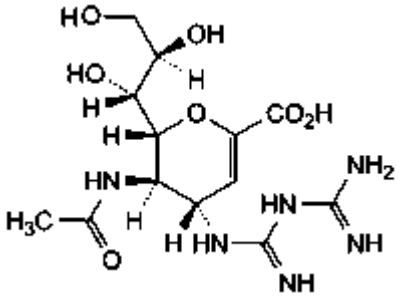


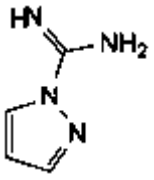
C. (2*R*,3*R*,4*S*)-3-acetamido-4-amino-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid,



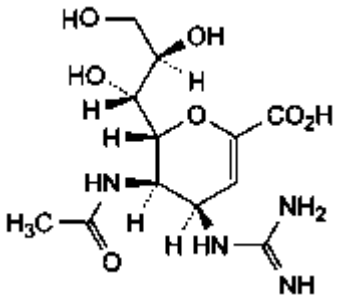
D. (2*R*,3*R*,4*S*)-3-acetamido-4-(carbamoylamino)-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid,



E. (2*R*,3*R*,4*S*)-3-acetamido-4-(*N*′-carbamimidoylcarbamimidamido)-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid,



F. 1*H*-pyrazole-1-carboximidamide,



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H. (2*R*,3*R*,4*R*)-3-acetamido-4-carbamimidamido-2-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid.

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Zanamivir Inhalation Powder, pre-metered

General Notices

Zanamivir Inhalation Powder, pre-dispensed

Action and use

Neuraminidase inhibitor; treatment and prophylaxis of influenza.

DEFINITION

Zanamivir Inhalation Powder, pre-metered consists of Zanamivir Hydrate, in *microfine powder* or equivalent, either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of zanamivir, $C_{12}H_{20}N_4O_7$

92.0 to 108.0% of the stated amount.

IDENTIFICATION

A. Dissolve an amount of the inhalation powder in sufficient *water* to produce a solution containing the equivalent of 0.002% w/v of zanamivir. The light absorption, Appendix II B, of this solution in the range 200 to 320 nm exhibits a maximum at 234 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the peak due to zanamivir in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

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Solution A 40 volumes of *water* and 60 volumes of *acetonitrile*.

(1) Collect single doses of the preparation being examined using the procedure described under *Inhalation Powders*, *Uniformity of delivered dose* and dissolve the collected dose in sufficient solution A to produce a solution containing the equivalent of 0.005% w/v of zanamivir.

(2) 0.005% w/v of *zanamivir for assay EPCRS*.

(3) 0.005% w/v of *zanamivir for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *amino alkyl vinyl polymer for chromatography* (5 µm) (Asahipak NH2P-50 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 234 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of 0.005M *sulfuric acid*, adjusted to pH 6.2 with 50% v/v of *ammonia*, and 60 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 2.5, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C.

DETERMINATION OF CONTENT

Calculate the content of zanamivir, $C_{12}H_{20}N_4O_7$, per delivered dose from the chromatograms obtained and using the declared content of $C_{12}H_{20}N_4O_7$ in *zanamivir for assay EPCRS*. Repeat the procedure as described for pre-metered systems under *Inhalation Powders*, *Uniformity of delivered dose*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound, a quantity of the powder containing the equivalent of 10 mg of zanamivir with 20 mL of the mobile phase and dilute to 25 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.045% w/v of *zanamivir for system suitability EPCRS* in the mobile phase.

(4) 0.000004% w/v of *zanamivir impurity F EPCRS* in the mobile phase.

(5) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Uniformity of delivered dose may be used. Allow the chromatography to proceed for 4 times the retention time of zanamivir.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to zanamivir (retention time about 9 minutes) are: impurity F, about 0.3; impurity B, about 0.6; impurity C, about 0.75; impurity E, about 0.8 and impurity A, about 2.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 2.5, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C.

LIMITS

Identify any peak corresponding to impurity E in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of the peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.01%);

the area of any *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.4 times the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak, except for impurity F, with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 40 volumes of *water* and 60 volumes of *acetonitrile*.

(1) Shake a quantity of the mixed contents of 20 pre-metered units containing the equivalent of 48 mg of zanamivir with 90 mL of *water*, mix with the aid of ultrasound, and add sufficient water to produce 100 mL. Dilute 1 volume to 10 volumes with solution A.

(2) 0.0048% w/v of *zanamivir for assay EPCRS*.

(3) 0.0045% w/v of *zanamivir for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

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The chromatographic conditions described under Uniformity of delivered dose may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 2.5, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C.

DETERMINATION OF CONTENT

Calculate the content of zanamivir, $C_{12}H_{20}N_4O_7$, in the inhalation powder from the chromatograms obtained and using the declared content of $C_{12}H_{20}N_4O_7$ in *zanamivir for assay EPCRS*.

LABELLING

The label states the content of active ingredient in terms of the equivalent metered dose. The quantity of active ingredient is stated in terms of the equivalent amount of zanamivir.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Zanamivir Hydrate.

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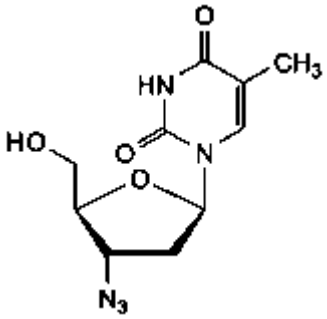
Zidovudine

General Notices

(Ph. Eur. monograph 1059)



$C_{10}H_{13}N_5O_4$ 267.2 *30516-87-1*

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Preparations

Zidovudine Capsules

Zidovudine Tablets

Zidovudine and Lamivudine Tablets

Zidovudine Infusion

Abacavir, Zidovudine and Lamivudine Tablets

Ph Eur

DEFINITION

3′-Azido-3′-deoxythymidine.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

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White or slightly brownish powder.

Solubility

Sparingly soluble in water, soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *zidovudine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *water R*, evaporate to dryness in a desiccator, under high vacuum over *diphosphorus pentoxide R* and record new spectra using the residues.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension I (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 0.5 g in 50 mL of *water R*, heating if necessary.

Specific optical rotation (*2.2.7*)

+ 60.5 to + 63.0 (dried substance), measured at 25 °C.

Dissolve 0.50 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

Related substances

A. Liquid chromatography (*2.2.29*).

Solvent mixture Mix 4 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 76 volumes of a 2 g/L solution of *ammonium acetate R* previously adjusted to pH 6.8 with *dilute acetic acid R*.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dilute 10.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *zidovudine impurity B CRS* in the solvent mixture and dilute to 50 mL with the solvent mixture. Dilute 1 mL of the solution to 20 mL with the solvent mixture.

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Reference solution (b) Dissolve 5 mg of *zidovudine for system suitability A CRS* (containing impurity G) in reference solution (a) and dilute to 5 mL with reference solution (a).

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of *zidovudine CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (e) Dissolve 1 mg of *zidovudine impurity D CRS* in a mixture of 4 volumes of *acetonitrile R*, 40 volumes of *methanol R* and 56 volumes of a 2 g/L solution of *ammonium acetate R* previously adjusted to pH 6.8 with *dilute acetic acid R* and dilute to 50 mL with the same mixture of solvents. Dilute 5 mL of the solution to 10 mL with the same mixture of solvents.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 2 g/L solution of *ammonium acetate R* adjusted to pH 6.8 with *dilute acetic acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	95	5
3 - 18	95 → 85	5 → 15
18 - 28	85 → 30	15 → 70
28 - 43	30	70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c) and (e).

Identification of impurities Use the chromatogram supplied with *zidovudine for system suitability A CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, and G; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity D.

Relative retention With reference to zidovudine (retention time = about 16 min): impurity B = about 1.05; impurity G = about 1.5; impurity D = about 2.0.

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System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to zidovudine and impurity B.

Calculation of percentage contents:

— for each impurity, use the concentration of zidovudine in reference solution (c).

Limits:

— *impurity G*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak due to impurity D and any peak eluting after this impurity.

B. Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.5 g of the substance to be examined in 10 mL of *acetonitrile R* and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *zidovudine impurity D CRS* in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1 mL of reference solution (a) to 50 mL with the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *acetonitrile R1* (30:70 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 10 times the retention time of zidovudine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to zidovudine (retention time = about 1.5 min): impurity D = about 2.5.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to zidovudine and impurity D.

Calculation of percentage contents:

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— for each impurity, use the concentration of impurity D in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak eluting before impurity D.

Limit:

— *total for tests A and B*: maximum 1.0 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in test A for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{10}H_{13}N_5O_4$ taking into account the assigned content of *zidovudine CRS*.

STORAGE

Protected from light.

IMPURITIES

Test A for related substances: A, B, C, E, F, G.

Test B for related substances: D, J, K.

Specified impurities *G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, J, K.*

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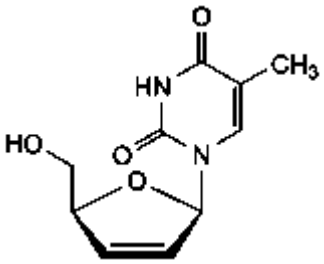
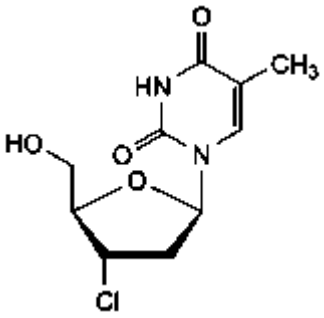
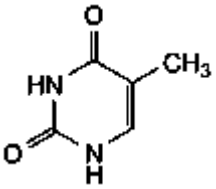


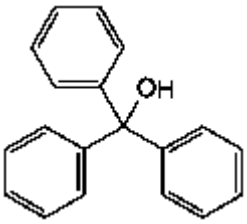
A. 3′-deoxy-2′,3′-didehydrothymidine,



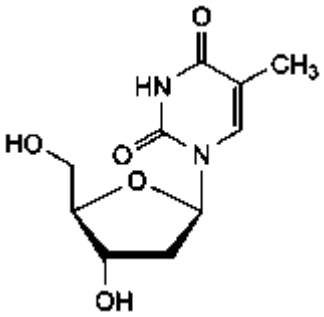
B. 3′-chloro-3′-deoxythymidine,



C. 5-methylpyrimidine-2,4(1*H*,3*H*)-dione (thymine),



D. triphenylmethanol,



E. thymidine,

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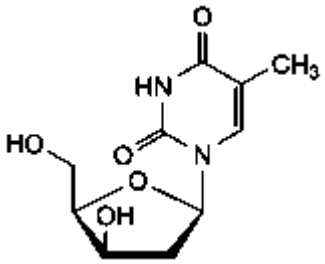
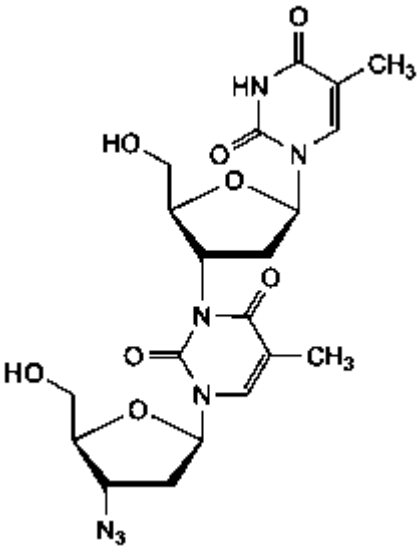
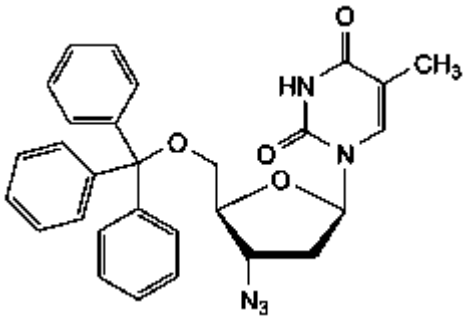


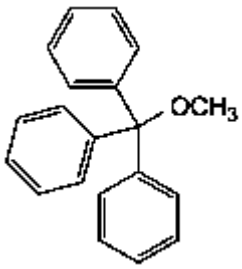
F. 3′-*epi*-thymidine,



G. 3′-(3′-azido-3′-deoxythymidin-3-yl)-3′-deoxythymidine,



J. 3′-azido-3′-deoxy-5′-*O*-(triphenylmethyl)thymidine (trityl-zidovudine),



K. 1,1′,1″-(methoxymethanetriyl)tribenzene (methyl trityl ether).

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Zidovudine and Lamivudine Tablets

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Zidovudine and Lamivudine Tablets contain Zidovudine and Anhydrous Lamivudine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of zidovudine, $C_{10}H_{13}N_5O_4$

95.0 to 105.0% of the stated amount.

Content of lamivudine, $C_8H_{11}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing 0.1 g of Zidovudine with 50 mL of *methanol*, filter and use the filtrate.

(2) 0.2% w/v of *zidovudine BPCRS* in *methanol*.

(3) 0.1% w/v of *lamivudine BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel F_{254}* plates (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry it in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (1) shows two clearly separated spots.

CONFIRMATION

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The chromatogram obtained with solution (1) shows two principal spots corresponding in position, colour and size to the principal spots in the chromatograms obtained with solutions (2) and (3).

B. In the Assay, the chromatogram obtained with solution (1) shows principal peaks with the same retention times as the principal peaks due to zidovudine and lamivudine in the chromatograms obtained with solutions (2) and (3) respectively.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 10-mL sample of the medium and filter.

(2) Dissolve suitable quantities of *zidovudine BPCRS* and *lamivudine BPCRS* in solvent A, described under Related substances, to produce the same concentrations as that expected for solution (1).

(3) 0.01% w/v of *zidovudine and lamivudine impurity standard BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of zidovudine, $C_{10}H_{13}N_5O_4$, and lamivudine, $C_8H_{11}N_3O_3S$, in the medium using the declared contents of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS* and of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

LIMITS

The amounts of zidovudine and lamivudine released are not less than 75% (Q) of the stated amounts.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A Dissolve 1.9 g of *ammonium acetate* in 900 mL of *water*, adjust the pH to 4.0 with *glacial acetic acid* and dilute to 1000 mL. Mix 95 volumes of this solution with 5 volumes of *methanol*.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Zidovudine in 60 mL with the aid of ultrasound for 30 minutes, dilute to 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

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(4) 0.002% w/v of *thymine*.

(5) 0.1% w/v of *zidovudine and lamivudine impurity standard BPCRS*.

(6) Dilute 1 volume of solution (3) to 2 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (YMC ODS-A is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.025M *ammonium acetate*, the pH adjusted to 4.0 with *glacial acetic acid*.

Mobile phase B *methanol*.

Mobile phase C *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-15	95	5	0	isocratic
15-30	95→70	5→30	0	linear gradient
30-38	70	30	0	isocratic
38-39	70→0	30→0	0→100	change of solvent
39-45	0	0	100	washing column
45-46	0→95	0→5	100→0	change of solvent
46-60	95	5	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (5) closely resembles the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS*;

the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0;

the *resolution* between the peaks due to lamivudine and thymidine is at least 2.0;

the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 4.0.

LIMITS

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Using the chromatogram obtained with solution (5) and the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS* identify any peaks in solution (1) corresponding to the named lamivudine and zidovudine impurities.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to thymine (zidovudine impurity C) is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2.0%);

the area of any peak corresponding to zidovudine impurity B is not greater than the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to zidovudine impurity G (the retention relative to zidovudine is about 1.4) is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to lamivudine impurity A is not greater than 3 times the area of the peak due to lamivudine in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the peak due to zidovudine in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5.2 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (5.2%).

Disregard any peak with an area less than the area of the peak due to zidovudine in the chromatogram obtained with solution (6) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions dissolved in solvent A described under Related substances.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Zidovudine with 50 mL of solvent A in a 100 mL amber volumetric flask for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume to 5 volumes.
(2) 0.02% w/v of *zidovudine BPCRS*.
(3) 0.01% w/v of *lamivudine BPCRS*.
(4) 0.1% w/v *of* *zidovudine and lamivudine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0;

the *resolution* between the peaks due to lamivudine and thymidine is at least 2.0;

the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 4.0.

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DETERMINATION OF CONTENT

Using solutions (1) and (2), calculate the total content of $C_{10}H_{13}N_5O_4$ in the tablets from the chromatograms obtained using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

Using solutions (1) and (3) calculate the total content $C_8H_{11}N_3O_3S$ in the tablets from the chromatograms obtained using the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed separately under Zidovudine and Anhydrous Lamivudine respectively.

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Zidovudine Capsules

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Zidovudine Capsules contain Zidovudine.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of zidovudine, $C_{10}H_{13}N_5O_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.2 g of Zidovudine with 50 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of zidovudine (*RS 447*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes, withdraw a 10-mL sample of the medium and filter. Measure the *absorbance* of the filtered medium, diluted if necessary with *water*, at the maximum at 266 nm using *water* in the reference cell, Appendix II B. Calculate the total content of zidovudine, $C_{10}H_{13}N_5O_4$, in the medium from the *absorbance* obtained from a 0.0017% w/v solution of *zidovudine BPCRS* in *water* and using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

LIMITS

The amount of zidovudine released is not less than 75% (Q) of the stated amount.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the contents of the capsules containing 0.3 g of Zidovudine with 5 mL of *water* in a 100 mL volumetric flask, add 30 mL of *methanol*, mix with the aid of ultrasound for 10 minutes, dilute to 100 mL with *water* and filter. Dilute 2 volumes of the filtrate to 5 volumes with *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

(4) 0.01% w/v of *zidovudine impurity standard BPCRS* in the mobile phase.

(5) 0.0036% w/v of *thymine* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the chromatogram closely resembles the reference chromatogram supplied with *zidovudine impurity standard BPCRS*;

the *resolution* between the peaks due to zidovudine and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C (thymine) is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (3.0%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity G (retention relative to zidovudine about 2.8) is not greater than 0.5 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

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the sum of the areas of all the *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the mixed contents of 20 capsules containing 0.1 g of Zidovudine with 40 mL of *methanol* in a 200 mL volumetric flask, shake for 30 minutes, dilute to 200 mL with *water* and filter. Dilute 2 volumes to 5 volumes with the mobile phase.

(2) 0.02% w/v of *zidovudine BPCRS* in the mobile phase.

(3) 0.01% w/v of *zidovudine impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between zidovudine and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{13}N_5O_4$ in the capsules from the chromatograms obtained using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and G listed under Zidovudine.

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Zidovudine Infusion

General Notices

Zidovudine Concentrate for Intravenous Infusion

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Zidovudine Infusion is a sterile solution containing Zidovudine. It is prepared by diluting Zidovudine Concentrate for Infusion in a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations.

STORAGE

Zidovudine Infusion should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

ZIDOVUDINE CONCENTRATE FOR INFUSION

DEFINITION

Zidovudine Concentrate for Infusion is a sterile solution consisting of Zidovudine with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of zidovudine, $C_{10}H_{13}N_5O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions protected from light.

(1) Dilute a volume of the contents of the sealed container in sufficient *methanol (50%)* to produce a solution containing 0.1% w/v of Zidovudine.

(2) 0.1% w/v of *zidovudine BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

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(a) Use precoated *silica gel F_{254}* plates (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry it in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

CONFIRMATION

The chromatogram obtained with solution (1) shows a principal spot corresponding in position, colour and size to the principal spot in the chromatograms obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak due to zidovudine in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH of a solution containing 0.01% w/v of Zidovudine, 3.5 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase protected from light.

(1) Dilute a volume of the contents of the sealed container to produce a solution containing 0.1% w/v of Zidovudine.

(2) Dilute 1 volume of solution (1) to 500 volumes.

(3) 0.01% w/v of *zidovudine impurity standard BPCRS*.

(4) 0.003% w/v of *thymine*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of *water*.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3):

the chromatogram closely resembles the reference chromatogram supplied with *zidovudine impurity standard BPCRS*;

the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to Impurity C (thymine) is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (3.0%);

the area of any peak with a relative retention time of 2.8 (Impurity G) is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the area of any peak corresponding to Impurity G and any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained solution (2) (1.0%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase protected from light.

(1) Dilute a volume of the contents of the sealed container to produce a solution containing 0.02% w/v of Zidovudine.
(2) 0.02% w/v of *zidovudine BPCRS*.
(3) 0.01% w/v of *zidovudine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{13}N_5O_4$ in the infusion from the chromatograms obtained using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C, E and G listed under Zidovudine.

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Zidovudine Tablets

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Zidovudine Tablets contain Zidovudine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of zidovudine, $C_{10}H_{13}N_5O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.2 g of Zidovudine with 50 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of zidovudine (*RS 447*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 10-mL sample of the medium and filter. Measure the *absorbance* of the filtered medium, diluted if necessary with *water*, at the maximum at 266 nm using *water* in the reference cell, Appendix II B. Calculate the total content of zidovudine $C_{10}H_{13}N_5O_4$, in the medium from the *absorbance* obtained from a 0.0017% w/v solution of *zidovudine BPCRS* in *water* and using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

LIMITS

The amount of zidovudine released is not less than 75% (Q) of the stated amount.

Related substances

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Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Zidovudine with 5 mL of *water* in a 100 mL volumetric flask, add 30 mL *methanol* and mix with the aid of ultrasound for 10 minutes; dilute to 100 mL with *water* and filter. Dilute 2 volumes of the filtrate to 5 volumes with *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

(4) 0.01% w/v of *zidovudine impurity standard BPCRS* in the mobile phase.

(5) 0.0036% w/v of *thymine* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the chromatogram closely resembles the reference chromatogram supplied with *zidovudine impurity standard*;

the *resolution* between the peaks due to zidovudine and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C (thymine) is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (3.0%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity G (retention relative to zidovudine about 2.8) is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

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the sum of the areas of any other *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained solution (2) (4.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Zidovudine with 100 mL of mobile phase for 10 minutes and filter. Dilute 1 volume to 5 volumes with the mobile phase.
(2) 0.02% w/v of *zidovudine BPCRS* in the mobile phase.
(3) 0.01% w/v of *zidovudine impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to zidovudine and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{13}N_5O_4$ in the tablets from the chromatograms obtained using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and G listed under Zidovudine.

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Zinc Acetate

General Notices

(Zinc Acetate Dihydrate, Ph. Eur. monograph 1482)

$C_4H_6O_4Zn,2H_2O$ 219.5 *5970-45-6*

Action and use

Astringent.

Preparation

Erythromycin and Zinc Acetate Lotion

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent of $C_4H_6O_4Zn,2H_2O$.

CHARACTERS

Appearance

White or almost white crystalline powder or flakes.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives reaction (a) of acetates (*2.3.1*).

B. It gives the reaction of zinc (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

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Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.8 to 7.0.

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Reducing substances

Boil for 5 min a mixture of 10 mL of solution S, 90 mL of *water R*, 5 mL of *dilute sulfuric acid R* and 1.5 mL of a 0.3 g/L solution of *potassium permanganate R*. The pink colour of the solution remains.

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Aluminium

Maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 2.50 g in 20 mL of a 200 g/L solution of *cadmium- and lead-free nitric acid R* and dilute to 25.0 mL with the same acid solution.

Reference solutions Prepare the reference solutions using *aluminium standard solution (200 ppm Al) R*, diluting with a 200 g/L solution of *cadmium- and lead-free nitric acid R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Air-acetylene or acetylene-nitrous oxide flame.

Cadmium

Maximum 1 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Use the solution described in the test for aluminium.

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Reference solutions Prepare the reference solutions using *cadmium standard solution (0.1 per cent Cd) R*, diluting with a 200 g/L solution of *cadmium- and lead-free nitric acid R*.

Source Cadmium hollow-cathode lamp.

Wavelength 228.8 nm.

Atomisation device Air-acetylene flame.

Iron

Maximum 50 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 1.25 g in 20 mL of a 200 g/L solution of *cadmium- and lead-free nitric acid R* and dilute to 25.0 mL with the same acid solution.

Reference solutions Prepare the reference solutions using *iron standard solution (20 ppm Fe) R*, diluting with a 200 g/L solution of *cadmium- and lead-free nitric acid R*.

Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Lead

Maximum 1 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 5.00 g in 20 mL of a 200 g/L solution of *cadmium- and lead-free nitric acid R* and dilute to 25.0 mL with the same acid solution.

Reference solutions Prepare the reference solutions using *lead standard solution (0.1 per cent Pb) R*, diluting with a 200 g/L solution of *cadmium- and lead-free nitric acid R*.

Source Lead hollow-cathode lamp.

Wavelength 283.3 nm.

Atomisation device Air-acetylene flame.

ASSAY

Dissolve 0.200 g in 5 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

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1 mL of *0.1 M sodium edetate* is equivalent to 21.95 mg of $C_4H_6O_4Zn,2H_2O$.

STORAGE

In a non-metallic container.

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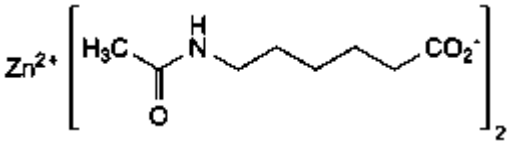
Zinc Acexamate

General Notices

(Ph. Eur. monograph 1279)



$C_{16}H_{28}N_2O_6Zn$ 409.8 *70020-71-2*

Ph Eur

DEFINITION

Zinc bis(6-acetamidohexanoate).

Content

97.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in acetone and in ethanol (96 per cent). It dissolves in dilute nitric acid.

mp

About 198 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *zinc acexamate CRS*.

B. 5 mL of solution S (see Tests) gives the reaction of zinc (*2.3.1*).

TESTS

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TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension IV (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.0 to 7.0 for solution S.

Impurity B

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.30 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 15 mg of *6-aminohexanoic acid R* (impurity B) in *water R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 10 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *ammonia R*, *water R*, *ethanol (96 per cent) R* (2:30:68 *V/V/V*).

Application 5 µL; allow to dry in air.

Development Over a path of 15 cm.

Drying In a current of warm air.

Detection Spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min.

Limit:

— *impurity B*: any spot due to impurity B is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.5 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 0.50 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Test solution (b) To 20.0 mL of test solution (a), add 20 mL of the mobile phase and 0.4 mL of a 100 g/L solution of *phosphoric acid R*, then dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 40 mg of *N-acetyl-ε-caprolactam R* (impurity C) in *water R* and dilute to 100.0 mL with the same solvent.

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Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with *water R*.

Reference solution (c) Dissolve 20 mg of *zinc acexamate impurity A CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (d) Dissolve 40 mg of *ε-caprolactam R* (impurity D) in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (e) To 20 mL of test solution (a), add 5 mL of reference solution (b), 5 mL of reference solution (c), 5 mL of reference solution (d) and 0.4 mL of a 100 g/L solution of *phosphoric acid R*, then dilute to 50 mL with the mobile phase.

Reference solution (f) To 5.0 mL of reference solution (c), add 5.0 mL of reference solution (b), 5.0 mL of reference solution (d) and 0.4 mL of a 100 g/L solution of *phosphoric acid R*, then dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 0.2 volumes of *phosphoric acid R*, 8 volumes of *acetonitrile R1* and 92 volumes of *water for chromatography R*, then adjust to pH 4.5 with *dilute ammonia R1*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (e) and (f).

Run time 8 times the retention time of zinc acexamate.

Elution order Zinc acexamate, impurity D, impurity A, impurity C.

System suitability Reference solution (e):

— *resolution*: minimum 3.0 between the peaks due to zinc acexamate and impurity D; if necessary, adjust the mobile phase to pH 4.7 with *dilute ammonia R1*.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (2 per cent);

— *impurities C, D*: for each impurity, not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to impurity C in the chromatogram obtained with reference solution (f) (0.05 per cent);

— *sum of impurities other than A*: not more than 5 times the area of the peak due to impurity C in the chromatogram obtained with reference solution (f) (0.5 per cent);

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— *disregard limit*: 0.5 times the area of the peak due to impurity C in the chromatogram obtained with reference solution (f) (0.05 per cent).

Iron

Maximum 50 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 1.25 g in 20 mL of a 200 g/L solution of *cadmium- and lead-free nitric acid R* and dilute to 25.0 mL with the same acid solution.

Reference solutions Prepare the reference solutions using *iron standard solution (20 ppm Fe) R*, diluting with a 200 g/L solution of *cadmium- and lead-free nitric acid R*.

Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.400 g in 10 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

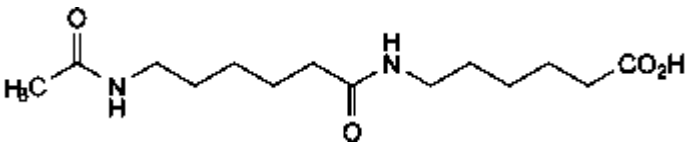
1 mL of *0.1 M sodium edetate* is equivalent to 40.98 mg of $C_{16}H_{28}N_2O_6Zn$.

STORAGE

In a non-metallic container.

IMPURITIES

Specified impurities *A, B, C, D.*



A. 6-(6-acetamidohexanamido)hexanoic acid,

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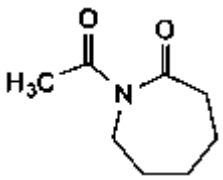
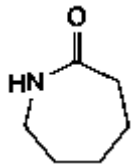
B. 6-aminohexanoic acid (6-aminocaproic acid),



C. 1-acetylazepan-2-one (*N*-acetyl-ε-caprolactam),



D. azepan-2-one (ε-caprolactam).

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Zinc and Castor Oil Ointment

General Notices

Zinc and Castor Oil Cream

DEFINITION

Zinc Oxide, finely sifted	75 g
Virgin Castor Oil	500 g
Cetostearyl Alcohol	20 g
White Beeswax	100 g
Arachis Oil	305 g

Extemporaneous preparation

The following directions apply.

Triturate the Zinc Oxide with a portion of the Virgin Castor Oil until smooth and add the mixture to the remainder of the ingredients previously melted together. Stir while cooling until the temperature is about 40°.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc oxide, ZnO

7.0 to 8.0% w/w.

IDENTIFICATION

A. Heat 1.3 g of the ointment gently in a porcelain dish over a small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. The residue obtained is yellow when hot and white when cold.

B. Dissolve the cooled residue obtained in test A in 5 mL of 1M *hydrochloric acid*. The resulting solution yields the reaction characteristic of *zinc salts*, Appendix VI.

ASSAY

Heat 1 g of the ointment gently in a porcelain dish over a small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. Dissolve the residue in 10 mL of 2M *acetic acid* and add sufficient *water* to produce 50 mL. To the resulting solution add 50 mg of *xylenol orange triturate* and sufficient *hexamine* to produce a violet-pink colour. Add a further 2 g of *hexamine* and titrate with 0.05M *disodium edetate VS* until the solution becomes yellow. Each mL of 0.05M *disodium edetate VS* is equivalent to 4.069 mg of ZnO.

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Zinc and Coal Tar Paste

General Notices

White's Tar Paste

DEFINITION

Zinc and Coal Tar Paste contains 6% w/w each of Zinc Oxide and Coal Tar with 38% w/w of Starch in a suitable hydrophobic basis.

Extemporaneous preparation

The following formula and directions apply.

Emulsifying Wax	50 g
Coal Tar	60 g
Zinc Oxide, finely sifted	60 g
Starch	380 g
Yellow Soft Paraffin	450 g

Melt the Emulsifying Wax at 70°, add the Coal Tar and 225 g of the Yellow Soft Paraffin, stir at 70° until completely melted, add the remainder of the Yellow Soft Paraffin, cool to 30°, add the Zinc Oxide and the Starch, stirring constantly, and stir until cold.

The paste complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc oxide, ZnO

5.7 to 6.3% w/w.

IDENTIFICATION

The residue obtained in the Assay is yellow when hot and white when cool.

ASSAY

Heat 1.0 g of the paste gently in a porcelain dish over a small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. Dissolve the residue in 10 mL of 2M *acetic acid* and add sufficient *water* to produce 50 mL. To the resulting solution add 50 mg of *xylenol orange triturate* and sufficient *hexamine* to produce a violet-pink colour. Add a further 2 g of *hexamine* and titrate with 0.05M *disodium edetate VS* until the solution becomes yellow. Each mL of 0.05M *disodium edetate VS* is equivalent to 4.069 mg of ZnO.

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Zinc and Ichthammol Cream

General Notices

DEFINITION

Zinc and Ichthammol Cream contains 5% w/w of Ichthammol dispersed in a suitable basis of which about 82% w/w is Zinc Cream.

Extemporaneous preparation

The following formula and directions apply.

Ichthammol	50 g
Cetostearyl Alcohol	30 g
Wool Fat	100 g
Zinc Cream	Sufficient to produce 1000 g

Melt together the Wool Fat and the Cetostearyl Alcohol with the aid of gentle heat, triturate the mixture with 800 g of Zinc Cream until smooth, incorporate the Ichthammol, add sufficient Zinc Cream to produce 1000 g and mix.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc oxide, ZnO

23.4 to 29.3% w/w.

ASSAY

Gently heat 0.4 g, taking precautions to avoid loss caused by spitting, until the basis is completely volatilised or charred, cool, dissolve the residue in 10 mL of 2M *sulfuric acid*, add 40 mL of *water*, adjust the solution to about pH 10 with 5M *ammonia*, add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 4.069 mg of ZnO.

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Zinc and Salicylic Acid Paste

General Notices

Lassar's Paste

DEFINITION

Zinc Oxide, finely sifted	240 g
Salicylic Acid, finely sifted	20 g
Starch, finely sifted	240 g
White Soft Paraffin	500 g

Extemporaneous preparation

The following directions apply.

Melt the White Soft Paraffin, incorporate the Zinc Oxide, the Salicylic Acid and the Starch and stir until cold.

The paste complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc oxide, ZnO

22.5 to 25.5% w/w.

Content of salicylic acid, $C_7H_6O_3$

1.9 to 2.1% w/w.

IDENTIFICATION

A. Shake 1 g with 10 mL of *water*, filter and add *iron(III) chloride solution R1* to the filtrate. An intense reddish violet colour is produced which remains on the addition of 5M *acetic acid* but disappears on the addition of 2M *hydrochloric acid* with the separation of a white, crystalline precipitate.

B. Heat 0.5 g gently in a porcelain dish over a very small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. The residue is yellow when hot and white when cool.

TESTS

ASSAY

For salicylic acid

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Shake 0.5 g with 10 mL of 1M *hydrochloric acid* and 10 mL of *ether* until fully dispersed. Decant and reserve the aqueous layer. Extract the ether layer with two further 10 mL quantities of 1M *hydrochloric acid*, combine the aqueous extracts with the reserved aqueous layer, wash with 10 mL of *ether* and reserve for the Assay for zinc oxide. Combine the ether extracts, add 15 mL of *petroleum spirit* (*boiling range, 40° to 60°*) and extract with successive quantities of 20 mL, 10 mL and 10 mL of a mixture of equal volumes of *ethanol* (*90%*) and 1M *sodium hydroxide*. Dilute the combined extracts to 100 mL with 2M *hydrochloric acid*, further dilute 15 mL of the resulting solution to 50 mL with the same solvent and measure the *absorbance* of the final solution at the maximum at 302 nm, Appendix II B. Calculate the content of $C_7H_6O_3$ taking 260 as the value of A(1%, 1 cm) at the maximum at 302 nm.

For zinc oxide

To the combined aqueous extracts obtained in the Assay for salicylic acid add 20 mL of 1M *sodium hydroxide* and 50 mg of *xylenol orange triturate*. To the resulting solution add sufficient *hexamine* to change the colour of the solution to red and then a further 3 g of *hexamine* and titrate with 0.1M *disodium edetate VS*. Each mL of 0.1M *disodium edetate VS* is equivalent to 8.139 mg of ZnO.

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Zinc Cream

General Notices

DEFINITION

Zinc Cream contains 32% w/w of Zinc Oxide in a suitable water-in-oil emulsified basis.

Extemporaneous preparation

The following formula and directions apply.

Zinc Oxide, finely sifted	320 g
Calcium Hydroxide	0.45 g
Oleic Acid	5 mL
Arachis Oil	320 mL
Wool Fat	80 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 g

Mix the Zinc Oxide and the Calcium Hydroxide, triturate to a smooth paste with a mixture of the Oleic Acid and Arachis Oil, incorporate the Wool Fat and add gradually with continuous stirring sufficient Purified Water to produce 1000 g.

The suitability of the Cream for use as a diluent should be confirmed before use.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc oxide, ZnO

30.0 to 34.0% w/w.

IDENTIFICATION

The residue obtained in the Assay is yellow when hot and white when cool.

ASSAY

Heat 0.5 g of the cream gently in a porcelain dish over a small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. Dissolve the residue in 10 mL of 2M *acetic acid* and add sufficient *water* to produce 50 mL. To the resulting solution add 50 mg of *xylenol orange triturate* and sufficient *hexamine* to produce a violet-pink colour. Add a further 2 g of *hexamine* and

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titrate with 0.1M *disodium edetate VS* until the solution becomes yellow. Each mL of 0.1M *disodium edetate VS* is equivalent to 8.138 mg of ZnO.

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Zinc Chloride

General Notices

(Ph. Eur. monograph 0110)

$ZnCl_2$ 136.3 *7646-85-7*

Ph Eur

DEFINITION

Content

95.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or cast in white or almost white sticks, deliquescent.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent) and in glycerol.

IDENTIFICATION

A. Dissolve 0.5 g in *dilute nitric acid R* and dilute to 10 mL with the same acid. The solution gives reaction (a) of chlorides (*2.3.1*).

B. 5 mL of solution S (see Tests) gives the reaction of zinc (*2.3.1*).

TESTS

Solution S

To 2.0 g add 38 mL of *carbon dioxide-free water R* prepared from *distilled water R* and add *dilute hydrochloric acid R* dropwise until dissolution is complete. Dilute to 40 mL with *carbon dioxide-free water R* prepared from *distilled water R*.

pH (*2.2.3*)

4.6 to 5.5.

Dissolve 1.0 g in 9 mL of *carbon dioxide-free water R*, ignoring any slight turbidity.

Oxychlorides

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Dissolve 10.0 g in 10 mL of *carbon dioxide-free water R*. The solution is not more opalescent than reference suspension II (*2.2.1*). To 1.5 mL of the solution add 7.5 mL of *ethanol (96 per cent) R*. The solution may become cloudy within 10 min. Any cloudiness disappears on the addition of 0.2 mL of *dilute hydrochloric acid R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*. Prepare the standard using a mixture of 5 mL of *sulfate standard solution (10 ppm SO_4) R* and 10 mL of *distilled water R*.

Aluminium, calcium, iron, magnesium

To 8 mL of solution S add 2 mL of *concentrated ammonia R* and shake. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*). Add 1 mL of *disodium hydrogen phosphate solution R*. The solution remains clear for at least 5 min. Add 0.2 mL of *sodium sulfide solution R*. A white precipitate is formed and the supernatant remains colourless.

Ammonium (*2.4.1*)

Maximum 400 ppm.

Dilute 0.5 mL of solution S to 15 mL with *water R*.

ASSAY

Dissolve 0.250 g in 5 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 13.63 mg of $ZnCl_2$.

STORAGE

In a non-metallic container.

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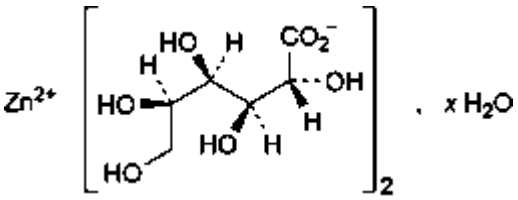
Zinc Gluconate

General Notices

(Ph. Eur. monograph 2164)



$C_{12}H_{22}ZnO_{14},xH_2O$ 455.7 (anhydrous substance)

Ph Eur

DEFINITION

Zinc D-gluconate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

It may be anhydrous or contain a variable quantity of water.

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Soluble in water, practically insoluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *water R*.

Reference solution Dissolve 20 mg of *calcium gluconate CRS* in 1 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Plate *TLC silica gel plate R* (5-40 µm) [or *TLC silica gel plate R* (2-10 µm)].

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Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *water R*, *ethanol (96 per cent) R* (10:10:30:50 *V/V/V/V*).

Application 1 µL.

Development Over 3/4 of the plate.

Drying At 100-105 °C for 20 min, then allow to cool to room temperature.

Detection Spray with a solution containing 25 g/L of *ammonium molybdate R* and 10 g/L of *cerium sulfate R* in *dilute sulfuric acid R*, and heat at 100-105 °C for about 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve 0.1 g in *water R*. Add 0.5 mL of *potassium ferrocyanide solution R*. A white precipitate is formed that does not dissolve upon the addition of 5 mL of *hydrochloric acid R*.

TESTS

Solution S

Dissolve 0.50 g in *water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Sucrose and reducing sugars

Dissolve 0.5 g in a mixture of 2 mL of *hydrochloric acid R1* and 10 mL of *water R*. Boil for 5 min, allow to cool, add 10 mL of *sodium carbonate solution R* and allow to stand for 10 min. Dilute to 25 mL with *water R* and filter. To 5 mL of the filtrate add 2 mL of *cupri-tartaric solution R* and boil for 1 min. Allow to stand for 2 min. No red precipitate is formed.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

Dissolve 2.0 g in a mixture of 10 mL of *acetic acid R* and 90 mL of *distilled water R*.

Elemental impurities

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Any method that fulfils the requirements of general chapter *2.4.20. Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Cadmium	1
Lead	2
Thallium	2

Water (*2.5.32*)

Maximum 12.0 per cent, determined on 80.0 mg.

ASSAY

Dissolve 0.400 g in 5 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 45.57 mg of $C_{12}H_{22}ZnO_{14}$.

STORAGE

In a non-metallic, airtight container.

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Zinc Ointment

General Notices

DEFINITION

Zinc Ointment contains 15% w/w of Zinc Oxide in a suitable water-emulsifying basis.

Extemporaneous preparation

The following formula and directions apply.

Zinc Oxide, finely sifted	150 g
Simple Ointment	850 g

Triturate the Zinc Oxide with a portion of the Simple Ointment until smooth, gradually add the remainder of the Simple Ointment and mix thoroughly.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc oxide, ZnO

14.0 to 16.0% w/w.

IDENTIFICATION

The residue obtained in the Assay is yellow when hot and white when cool.

ASSAY

Heat 0.5 g of the ointment gently in a porcelain dish over a small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. Dissolve the residue in 10 mL of 2M *acetic acid* and add sufficient *water* to produce 50 mL. To the resulting solution add 50 mg of *xylenol orange triturate* and sufficient *hexamine* to produce a violet-pink colour. Add a further 2 g of *hexamine* and titrate with 0.05M *disodium edetate VS* until the solution becomes yellow. Each mL of 0.05M *disodium edetate VS* is equivalent to 4.069 mg of ZnO.

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Zinc Oxide

General Notices

(Ph. Eur. monograph 0252)

ZnO 81.4 *1314-13-2*

Action and use

Mild astringent.

Preparations

Zinc Cream

Coal Tar and Zinc Ointment

Zinc Ointment

Zinc and Castor Oil Ointment

Compound Zinc Paste

Zinc and Salicylic Acid Paste

Zinc and Coal Tar Paste

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent (ignited substance).

CHARACTERS

Appearance

Soft, white or faintly yellowish-white, amorphous powder, free from gritty particles.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute mineral acids.

IDENTIFICATION

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IDENTIFICATION

A. It becomes yellow when strongly heated; the yellow colour disappears on cooling.

B. Dissolve 0.1 g in 1.5 mL of *dilute hydrochloric acid R* and dilute to 5 mL with *water R*. The solution gives the reaction of zinc (*2.3.1*).

TESTS

Alkalinity

Shake 1.0 g with 10 mL of boiling *water R*. Add 0.1 mL of *phenolphthalein solution R* and filter. If the filtrate is red, not more than 0.3 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Carbonates and substances insoluble in acids

Dissolve 1.0 g in 15 mL of *dilute hydrochloric acid R*. It dissolves without effervescence and the solution is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Cadmium	5
Lead	10
Thallium	5

Iron (*2.4.9*)

Maximum 200 ppm.

Dissolve 50 mg in 1 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. Use 0.5 mL of *thioglycollic acid R* in this test.

Loss on ignition

Maximum 1.0 per cent, determined on 1.00 g by ignition to constant mass at 500 ± 50 °C.

ASSAY

Dissolve 0.150 g in 10 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 8.14 mg of ZnO.

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Zinc Stearate

General Notices

(Ph. Eur. monograph 0306)

557-05-1

Action and use

Excipient.

Ph Eur

DEFINITION

Zinc stearate [$(C_{17}H_{35}COO)_2Zn$; M_r 632] may contain varying proportions of zinc palmitate [$(C_{15}H_{31}COO)_2Zn$; M_r 576.2] and zinc oleate [$(C_{17}H_{33}COO)_2Zn$; M_r 628].

Content

10.0 per cent to 12.0 per cent of Zn.

CHARACTERS

Appearance

Light, white or almost white, amorphous powder, free from gritty particles.

Solubility

Practically insoluble in water and in anhydrous ethanol.

IDENTIFICATION

A. Freezing point (2.2.18): minimum 53 °C, determined on the residue obtained in the preparation of solution S (see Tests).

B. Neutralise 5 mL of solution S to *red litmus paper R* with *strong sodium hydroxide solution R*. The solution gives the reaction of zinc (2.3.1).

TESTS

Solution S

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To 5.0 g add 50 mL of *ether R* and 40 mL of a 7.5 per cent *V/V* solution of *nitric acid R* in *distilled water R*. Heat under a reflux condenser until dissolution is complete. Allow to cool. In a separating funnel, separate the aqueous layer and shake the ether layer with 2 quantities, each of 4 mL, of *distilled water R*. Combine the aqueous layers, wash with 15 mL of *ether R* and heat on a water-bath until ether is completely eliminated. Allow to cool and dilute to 50.0 mL with *distilled water R* (solution S). Evaporate the ether layer to dryness and dry the residue at 105 °C.

Appearance of solution

Solution S is not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Appearance of solution of fatty acids

Dissolve 0.5 g of the residue obtained in the preparation of solution S in 10 mL of *chloroform R*. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Acidity or alkalinity

Shake 1.0 g with 5 mL of *ethanol (96 per cent) R* and add 20 mL of *carbon dioxide-free water R* and 0.1 mL of *phenol red solution R*. Not more than 0.3 mL of *0.1 M hydrochloric acid* or 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Acid value of the fatty acids (*2.5.1*)

195 to 210.

Dissolve 0.20 g of the residue obtained in the preparation of solution S in 25 mL of the prescribed mixture of solvents.

Chlorides (*2.4.4*)

Maximum 250 ppm.

Dilute 2 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.6 per cent.

Dilute 1 mL of solution S to 50 mL with *distilled water R*. Dilute 12.5 mL of this solution to 15 mL with *distilled water R*.

ASSAY

To 1.000 g add 50 mL of *dilute acetic acid R* and boil for at least 10 min or until the layer of fatty acids is clear, adding more *water R* as necessary to maintain the original volume. Cool and filter. Wash the filter and the flask with *water R* until the washings are no longer acid to *blue litmus paper R*. Combine the filtrate and washings. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 6.54 mg of Zn.

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Zinc Sulfate Capsules

General Notices

Zinc Sulphate Capsules

DEFINITION

Zinc Sulfate Capsules contain Zinc Sulfate Monohydrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of zinc sulfate monohydrate, $ZnSO_4,H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. A quantity of the contents of the capsules containing 0.1 g of Zinc Sulfate Monohydrate yields the reaction characteristic of *zinc* and *zinc salts*, Appendix VI.

B. A quantity of the contents of the capsules containing 45 mg of Zinc Sulfate Monohydrate yields the reactions characteristic of *sulfates*, Appendix VI.

ASSAY

Disperse a quantity of the mixed contents of 20 capsules containing 0.16 g of Zinc Sulfate Monohydrate in 5 mL of *dilute acetic acid*. Carry out the *complexemetric titration of zinc*, Appendix VIII D.

Each mL of 0.1M *sodium edetate* is equivalent to 17.95 mg of $ZnSO_4,H_2O$.

STORAGE

Zinc Sulfate Capsules should be protected from light and moisture.

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Zinc Sulfate Eye Drops

General Notices

Zinc Sulphate Eye Drops

DEFINITION

Zinc Sulfate Eye Drops are a sterile solution containing 0.25% w/v of Zinc Sulfate Heptahydrate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of zinc sulfate heptahydrate, $ZnSO_4,7H_2O$

0.22 to 0.28% w/v.

ASSAY

To 5 mL add 50 mL of *water* and 5 mL of *ammonia buffer pH 10.9* and titrate with 0.01M *disodium edetate VS* using *mordant black 11 solution* as indicator. Each mL of 0.01M *disodium edetate VS* is equivalent to 2.875 mg of $ZnSO_4,7H_2O$.

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Zinc Sulfate Heptahydrate

General Notices

(Ph. Eur. monograph 0111)

$ZnSO_4,7H_2O$ 287.5 *7446-20-0*

Action and use

Astringent.

Preparations

Zinc Sulfate Eye Drops

Zinc Sulfate Injection

Zinc Sulfate Lotion

Ph Eur

DEFINITION

Content

99.0 per cent to 104.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless, transparent crystals, efflorescent.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives the reactions of sulfates (*2.3.1*).

B. Solution S gives the reaction of zinc (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

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Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.4 to 5.6 for solution S.

Chlorides (*2.4.4*)

Maximum 300 ppm.

Dilute 3.3 mL of solution S to 15 mL with *water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 2 mL of solution S to 10 mL with *water R*. Use in this test 0.5 mL of *thioglycollic acid R*.

ASSAY

Dissolve 0.200 g in 5 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 28.75 mg of $ZnSO_4,7H_20$.

STORAGE

In a non-metallic, airtight container.

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Zinc Sulfate Hexahydrate

General Notices

(Ph. Eur. monograph 1683)

$ZnSO_4,6H_2O$ 269.5 *13986-24-8*

Action and use

Astringent.

Ph Eur

DEFINITION

Content

99.0 per cent to 104.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless transparent crystals, efflorescent.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives the reactions of sulfates (*2.3.1*).

B. Solution S gives the reaction of zinc (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

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pH (*2.2.3*)

4.4 to 5.6 for solution S.

Chlorides (*2.4.4*)

Maximum 300 ppm.

Dilute 3.3 mL of solution S to 15 mL with *water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 2 mL of solution S to 10 mL with *water R*. Use in this test 0.5 mL of *thioglycollic acid R*.

ASSAY

Dissolve 0.200 g in 5 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 26.95 mg of $ZnSO_4,6H_20$.

STORAGE

In a non-metallic, airtight container.

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Zinc Sulfate Injection

General Notices

Zinc Sulphate Injection

DEFINITION

Zinc Sulfate Injection is a sterile solution of Zinc Sulfate Heptahydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of zinc sulfate heptahydrate, $ZnSO_4,7H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. A volume of the injection containing 0.1 g of Zinc Sulfate Heptahydrate yields the reaction characteristic of *zinc and zinc salts*, Appendix VI.

B. A volume of the injection containing 45 mg of Zinc Sulfate Heptahydrate yields the reactions characteristic of *sulfates*, Appendix VI.

ASSAY

To a volume of the injection containing 0.16 g of Zinc Sulfate Heptahydrate add 5 mL of *dilute acetic acid*. Carry out the *complexemetric titration of zinc*, Appendix VIII D.

Each mL of 0.1M *sodium edetate* is equivalent to 28.75 mg of $ZnSO_4,7H_2O$.

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Zinc Sulfate Lotion

General Notices

Zinc Sulphate Lotion

Zinc Sulfate Cutaneous Solution

DEFINITION

Zinc Sulfate Lotion is a *cutaneous solution*. It contains 1% w/v of Zinc Sulfate Heptahydrate in a suitable aqueous vehicle.

The lotion complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of zinc sulfate heptahydrate, $ZnSO_4,7H_2O$

0.95 to 1.05% w/v.

ASSAY

To 20 mL add 25 mL of 0.1M *hydrochloric acid* and 0.1 g of *activated charcoal*, shake, filter and wash the residue with 100 mL of 0.01M *hydrochloric acid*. To the combined filtrate and washings add 5 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. Repeat the procedure using 20 mL of *water* in place of the preparation being examined. The difference between the titrations represents the amount of disodium edetate required. Each mL of 0.05M *disodium edetate VS* is equivalent to 14.38 mg of $ZnSO_4,7H_2O$.

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Zinc Sulfate Monohydrate

General Notices

(Ph. Eur. monograph 2159)

$ZnSO_4,H_2O$ 179.5

Action and use

Astringent.

Preparations

Zinc Sulfate Capsules

Zinc Sulfate Tablets

Ph Eur

DEFINITION

Content

99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder, or colourless, transparent crystals.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives the reactions of sulfates (*2.3.1*).

B. Solution S gives the reaction of zinc (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Solution S

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Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.0 to 5.6 for solution S.

Chlorides (*2.4.4*)

Maximum 300 ppm.

Dilute 3.3 mL of solution S to 15 mL with *water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 2 mL of solution S to 10 mL with *water R*. Use 0.5 mL of *thioglycollic acid R* in this test.

ASSAY

Dissolve 0.160 g in 5 mL of *dilute acetic acid R*. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 17.95 mg of $ZnSO_4,H_2O$.

STORAGE

In a non-metallic container.

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Zinc Sulfate Tablets

General Notices

Zinc Sulphate Tablets

DEFINITION

Zinc Sulfate Tablets contain Zinc Sulfate Monohydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of zinc sulfate monohydrate, $ZnSO_4,H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. A quantity of the powdered tablets containing 0.1 g of Zinc Sulfate Monohydrate yields the reaction characteristic of *zinc* and *zinc salts*, Appendix VI.

B. A quantity of the powdered tablets containing 45 mg of Zinc Sulfate Monohydrate yields the reactions characteristic of *sulfates*, Appendix VI.

ASSAY

Weigh and powder 20 tablets. Disperse a quantity of the powdered tablets containing 0.16 g of Zinc Sulfate Monohydrate in 5 mL of *dilute acetic acid*. Carry out the *complexemetric titration of zinc*, Appendix VIII D.

Each mL of 0.1M *sodium edetate* is equivalent to 17.95 mg of $ZnSO_4,H_2O$.

STORAGE

Zinc Sulfate tablets should be protected from light and moisture.

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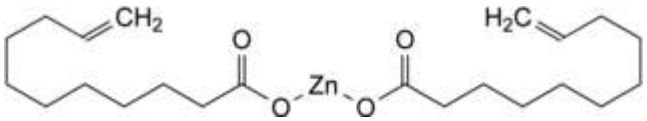
Zinc Undecenoate

General Notices

(Zinc Undercylenate, Ph. Eur. monograph 0539)



$C_{22}H_{38}O_4Zn$ 431.9 *557-08-4*

Action and use

Used topically in treatment of fungal infections.

Ph Eur

DEFINITION

Zinc di(undec-10-enoate).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, fine powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent).

mp

116 °C to 121 °C, it may leave a slight solid residue.

IDENTIFICATION

A. To 2.5 g add 10 mL of *water R* and 10 mL of *dilute sulfuric acid R*. Shake with 2 quantities, each of 10 mL, of *ether R*. Reserve the aqueous layer for identification test C. Wash the combined ether layers with *water R* and evaporate to dryness. To the residue add 2 mL of freshly distilled *aniline R* and boil under a reflux condenser for 10 min. Allow to cool and add 30 mL of *ether R*. Shake with 3 quantities,

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each of 20 mL, of *dilute hydrochloric acid R* and then with 20 mL of *water R*. Evaporate the organic layer to dryness on a water-bath. The residue, after recrystallisation twice from *ethanol (70 per cent V/V) R* and drying *in vacuo* for 3 h, melts (*2.2.14*) at 66 °C to 68 °C.

B. Dissolve 0.1 g in a mixture of 2 mL of *dilute sulfuric acid R* and 5 mL of *glacial acetic acid R*. Add dropwise 0.25 mL of *potassium permanganate solution R*. The colour of the potassium permanganate solution is discharged.

C. A mixture of 1 mL of the aqueous layer obtained in identification test A and 4 mL of *water R* gives the reaction of zinc (*2.3.1*).

TESTS

Alkalinity

Mix 1.0 g with 5 mL of *ethanol (96 per cent) R* and 0.5 mL of *phenol red solution R*. Add 50 mL of *carbon dioxide-free water R* and examine immediately. No reddish colour appears.

Alkali and alkaline-earth metals

Maximum 2.0 per cent.

To 1.0 g add 25 mL of *water R* and 5 mL of *hydrochloric acid R* and heat to boiling. Filter whilst hot. Wash the filter and the residue with 25 mL of hot *water R*. Combine the filtrate and washings and add *concentrated ammonia R* until alkaline. Add 7.5 mL of *thioacetamide solution R* and heat on a water-bath for 30 min. Filter and wash the precipitate with 2 quantities, each of 10 mL, of *water R*. Combine the filtrate and washings, evaporate to dryness on a water-bath and ignite. The residue weighs a maximum of 20 mg.

Sulfates (*2.4.13*)

Maximum 500 ppm.

To 0.1 g add a mixture of 2 mL of *dilute hydrochloric acid R* and 10 mL of *distilled water R* and heat to boiling. Cool, filter and dilute to 15 mL with *distilled water R*. Prepare the standard using 5 mL of *sulfate standard solution (10 ppm SO_4) R* and 10 mL of *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 1.5 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Degree of unsaturation

Dissolve 0.100 g in a mixture of 5 mL of *dilute hydrochloric acid R* and 30 mL of *glacial acetic acid R*. Using 0.05 mL *indigo carmine solution R1*, added towards the end of the titration as indicator. Titrate with *0.0167 M bromide-bromate* until the colour changes from blue to yellow. 9.1 mL to 9.4 mL of *0.0167 M bromide-bromate* is required. Carry out a blank titration.

ASSAY

To 0.350 g add 25 mL of *dilute acetic acid R* and heat to boiling. Carry out the complexometric titration of zinc (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 43.19 mg of $C_{22}H_{38}O_4Zn$.

STORAGE

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Protected from light.

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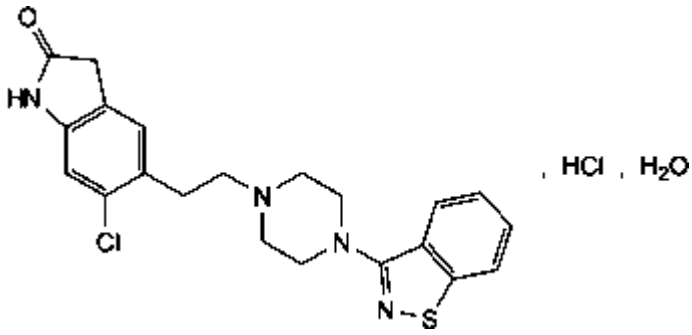
Ziprasidone Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 2421)



$C_{21}H_{22}Cl_2N_4OS,H_2O$ 467.4 *138982-67-9*

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

5-[2-[4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one hydrochloride monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly pink powder.

Solubility

Practically insoluble in water, slightly soluble in methanol and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

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A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ziprasidone hydrochloride monohydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Suspend 30 mg in 2 mL of *water R*, acidify with 0.15 mL of *dilute nitric acid R* and filter. The clear filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Solvent mixture A *water R*, *methanol R* (40:60 *V/V*).

Solvent mixture B *hydrochloric acid R*, *water R*, *methanol R* (0.04:20:80 *V/V/V*).

Test solution (a) Dissolve 23 mg of the substance to be examined in solvent mixture A and dilute to 100.0 mL with solvent mixture A.

Test solution (b) Dissolve 23 mg of the substance to be examined in solvent mixture B and dilute to 50.0 mL with solvent mixture B.

Reference solution (a) Dissolve 2.5 mg of *ziprasidone for system suitability 1 CRS* (containing impurities A, B and C) in solvent mixture A and dilute to 10.0 mL with solvent mixture A.

Reference solution (b) Dilute 1.0 mL of test solution (b) to 100.0 mL with solvent mixture B. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture B.

Reference solution (c) Dissolve the contents of a vial of *ziprasidone for system suitability 2 CRS* (containing impurities D and E) in 1.0 mL of solvent mixture B.

A. *Column*:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 40 volumes of *methanol R* and 60 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.5 with *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 21	100 → 0	0 → 100
21 - 24	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 20 µL of test solutions (a) and (b) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *ziprasidone for system suitability 1 CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to ziprasidone (retention time = about 7 min): impurity A = about 0.4; impurity B = about 0.8; impurity C = about 0.9.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.7;

— *impurity B in test solution (b)*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity A in test solution (b)*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity C in test solution (a)*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities in test solution (b)*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *disregard limit in test solution (b)*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to impurity C and any peak with a retention time greater than 20 min.

B. *Column*:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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— *stationary phase*: spherical *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 5 volumes of *methanol R*, 40 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 6.0 with a 280 g/L solution of *potassium hydroxide R*, and 55 volumes of *acetonitrile R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 20 µL of test solution (b) and reference solutions (b) and (c).

Run time 11 times the retention time of ziprasidone.

Identification of impurities Use the chromatogram supplied with *ziprasidone for system suitability 2 CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and E.

Relative retention With reference to ziprasidone (retention time = about 4.5 min): impurity D = about 2.0; impurity E = about 3.0.

System suitability Reference solution (c):

— *resolution*: minimum 6.0 between the peaks due to ziprasidone and impurity D.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.4; impurity E = 0.5;

— *impurities D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak eluting before the peak due to ziprasidone.

Limit:

— *total for tests A and B*: maximum 0.5 per cent.

Water (*2.5.12*)

3.7 per cent to 5.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

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ASSAY

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use*.

Solvent mixture water R, methanol R (40:60 *V/V*).

Test solution Dissolve 23.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution Dissolve 23.0 mg of ziprasidone hydrochloride monohydrate CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 40 volumes of methanol R and 60 volumes of a 6.8 g/L solution of potassium dihydrogen phosphate R adjusted to pH 3.0 with phosphoric acid R.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 20 µL.

Run time Twice the retention time of ziprasidone.

Retention time Ziprasidone = about 7 min.

System suitability Reference solution:

— symmetry factor: maximum 2.0 for the peak due to ziprasidone.

Calculate the percentage content of $C_{21}H_{22}Cl_2N_4OS$ from the declared content of ziprasidone hydrochloride monohydrate CRS.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*

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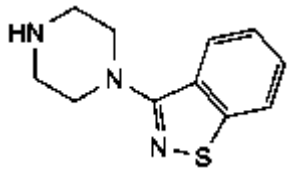
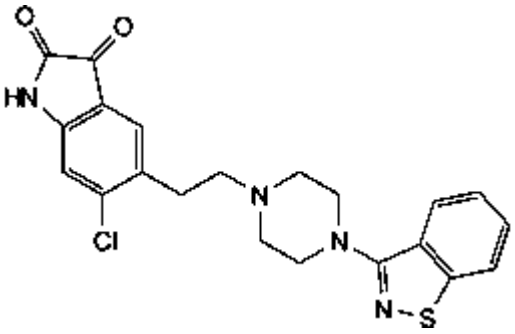
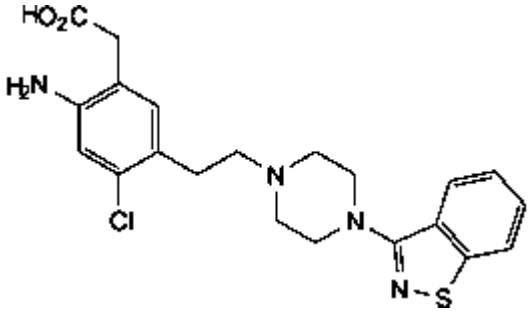


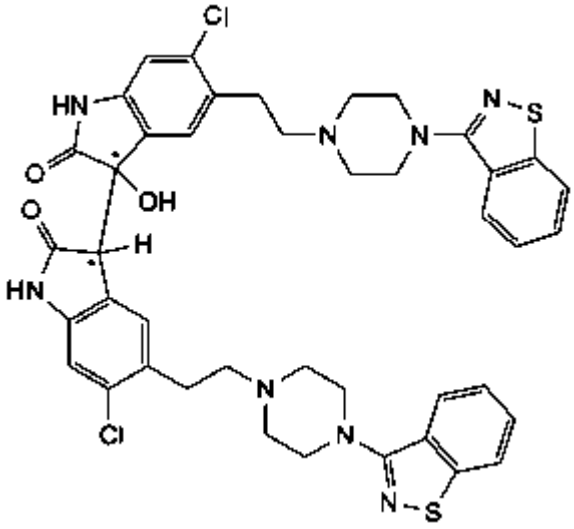
A. 3-piperazin-1-yl-1,2-benzisothiazole,



B. 5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1*H*-indole-2,3-dione,



C. 2-[2-amino-5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-4-chlorophenyl]acetic acid,



D. 5,5′-bis[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6,6′-dichloro-3-hydroxy-1,1′,3,3′-tetrahydro-2*H*,2′*H*-3,3′-biindole-2,2′-dione,

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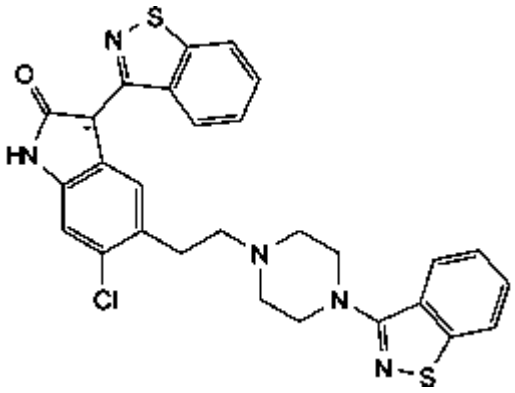

E. 3-(1,2-benzisothiazol-3-yl)-5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one.

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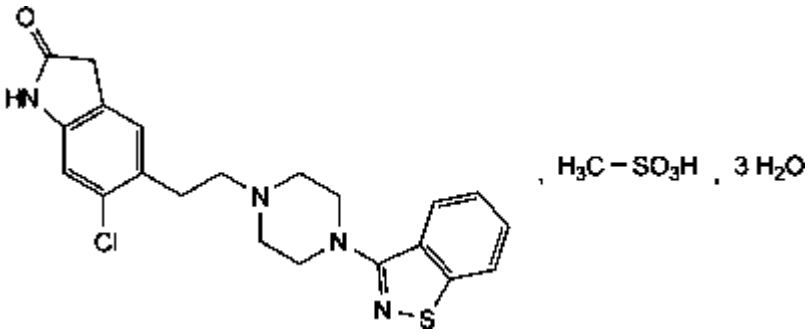
Ziprasidone Mesilate Trihydrate

General Notices

(Ph. Eur. monograph 2649)



$C_{22}H_{25}ClN_4O_4S_2,3H_2O$ 563.1 *199191-69-0*

Action and use

Dopamine D_2 receptor antagonist; serotonin 5HT2 receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

5-[2-[4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one methanesulfonate trihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in ziprasidone mesilate trihydrate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods 2.5.37. *Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, 2.5.38. *Methyl, ethyl and isopropyl methanesulfonate in active substances* and 2.5.39. *Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

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White or almost white powder.

Solubility

Very slightly soluble in water, slightly soluble in methanol, practically insoluble in acetonitrile.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *ziprasidone mesilate trihydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Carry out the tests protected from light and prepare the solutions immediately before use.

A. Liquid chromatography (2.2.29).

Solvent mixture *hydrochloric acid R*, *water R*, *methanol R* (0.04:40:60 *V/V/V*).

Test solution (a) Dissolve 27.0 mg of the substance to be examined in 35 mL of the solvent mixture, sonicate for about 2 min and shake. Dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 2.0 mL of test solution (a) to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 27.0 mg of *ziprasidone hydrochloride monohydrate CRS* in 35 mL of the solvent mixture, sonicate for about 2 min and shake. Dilute to 50.0 mL with the solvent mixture. Dilute 2.0 mL of the solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of *ziprasidone for system suitability 1 CRS* (containing impurities B and C) in a mixture of 40 volumes of *water R* and 60 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

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Mobile phase:

— *mobile phase A*: mix 40 volumes of *methanol R1* and 60 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	100	0
40 - 41	100 → 0	0 → 100
41 - 50	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 20 µL of test solution (a) and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *ziprasidone for system suitability 1 CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to ziprasidone (retention time = about 6 min): impurity B = about 0.8; impurity C = about 0.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline for the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B; minimum 2.0, where H_p = height above the baseline for the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ziprasidone.

Calculation of percentage contents:

— for each impurity, use the concentration of ziprasidone mesilate trihydrate in reference solution (c).

Limits:

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak with a retention time greater than 40 min.

B. Liquid chromatography (*2.2.29*).

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Solvent mixture hydrochloric acid R, water R, methanol R (0.04:20:80 *V/V/V*).

Test solution Dissolve 27 mg of the substance to be examined in 35 mL of the solvent mixture, sonicate for about 2 min and shake. Dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of ziprasidone for system suitability 2 CRS (containing impurities D and E) in 1 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 8 volumes of methanol R1, 42 volumes of acetonitrile for chromatography R and 50 volumes of a solution prepared as follows: dissolve 3.4 g of potassium dihydrogen phosphate R and 21.6 g of sodium octanesulfonate R in 900 mL of water for chromatography R, adjust to pH 3.0 with phosphoric acid R and dilute to 1000 mL with water for chromatography R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 20 µL.

Run time 15 times the retention time of ziprasidone.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities D and E.

Relative retention With reference to ziprasidone (retention time = about 3 min): impurity E = about 2.6; impurity D = about 7.8.

System suitability Reference solution (a):

— resolution: minimum 5.0 between the peaks due to impurities E and D.

Calculation of percentage contents:

— for each impurity, use the concentration of ziprasidone mesilate trihydrate in reference solution (b).

Limits:

— *impurity D*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak eluting before the peak due to ziprasidone.

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Limit:

— *total for tests A and B*: maximum 0.2 per cent.

Water (2.5.12)

8.5 per cent to 10.1 per cent, determined on 0.050 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 17.5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in test A for related substances with the following modifications.

Injection 20 µL of test solution (b) and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 1.7 for the peak due to ziprasidone.

Calculate the percentage content of $C_{22}H_{25}ClN_4O_4S_2$ taking into account the assigned content of *ziprasidone hydrochloride monohydrate CRS* and a conversion factor of 1.133.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Test A for related substances

A, B, C.

Test B for related substances

D, E.

Specified impurities *B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

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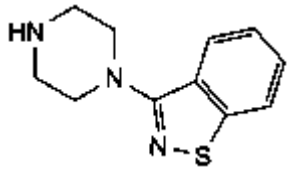
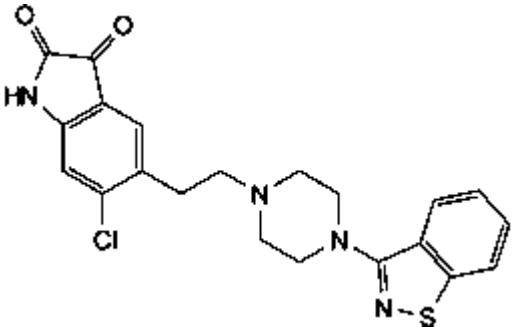
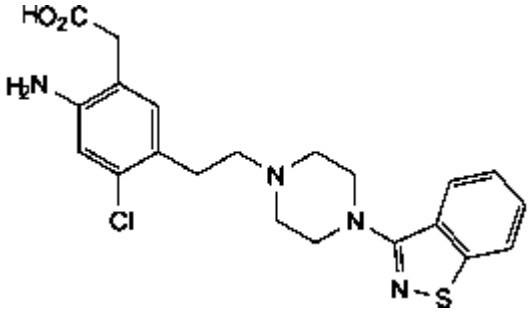
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, E.*



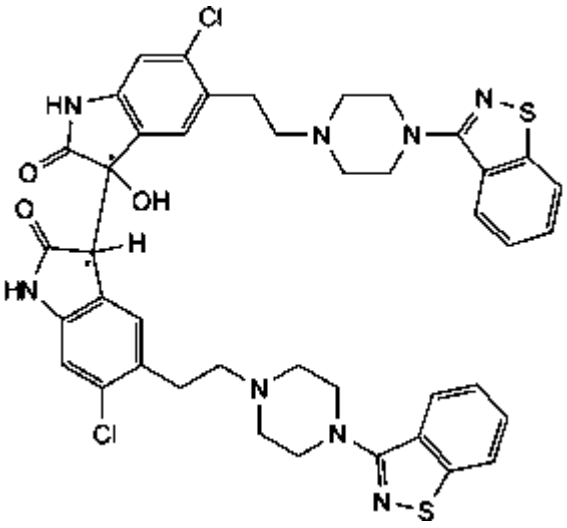
A. 3-piperazin-1-yl-1,2-benzisothiazole,



B. 5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1*H*-indole-2,3-dione,



C. 2-[2-amino-5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-4-chlorophenyl]acetic acid,



D. 5,5′-bis[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6,6′-dichloro-3-hydroxy-1,1′,3,3′-tetrahydro-2*H*,2′*H*-3,3′-biindole-2,2′-dione,

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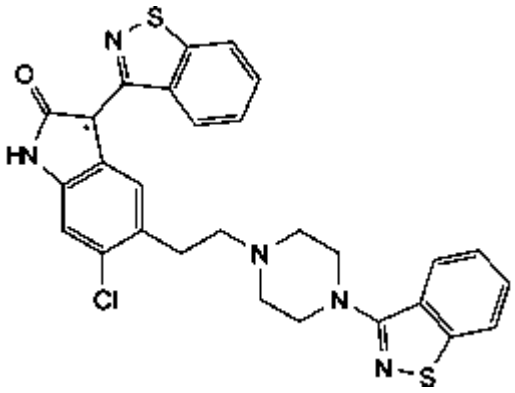

E. 3-(1,2-benzisothiazol-3-yl)-5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one.

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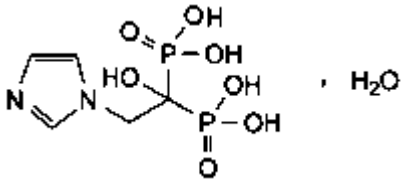
Zoledronic Acid Monohydrate

General Notices

(Ph. Eur. monograph 2743)



$C_5H_{10}N_2O_7P_2,H_2O$ 290.1 *165800-06-6*

Action and use

Bisphosphonate; treatment of osteolytic lesions, hypercalcaemia.

Ph Eur

DEFINITION

[1-Hydroxy-2-(1*H*-imidazol-1-yl)ethane-1,1-diyl]bis(phosphonic acid) monohydrate.

Content

99.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, practically insoluble in anhydrous ethanol and in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *zoledronic acid monohydrate CRS*.

B. Water (see Tests).

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TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 or BY_7 (2.2.2, Method II).

Dissolve 0.5 g in a 4 g/L solution of *sodium hydroxide R* and dilute to 50.0 mL with the same solution.

pH (2.2.3)

1.8 to 2.8.

Dissolve 0.150 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent. Sonicate for 10 min, if necessary.

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 10.8 g of *sodium octanesulfonate R* and 37 mg of *sodium edetate R* in *water for chromatography R*, add 10 mL of *perchloric acid R* and 2 mL of *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase, sonicate for 30 min, and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *zoledronic acid impurity A CRS*, 5 mg of *zoledronic acid impurity B CRS* and 2 mg of *sodium nitrate R* in the mobile phase and dilute to 50 mL with the mobile phase. To 1 mL of the solution add 7 mL of the mobile phase and dilute to 20 mL with the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylhexylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 20 °C.

Mobile phase *acetonitrile R1*, solution A (4:96 *V/V*).

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 215 nm.

Preconditioning Precondition the instrument and the column once before each series of injections as follows:

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— *instrument*: rinse the instrument without a column with a 25 per cent *V/V* solution of *acetic acid R* at 5 mL/min for about 20 min. Then, rinse with *water for chromatography R* at 5 mL/min for about 2 h;

— *column*: rinse the column with the mobile phase at 0.6 mL/min for about 1 h. During the rinsing, inject the test solution 15 times, applying a run time of about 3 min for each injection.

Injection 10 µL.

Run time 5 times the retention time of zoledronic acid.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B and the nitrate ion.

Relative retention With reference to zoledronic acid (retention time = about 6 min): nitrate = about 0.6; impurity B = about 0.7; impurity A = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity A and zoledronic acid; minimum 1.5 between the peaks due to the nitrate ion and impurity B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 1.9;

— for each impurity, use the concentration of zoledronic acid monohydrate in reference solution (b).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent, disregard the peak due to the nitrate ion.

Impurities E and F

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase B, sonicate if necessary, and dilute to 10.0 mL with mobile phase B.

Reference solution (a) Dissolve 95.0 mg of *anhydrous sodium dihydrogen phosphate R* and 79.0 mg of *phosphorous acid R* (impurity E) in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 34.0 mg of *sodium chloride R* in *water R* and dilute to 100.0 mL with the same solvent.

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Reference solution (c) To 1.0 mL of reference solution (a) add 0.5 mL of reference solution (b) and dilute to 100.0 mL with mobile phase B.

Reference solution (d) Dilute 0.1 mL of reference solution (a) to 100 mL with mobile phase B.

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4.0 mm;

— *stationary phase*: *anion-exchange resin R* (13 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *anion-exchange resin R* (9 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *carbon dioxide-free water R*;

— *mobile phase B*: 4.0 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 13	80 → 70	20 → 30
13 - 17	70 → 60	30 → 40
17 - 29	60	40

Flow rate 1.0 mL/min.

Detection Conductivity detector; use a self-regenerating anion suppressor.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities E and F; use the chromatogram obtained with reference solution (b) to identify the peak due to the chloride ion.

Relative retention With reference to chloride (retention time = about 5 min): impurity E = about 1.2; impurity F = about 3.4.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to the chloride ion and impurity E in the chromatogram obtained with reference solution (c);

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— *signal-to-noise ratio*: minimum 10 for the peak due to impurity F in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— for each impurity, use the concentration of the corresponding impurity in reference solution (c).

Limits:

— *impurities E, F*: for each impurity, maximum 0.15 per cent.

Water (2.5.12)

5.0 per cent to 7.5 per cent, determined on 0.100 g.

ASSAY

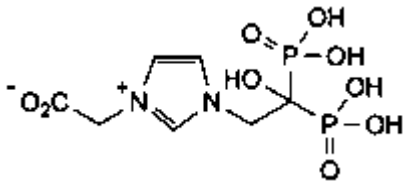
Dissolve 0.150 g in 50 mL of *carbon dioxide-free water R*. Sonicate for 10 min, if necessary. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Read the volume added at the 3rd inflexion point.

1 mL of *0.1 M sodium hydroxide* is equivalent to 9.07 mg of $C_5H_{10}N_2O_7P_2$.

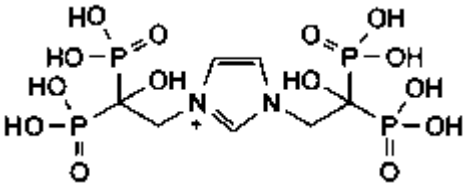
IMPURITIES

Specified impurities B, E, F.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D.



A. [1-(2-hydroxy-2,2-diphosphonoethyl)-1*H*-imidazol-3-ium-3-yl]acetate,



B. 1,3-bis(2-hydroxy-2,2-diphosphonoethyl)-1*H*-imidazol-3-ium,

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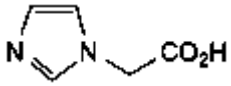
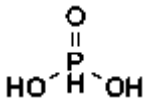
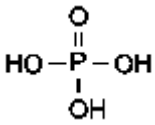
C. 1*H*-imidazole,



D. (1*H*-imidazol-1-yl)acetic acid,



E. phosphonic acid (phosphorous acid),



F. phosphoric acid.

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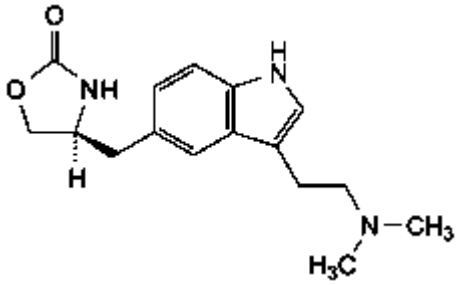
Zolmitriptan

General Notices

(Ph. Eur. monograph 2737)



$C_{16}H_{21}N_3O_2$ 287.4 *139264-17-8*

Action and use

Serotonin 5HT1 receptor agonist; treatment of migraine.

Ph Eur

DEFINITION

(4*S*)-4-[[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1,3-oxazolidin-2-one.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble or very slightly soluble in water, freely soluble in methanol, sparingly soluble in acetone.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

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Comparison *zolmitriptan CRS*.

TESTS

Enantiomeric purity

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *zolmitriptan impurity A CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase. To 1.0 mL of the solution add 1.0 mL of the test solution and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 35 °C.

Mobile phase *diethylamine R*, *2-propanol R*, *methanol R*, *heptane R* (0.1:10:15:75 *V/V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 285 nm.

Injection 10 µL.

Run time Twice the retention time of zolmitriptan.

Relative retention With reference to zolmitriptan (retention time = about 7 min): impurity A = 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and zolmitriptan.

Calculation of percentage content:

— for impurity A, use the concentration of zolmitriptan in reference solution (a).

Limit:

— *impurity A*: maximum 0.10 per cent.

Related substances

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Liquid chromatography (2.2.29).

Solvent mixture Mobile phase B, mobile phase A (10:90 *V/V*).

Test solution (a) Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 5.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *zolmitriptan for system suitability CRS* (containing impurities C, H and I) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (c) Dissolve 10.0 mg of *zolmitriptan CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped solid core phenylhexylsilyl silica gel for chromatography R* (2.7 µm);

— *temperature*: 20 °C.

Mobile phase A Dissolve 2.72 g of *potassium dihydrogen phosphate R* and 0.94 g of *sodium hexanesulfonate R* in *water for chromatography R*, adjust to pH 2.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

Mobile phase B *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	90	10
0.5 - 4	90 → 85	10 → 15
4 - 8	85	15
8 - 9	85 → 80	15 → 20
9 - 10	80	20
10 - 12	80 → 70	20 → 30
12 - 13	70	30

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 210 nm.

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Injection 2 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *zolmitriptan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C, H and I.

Relative retention With reference to zolmitriptan (retention time = about 5 min): impurity H = about 0.97; impurity I = about 1.1; impurity C = about 2.0.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 8, where H_p = height above the baseline of the peak due to impurity H and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to zolmitriptan; minimum 1.5, where H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to zolmitriptan.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 2.0;

— for each impurity, use the concentration of zolmitriptan in reference solution (a).

Limits:

— *impurity C*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 283 nm.

Injection 2 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{16}H_{21}N_3O_2$ taking into account the assigned content of *zolmitriptan CRS*.

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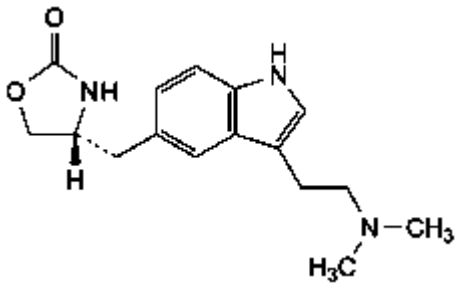
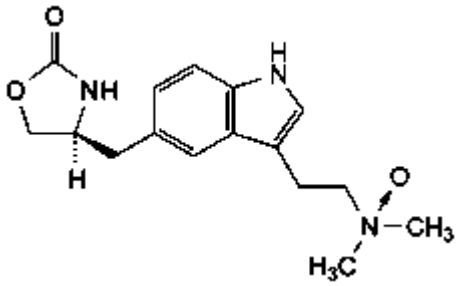
IMPURITIES

Specified impurities A, C.

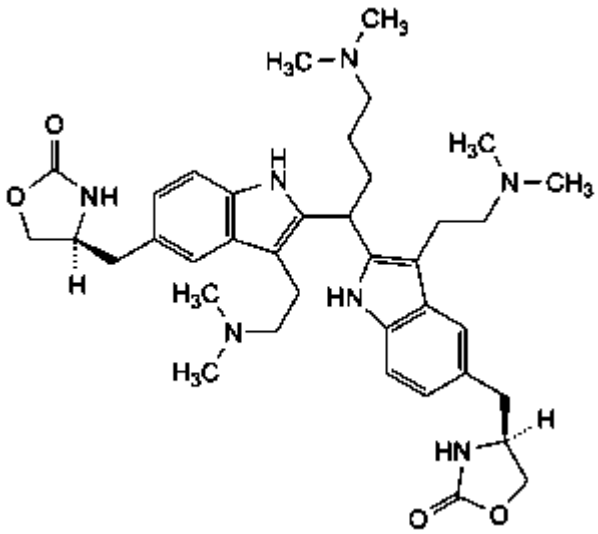
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D, E, F, G, H, I.



A. (4*R*)-4-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1,3-oxazolidin-2-one,



B. *N*,*N*-dimethyl-2-[5-[[(4*S*)-2-oxo-1,3-oxazolidin-4-yl]methyl]-1*H*-indol-3-yl]ethan-1-amine *N*-oxide,



C. (4*S*,4′*S*)-4,4′-[[4-(dimethylamino)butane-1,1-diyl]bis[[3-[2-(dimethylamino)ethyl]-1*H*-indole-2,5-diyl]methylene]]bis(1,3-oxazolidin-2-one),

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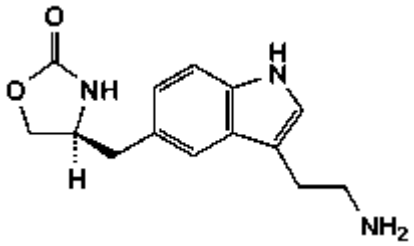
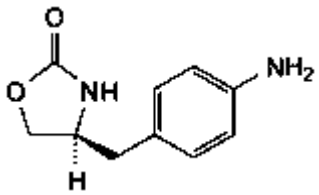
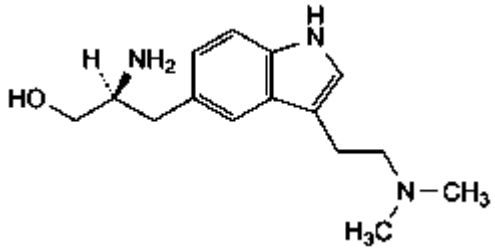


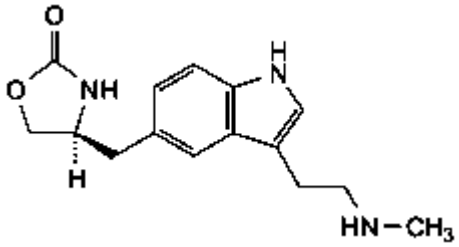
D. (4*S*)-4-[[3-(2-aminoethyl)-1*H*-indol-5-yl]methyl]-1,3-oxazolidin-2-one,



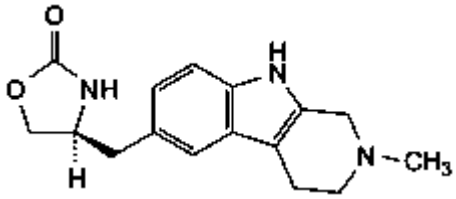
E. (4*S*)-4-[(4-aminophenyl)methyl]-1,3-oxazolidin-2-one,



F. (2*S*)-2-amino-3-[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]propan-1-ol,



G. (4*S*)-4-[[3-[2-(methylamino)ethyl]-1*H*-indol-5-yl]methyl]-1,3-oxazolidin-2-one,



H. (4*S*)-4-[(2-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-6-yl)methyl]-1,3-oxazolidin-2-one,

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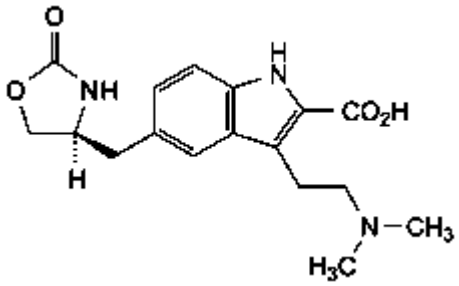

I. 3-[2-(dimethylamino)ethyl]-5-[[(4*S*)-2-oxo-1,3-oxazolidin-4-yl]methyl]-1*H*-indole-2-carboxylic acid.

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Zolpidem Tablets

General Notices

Action and use

Non-benzodiazepine hypnotic.

DEFINITION

Zolpidem Tablets contain Zolpidem Tartrate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of zolpidem tartrate, $C_{42}H_{48}N_6O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 30 mg of Zolpidem Tartrate with 5 mL of *water*, centrifuge and filter the supernatant liquid through a 0.45-µm nylon filter. To the filtrate add 0.1 mL of *diethylamine* and dilute to 10 mL with *methanol*.

(2) Dissolve 15 mg of *zolpidem tartate BPCRS* in 2.5 mL of *methanol*, add 0.05 mL of *diethylamine* and dilute to 5 mL with *methanol*.

(3) Dilute 1 volume of solution (2) to 2 volumes with a 0.3% w/v solution of *flunitrazepam BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *diethylamine*, 45 volumes of *cyclohexane* and 45 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.00055% w/v of Zolpidem Tartrate.

(2) 0.00055% w/v of *zolpidem* tartate *BPCRS* in the medium.

(3) 0.005% w/v each of *zolpidem tartrate BPCRS* and *zolpidem impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapack C18 column is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

18 volumes of *acetonitrile*, 23 volumes of *methanol* and 59 volumes of a solution containing 0.56% w/v of *orthophosphoric acid* adjusted to pH 5.5 with *triethylamine*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and zolpidem is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of zolpidem tartrate, $C_{42}H_{48}N_6O_8$, in the medium from the chromatograms obtained and using the declared content of $C_{42}H_{48}N_6O_8$ in *zolpidem tartate BPCRS*.

LIMITS

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The amount of Zolpidem Tartrate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 10 mg of Zolpidem Tartrate with 80 mL of mobile phase A, mix with the aid of ultrasound, add sufficient mobile phase A to produce 100 mL and filter through a 0.45-µm nylon filter.
(2) Dilute 1 volume of solution (1) to 50 volumes with mobile phase A. Dilute 1 volume of this solution to 10 volumes with mobile phase A.
(3) 0.005% w/v each of *zolpidem tartrate BPCRS* and *zolpidem impurity A BPCRS* in mobile phase A.
(4) Dilute 1 volume of solution (2) to 2 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapack C18 column is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 18 volumes of *acetonitrile*, 23 volumes of *methanol* and 59 volumes of a solution containing 0.56% w/v of *phosphoric acid* adjusted to pH 5.5 with *triethylamine*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0–20	100	0	isocratic
20–40	100→50	0→50	linear gradient
40–45	50	50	isocratic
45–46	50→100	50→0	linear gradient
46–60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to zolpidem (retention time about 10.5 minutes) are: tartaric acid, about 0.16 and impurity A, about 0.8.

SYSTEM SUITABILITY

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The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and zolpidem is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the area of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak:

with an area less than the area of the principal peak obtained with solution (4) (0.1%);

due to tartaric acid.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Add 80 mL of the mobile phase to a quantity of the powdered tablets containing 10 mg of Zolpidem Tartrate and mix with the aid of ultrasound. Add sufficient mobile phase to produce 100 mL and filter through a 0.45-µm nylon filter. Dilute 1 volume of the filtrate to 10 volumes.

(2) 0.001% w/v of *zolpidem tartrate BPCRS*.

(3) 0.005% w/v each of *zolpidem tartrate BPCRS* and *zolpidem impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and zolpidem is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{42}H_{48}N_6O_8$ in the tablets using the declared content of $C_{42}H_{48}N_6O_8$ in *zolpidem tartrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Zolpidem Tartrate.

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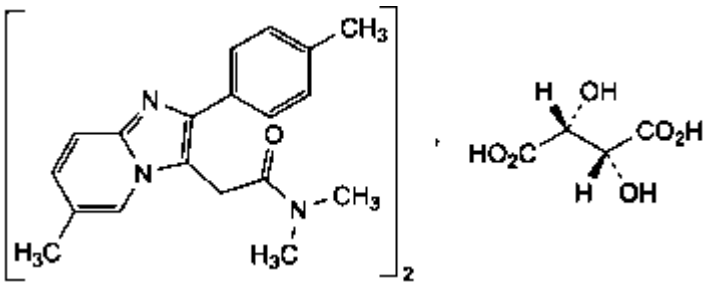
Zolpidem Tartrate

General Notices

(Ph. Eur. monograph 1280)



$C_{42}H_{48}N_6O_8$ 765 *99294-93-6*

Action and use

Non-benzodiazepine hypnotic.

Preparation

Zolpidem Tablets

Ph Eur

DEFINITION

Bis[*N*,*N*-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]acetamide] (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

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First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 0.10 g in 10 mL of a 10.3 g/L solution of *hydrochloric acid R*. Add 10 mL of *water R*. Add dropwise with stirring 1 mL of *dilute ammonia R2*. Filter and collect the resulting precipitate. Wash the precipitate with *water R* and then dry at 105 °C for 2 h. Examine the precipitate as a disc.

Comparison Repeat the operations using 0.10 g of *zolpidem tartrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in 5 mL of *methanol R*, add 0.1 mL of *diethylamine R* and dilute to 10 mL with *methanol R*.

Reference solution (a) Dissolve 50 mg of *zolpidem tartrate CRS* in 5 mL of *methanol R*, add 0.1 mL of *diethylamine R* and dilute to 10 mL with *methanol R*.

Reference solution (b) Dissolve 50 mg of *flunitrazepam CRS* in 5 mL of *methylene chloride R* and dilute to 10 mL with the same solvent. Mix 1 mL of this solution and 1 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *diethylamine R*, *cyclohexane R*, *ethyl acetate R* (10:45:45 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Zolpidem = about 0.3; flunitrazepam = about 0.5.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 0.1 g in 1 mL of *methanol R*, heating gently. 0.1 mL of this solution gives reaction (b) of tartrates (2.3.1).

TESTS

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Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 or BY_6 (2.2.2, Method II). *Prepare the solutions protected from light and carry out the test as rapidly as possible.*

Triturate 0.25 g with 0.125 g of *tartaric acid R*. Dissolve the mixture in 20 mL of *water R* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.5 mg of *zolpidem for system suitability CRS* (containing impurities A and B) in the mobile phase and dilute to 5 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase Mix 18 volumes of *acetonitrile R*, 23 volumes of *methanol R* and 59 volumes of a 5.6 g/L solution of *phosphoric acid R* previously adjusted to pH 5.5 with *triethylamine R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 4 times the retention time of zolpidem.

Identification of impurities Use the chromatogram supplied with *zolpidem for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to zolpidem (retention time = about 7 min): tartaric acid = about 0.1; impurity A = about 0.8; impurity B = about 3.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and zolpidem.

Calculation of percentage contents:

— for each impurity, use the concentration of zolpidem tartrate in reference solution (a).

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Limits:

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to tartaric acid.

Water (2.5.12)

Maximum 3.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 20 mL of *anhydrous acetic acid R* and 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 38.24 mg of $C_{42}H_{48}N_6O_8$.

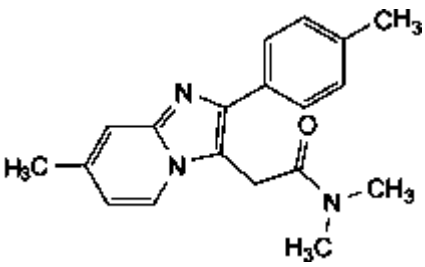
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D, E, F.



A. *N*,*N*-dimethyl-2-[7-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]acetamide,

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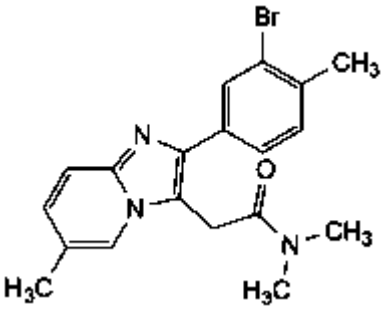
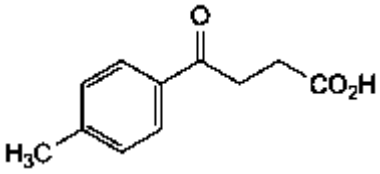
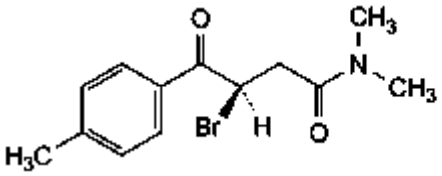


B. 2-[2-(3-bromo-4-methylphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl]-*N*,*N*-dimethylacetamide,

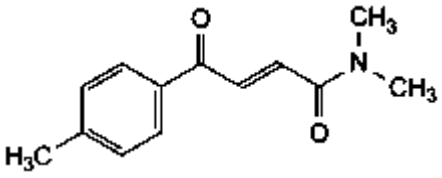


C. 4-(4-methylphenyl)-4-oxobutanoic acid,

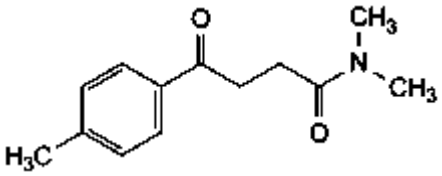


and enantiomer

D. (3*RS*)-3-bromo-*N*,*N*-dimethyl-4-(4-methylphenyl)-4-oxobutanamide,



E. (2*E*)-*N*,*N*-dimethyl-4-(4-methylphenyl)-4-oxobut-2-enamide,



F. *N*,*N*-dimethyl-4-(4-methylphenyl)-4-oxobutanamide.

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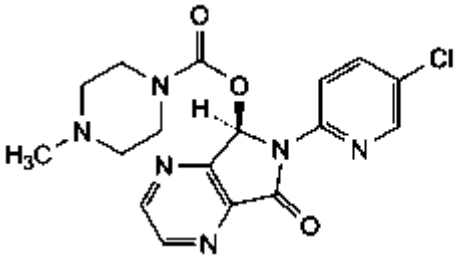
Zopiclone

General Notices

(Ph. Eur. monograph 1060)



and enantiomer

$C_{17}H_{17}ClN_6O_3$ 388.8 *43200-80-2*

Action and use

Non-benzodiazepine hypnotic.

Preparation

Zopiclone Tablets

Ph Eur

DEFINITION

(5*RS*)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

Content

98.5 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or slightly yellowish powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, practically insoluble in ethanol (96 per cent).

It dissolves in dilute mineral acids.

IDENTIFICATION

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IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in a 3.5 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with a 3.5 g/L solution of *hydrochloric acid R*.

Spectral range 220-350 nm.

Absorption maximum At 303 nm.

Specific absorbance at the absorption maximum 340 to 380.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *zopiclone CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *zopiclone CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *triethylamine R*, *acetone R*, *ethyl acetate R* (2:50:50 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 1.0 g in *dimethylformamide R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

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Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

Optical rotation (2.2.7)

-0.05° to + 0.05°.

Dilute 10.0 mL of solution S to 50.0 mL with dimethylformamide R.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4.0 mg of zopiclone oxide CRS (impurity A) in the mobile phase and dilute to 10.0 mL with the mobile phase. To 5.0 mL of the solution add 0.5 mL of the test solution and dilute to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 2.0 mg of zopiclone impurity B CRS in the mobile phase and dilute to 5.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 38 volumes of acetonitrile R and 62 volumes of a solution containing 8.1 g/L of sodium laurilsulfate R and 1.6 g/L of sodium dihydrogen phosphate R, previously adjusted to an apparent pH of 3.5 with a 10 per cent *V/V* solution of phosphoric acid R.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 303 nm.

Injection 20 µL.

Run time 1.5 times the retention time of zopiclone.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Retention time Zopiclone = 27 min to 31 min; if necessary, adjust the concentration of acetonitrile in the mobile phase.

Relative retention With reference to zopiclone: impurity B = about 0.1; impurity A = about 0.9.

System suitability Reference solution (b):

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— *resolution*: minimum 3.0 between the peaks due to impurity A and zopiclone; if necessary, adjust the mobile phase to pH 4.0 with a 10 per cent *V/V* solution of *phosphoric acid R*.

Limits:

— *impurity B*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total (excluding impurity B)*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

2-Propanol

Gas chromatography (*2.2.28*).

Internal standard solution Dilute 5 mL of *ethanol R1* to 100 mL with *ethylene chloride R*. Dilute 1 mL of the solution to 10 mL with *ethylene chloride R*.

Test solution Dissolve 0.25 g of the substance to be examined in *ethylene chloride R*, add 0.5 mL of the internal standard solution and dilute to 5.0 mL with *ethylene chloride R*.

Reference solution Dilute 4.5 mL of *2-propanol R* to 100.0 mL with *ethylene chloride R*. To 1.0 mL of the solution add 10.0 mL of the internal standard solution and dilute to 100.0 mL with *ethylene chloride R*.

Column:

— *material*: fused silica;

— *size*: *l* = 10 m, Ø = about 0.53 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (film thickness 20 µm).

Carrier gas *helium for chromatography R*.

Flow rate 4 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	50
	5 - 10	50 → 70

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	Time (min)	Temperature (°C)
	10 - 14	70
	14 - 20.5	70 → 200
	20.5 - 27.5	200
Injection port		150
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Calculate the percentage content *m/m* of 2-propanol taking its density to be 0.785 g/mL at 20 °C.

Limit:

— *2-propanol*: maximum 0.7 per cent *m/m*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 10 mL of *anhydrous acetic acid R* and 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 38.88 mg of $C_{17}H_{17}ClN_6O_3$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*

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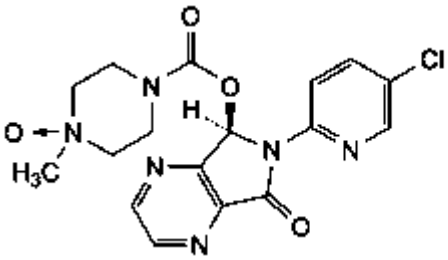
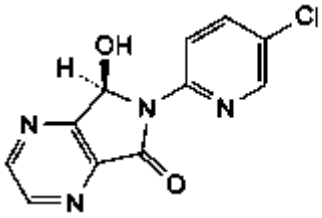
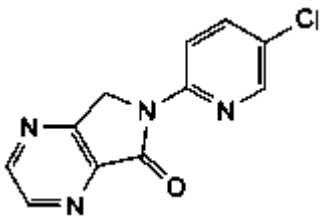

and enantiomer

A. (5*RS*)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate 4-oxide (zopiclone oxide),


and enantiomer

B. (7*RS*)-6-(5-chloropyridin-2-yl)-7-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one,



C. 6-(5-chloropyridin-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one.

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Zopiclone Tablets

General Notices

Action and use

Non-benzodiazepine hypnotic.

DEFINITION

Zopiclone Tablets contain Zopiclone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of zopiclone, $C_{17}H_{17}ClN_6O_3$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 37.5 mg of Zopiclone with 30 mL of *acetone*, add sufficient *acetone* to produce 50 mL and filter. Evaporate the filtrate to dryness on a water bath and dry the residue in an oven at 60° for 2 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of zopiclone *(RS 430)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 305 nm, Appendix II B using *0.1M hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of zopiclone *BPCRS* using *0.1M hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

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Calculate the total content of zopiclone, $C_{17}H_{17}ClN_6O_3$, in the medium using the declared content of $C_{17}H_{17}ClN_6O_3$ in *zopiclone BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 37.5 mg of Zopiclone with 50 mL of the mobile phase for 30 minutes, shake for a further 20 minutes. Cool the solution and add sufficient of the mobile phase to produce 100 mL, mix and filter through a 0.45-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.0006% w/v of *2-amino-5-chloropyridine BPCRS* and 0.0001% w/v of each *zopiclone BPCRS* *and* *zopiclone oxide EPCRS* in the mobile phase.

(4) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a detection wavelength of 303 nm.

(e) Use a column temperature of 30°.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of zopiclone.

When the chromatograms are recorded under the prescribed conditions the retention times relative to zopiclone (retention time, about 26 minutes) are: 2-amino-5-chloropyridine, about 0.3 and zopiclone oxide, about 0.8.

MOBILE PHASE

375 volumes of *acetonitrile* and 625 volumes of a solution containing 0.5% w/v of *sodium dodecyl sulfate* and 0.01% w/v of *sodium dihydrogen orthophosphate* previously adjusted to pH 4.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to zopiclone and zopiclone-*N*-oxide is at least 3.0;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of the principal peak is not less than 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of the peak due to 2-amino-5-chloropyridine is not greater than the area of the peak due to 2-amino-5-chloropyridine in solution (3) (1.5%);

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excluding 2-amino-5-chloropyridine, the area of any *secondary peak* is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the impurities is not greater than 2%.

Disregard any peak with an area less than the area of the principal peak in solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Zopiclone comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Finely crush one tablet, add sufficient of the mobile phase to produce a solution with an expected concentration of 0.0075% w/v, shake and filter.
(2) 0.0075% w/v of *zopiclone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a detection wavelength of 303 nm.
(e) Use a column temperature of 30°.
(f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of *acetonitrile* and 1 volume of a solution containing 0.5% w/v of *sodium dodecyl sulfate* and 0.1% w/v of *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to zopiclone is at most 1.4.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{17}ClN_6O_3$ in the tablets using the declared content of $C_{17}H_{17}ClN_6O_3$ in *zopiclone BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of zopiclone

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of zopiclone

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

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(1) Shake a quantity of the powdered tablets containing 37.5 mg of Zopiclone with 60 mL of the mobile phase for 20 minutes, add sufficient of the mobile phase to produce 500 mL, mix and filter (Whatman GF/C is suitable), discarding the first 10 mL of filtrate.

(2) 0.0075% w/v of *zopiclone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to zopiclone is at most 1.4.

DETERMINATION OF CONTENT

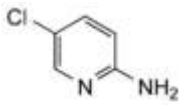
Calculate the content of $C_{17}H_{17}ClN_6O_3$ in the tablets using the declared content of $C_{17}H_{17}ClN_6O_3$ in *zopiclone BPCRS*.

STORAGE

Zopiclone Tablets should be protected from light.

IMPURITIES

In addition to the impurities listed under Zopiclone, the impurities limited by the requirements of this monograph include:



2-amino-5-chloropyridine.

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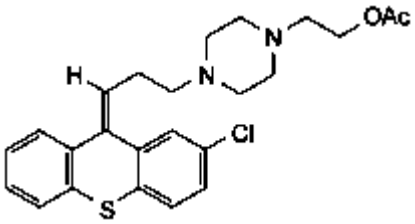
Zuclopenthixol Acetate

General Notices



$C_{24}H_{27}ClN_2O_2S$ 443.0 *85721-05-7*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Zuclopenthixol Acetate Injection

DEFINITION

Zuclopenthixol Acetate is (*Z*)-2-4-[3-(2-chlorothioxanthene-9-ylidene)propyl]piperazin-1-ylethyl acetate. It contains not less than 98.0% and not more than 102.0% of $C_{24}H_{27}ClN_2O_2S$, calculated with reference to the dried substance.

CHARACTERISTICS

A yellowish, viscous oil.

Very slightly soluble in *water*; very soluble in *dichloromethane*, in *ethanol (96%)* and in *ether*.

IDENTIFICATION

A. The *light absorption* of a 0.0015% w/v solution in *ethanol (96%)*, Appendix II B, in the range 210 to 350 nm exhibits two maxima at 230 and 268 nm. The *absorbances* at the maxima are about 1.18 and 0.51 respectively.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of zuclopenthixol acetate *(RS 363)*.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions protected from light.

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(1) 0.250% w/v of the substance being examined in *dichloromethane*.

(2) Dilute 1 volume of solution (1) to 100 volume with *dichloromethane*, further dilute 1 volume of this solution to 10 volumes with the same solvent.

(3) Dilute 1 volume of solution (2) to 2 volumes with *dichloromethane*.

(4) 0.00050% w/v of *2- chlorothioxanthone BPCRS* in *dichloromethane*.

(5) 0.000625% w/v of *zuclopenthixol hydrochloride BPCRS* in a solution containing 3 drops of *diethylamine* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F254 plates are suitable).

(b) Use an unlined tank and the mobile phase as described below.

(c) Apply 4 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, allow it to dry in air, spray with a mixture of equal volumes of *sulfuric acid* and *absolute ethanol*, heat at 110° for 5 minutes and examine under *ultraviolet light (365 nm)* immediately.

MOBILE PHASE

10 volumes of *diethylamine*, 40 volumes of *dichloromethane* and 50 volumes of *cyclohexane*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to 2-chlorothioxanthone is not more intense than the spot in the chromatogram obtained with solution (4) (0.2%);

any spot corresponding to zuclopenthixol is not more intense than the spot in the chromatogram obtained with solution (5) (0.25%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.1%);

not more than three other secondary spots are more intense than the spot in the chromatogram obtained with solution (3) (0.05%).

trans-Isomer

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *dichloromethane* protected from light.

(1) 0.040% w/v of the substance being examined.

(2) 0.00046% w/v of *trans-clopenthixol acetate dihydrochloride BPCRS* (equivalent to 0.00040% w/v of *trans*-clopenthixol acetate).

(3) 0.020% w/v of the substance being examined and 0.023% w/v of trans-*clopenthixol acetate dihydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use stainless steel column (25 cm x 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Spherisorb S 5W is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use ambient temperature.

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(e) Use a detection wavelength of 254 nm.

(f) Inject 15 µL of each solution.

MOBILE PHASE

0.03 volume of 13.5M *ammonia*, 45 volumes of *dichloromethane*, 45 volumes of *heptane* and 50 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the principal peaks is at least 2.6.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to *trans*-clopenthixol acetate is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%).

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, loses not more than 0.4% of its weight, Appendix XI D. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

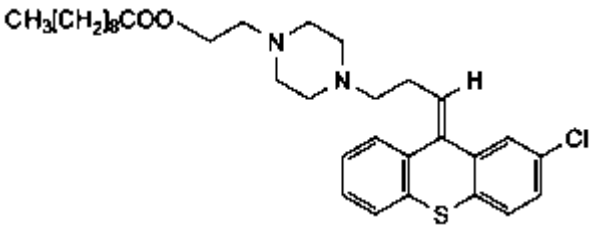
ASSAY

Dissolve 0.2 g in 50 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 22.15 mg of $C_{24}H_{27}ClN_2O_2S$.

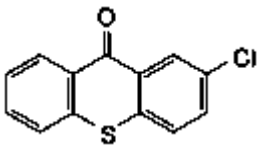
STORAGE

Zuclopenthixol Acetate should be protected from light and stored at a temperature not exceeding -20°.

IMPURITIES



A. *trans*-clopenthixol acetate*(*trans-*isomer),*



B. 2-chlorothioxanthone,

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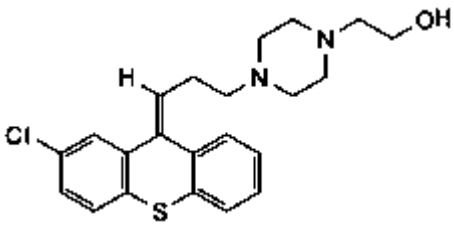

C. zuclopenthixol.

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Zuclopenthixol Acetate Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Zuclopenthixol Acetate Injection is a sterile solution of Zuclopenthixol Acetate in a suitable vegetable oil.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of zuclopenthixol acetate, $C_{24}H_{27}ClN_2O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

(1) Dilute a volume of the injection with *ethanol* (*96%*) to contain 0.5% w/v of Zuclopenthixol Acetate.

(2) 0.5% w/v of *zuclopenthixol acetate dihydrochloride BPCRS* in *ethanol* (*96%*).

(3) 0.5% w/v each of *zuclopenthixol acetate dihydrochloride BPCRS* and *zuclopenthixol decanoate dihydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a 1% w/v solution of *sodium molybdate* in *sulfuric acid*, heat at 110° for 20 minutes and examine in daylight.

MOBILE PHASE

3 volumes of *diethylamine* and 90 volumes of *cyclohexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

(1) Dissolve a quantity of the injection containing 0.10 g of Zuclopenthixol Acetate in sufficient *dichloromethane* to produce 50 mL.

(2) 0.0010% w/v of *2-chlorothioxanthone BPCRS* in *dichloromethane*.

(3) 0.0020% w/v of *zuclopenthixol hydrochloride BPCRS* in *dichloromethane* containing a few drops of *diethylamine*.

(4) 0.00040% w/v of *zuclopenthixol hydrochloride BPCRS* in *dichloromethane* containing a few drops of *diethylamine*.

(5) 0.00020% w/v of *zuclopenthixol hydrochloride BPCRS* in *dichloromethane* containing a few drops of *diethylamine*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a mixture of equal volumes of *sulfuric acid* and *absolute ethanol*, heat at 110° for 5 minutes and examine under *ultraviolet light* (*365 nm*).

MOBILE PHASE

10 volumes of *diethylamine*, 40 volumes of *dichloromethane* and 50 volumes of *cyclohexane*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to 2-chlorothioxanthone is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%);

any spot corresponding to zuclopenthixol is not more intense than the spot in the chromatogram obtained with solution (3) (1%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (4) (0.2%);

and not more than one other *secondary spot* spot is more intense than the spot in the chromatogram obtained with solution (5) (0.1%).

trans-Isomer

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) Dissolve a quantity of the injection containing 20 mg of Zuclopenthixol Acetate in 25 mL of *dichloromethane* and dilute to 50 mL with *dichloromethane*.

(2) Dissolve 23 mg of trans-*clopenthixol acetate dihydrochloride BPCRS* (equivalent to 20 mg of *trans*-clopenthixol acetate) in sufficient *dichloromethane* containing a few drops of *diethylamine* to produce 50 mL; dilute 1 mL of the resulting solution to 100 mL with *dichloromethane*.

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(3) Mix equal volumes of solution (1) and undiluted solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Spherisorb S 5W is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

0.08 of a volume of 13.5M *ammonia*, 45 volumes of *dichloromethane*, 45 volumes of n-*heptane* and 50 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the principal peaks is at least 2.6.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to *trans*-clopenthixol acetate is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Prepare a 0.2% w/v solution of cis-*flupenthixol propionate dihydrochloride BPCRS* (internal standard) in *dichloromethane*. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the injection containing 20 mg of Zuclopenthixol Acetate in 25 mL of *dichloromethane*, add 5 mL of the internal standard solution and dilute to 50 mL with *dichloromethane*.

(2) Dissolve 20 mg of *zuclopenthixol acetate dihydrochloride BPCRS* in 25 mL of *dichloromethane* containing a few drops of *diethylamine*, add 5 mL of the internal standard solution and dilute to 50 mL with *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under *trans*-Isomer may be used.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the injection, Appendix V G, and calculate the content of $C_{24}H_{27}ClN_2O_2S$ using the declared content of $C_{24}H_{27}ClN_2O_2S$ in *zuclopenthixol acetate dihydrochloride BPCRS*.

STORAGE

Zuclopenthixol Acetate Injection should be protected from light.

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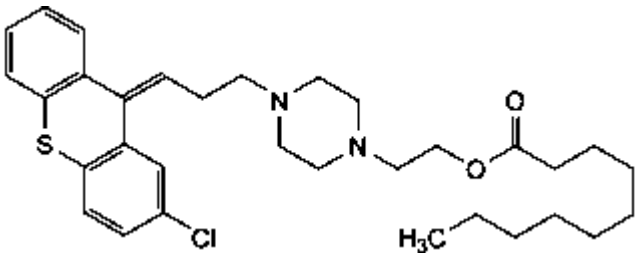
Zuclopenthixol Decanoate

General Notices

(Ph. Eur. monograph 1707)



$C_{32}H_{43}ClN_2O_2S$ 555.2 *64053-00-5*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Zuclopenthixol Decanoate Injection

Ph Eur

DEFINITION

2-[4-[3-[(9*Z*)-2-Chloro-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethyl decanoate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, viscous, oily liquid.

Solubility

Very slightly soluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

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Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of zuclopenthixol decanoate*.

TESTS

Appearance of solution

The solution is clear (2.2.1).

Using an ultrasonic bath, dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Solution A Dissolve 8.89 g of *docusate sodium R* in *water for chromatography R*, stirring for about 6-8 h, and dilute to 1000 mL with the same solvent.

Test solution Dissolve 25.0 mg of the substance to be examined in *acetonitrile R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 5.0 mg of *zuclopenthixol impurity B CRS* in *acetonitrile R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *acetonitrile R*.

Reference solution (c) Dissolve the contents of a vial of *zuclopenthixol for system suitability CRS* (containing impurities A, B and C) in 1 mL of *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 25 volumes of solution A and 75 volumes of *anhydrous ethanol R*, then add 0.1 volumes of *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL.

Run time Twice the retention time of zuclopenthixol decanoate.

Identification of impurities Use the chromatogram supplied with *zuclopenthixol for system suitability CRS* and the chromatograms obtained with reference solutions (b) and (c) to identify the peaks due to impurities A, B and C.

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Relative retention With reference to zuclopenthixol decanoate (retention time = about 12 min): impurity C = about 0.4; impurity B = about 0.5; impurity A = about 1.1.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B; and minimum 2.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to zuclopenthixol decanoate.

Limits:

— *impurity A*: not more than 1.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.3 per cent);

— *impurity B*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity C*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 27.76 mg of $C_{32}H_{43}ClN_2O_2S$.

STORAGE

Under an inert gas in an airtight container, protected from light, at -20 °C or below.

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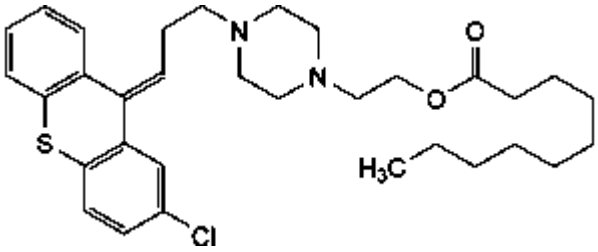
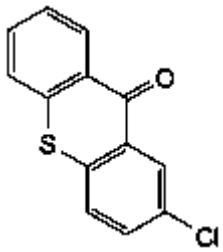
IMPURITIES

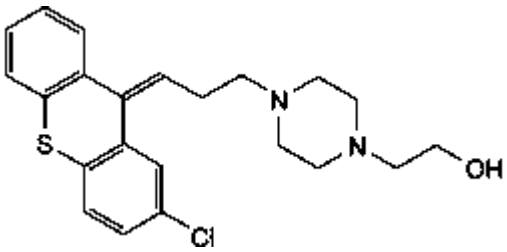
Specified impurities *A, B, C.*



A. 2-[4-[3-[(9*E*)-2-chloro-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethyl decanoate,



B. 2-chloro-9*H*-thioxanthen-9-one,



C. 2-[4-[3-[(9*Z*)-2-chloro-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethanol.

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Zuclopenthixol Decanoate Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Zuclopenthixol Decanoate Injection is a sterile solution of Zuclopenthixol Decanoate in a suitable vegetable oil.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of zuclopenthixol decanoate, $C_{32}H_{43}ClN_2O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions, protected from light.

(1) Dilute a volume of the injection with *ethanol (96%)* to contain 0.5% w/v of Zuclopenthixol Decanoate.

(2) 0.5% w/v of *zuclopenthixol decanoate dihydrochloride BPCRS* in *ethanol (96%)*.

(3) 0.5% w/v each of *zuclopenthixol decanoate dihydrochloride BPCRS* and *zuclopenthixol acetate dihydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable). Before use, heat the plate at 110° for 30 minutes.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with a 1% w/v solution of *sodium molybdate* in *sulfuric acid*, heat at 110° for 20 minutes and examine in daylight.

MOBILE PHASE

3 volumes of *diethylamine* and 90 volumes of *cyclohexane* as the mobile phase, using an unlined tank.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to zuclopenthixol decanoate in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *acetonitrile*, protected from light.

(1) Dilute the injection to contain 0.50% w/v of Zuclopenthixol Decanoate.

(2) 0.015% w/v of *zuclopenthixol hydrochloride BPCRS*.

(3) 0.0025% w/v of *2-chlorothioxanthone BPCRS*.

(4) 0.005% w/v of trans-*clopenthixol decanoate dihydrochloride BPCRS*.

(5) 0.015% w/v of *zuclopenthixol hydrochloride BPCRS*, 0.0025% w/v of *2-chlorothioxanthone BPCRS* and 0.005% w/v of trans-*clopenthixol decanoate dihydrochloride BPCRS* in solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice retention time of the principal peak.

MOBILE PHASE

0.1 volume of *orthophosphoric acid*, 26 volumes of 0.02M *dioctyl sodium sulfosuccinate* (prepared by dissolving 8.89 g of *dioctyl sodium sulfosuccinate* in 500 mL of *water*, stirring for 6 to 8 hours and diluting to 1000 mL with *water*) and 74 volumes of *ethanol (96%)*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (5) shows clearly separated peaks.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to zuclopenthixol is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to 2-chlorothioxanthone is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak corresponding to *trans*-clopenthixol decanoate is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1%).

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ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions solutions in *acetonitrile* protected from light.

(1) Dilute a volume of the injection to contain 0.50% w/v of Zuclopenthixol Decanoate.

(2) 0.57% w/v of *zuclopenthixol decanoate dihydrochloride BPCRS*.

(3) 0.015% w/v of *zuclopenthixol hydrochloride BPCRS*, 0.0025% w/v of *2-chlorothioxanthone BPCRS* and 0.005% w/v of trans-*clopenthixol decanoate dihydrochloride BPCRS* in solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows clearly separated peaks.

DETERMINATION OF CONTENT

Calculate the content of $C_{32}H_{43}ClN_3O_2S$ using the declared content of $C_{32}H_{43}ClN_3O_2S$ in *zuclopenthixol decanoate dihydrochloride BPCRS*. Each mg of zuclopenthixol decanoate dihydrochloride is equivalent to 0.8852 mg of zuclopenthixol decanoate.

STORAGE

Zuclopenthixol Decanoate Injection should be protected from light.

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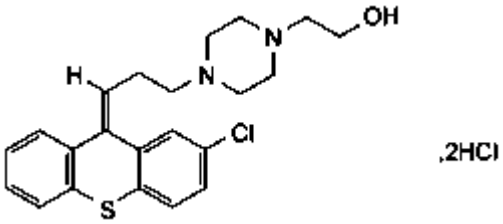
Zuclopenthixol Hydrochloride

General Notices



$C_{22}H_{25}ClN_2OS,2HCl$ 473.9 *633-59-0*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Zuclopenthixol Tablets

DEFINITION

Zuclopenthixol Hydrochloride is (*Z*)-2-4-[3-(2-chlorothioxanthene-9-ylidene)propyl]piperazin-1-ylethanol dihydrochloride. It contains not less than 98.0% and not more than 101.0% of $C_{22}H_{25}ClN_2OS,2HCl$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

An off-white, granular powder.

Very soluble in *water*; sparingly soluble in *ethanol (96%)*; very slightly soluble in *ether*.

IDENTIFICATION

A. The *light absorption* of a 0.0015% w/v solution in *ethanol (96%)*, Appendix II B, in the range 210 to 350 nm exhibits two maxima at 230 and 268 nm. The *absorbances* at the maxima are about 1.0 and 0.4, respectively.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of zuclopenthixol hydrochloride *(RS 365)*.

C. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

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pH of a 1.0% w/v solution, 2.0 to 3.0, Appendix V L.

Free amine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions protected from light.

Solvent A Shake 0.6 mL of *diethylamine* with 150 mL of *ethanol (96%)* and add sufficient *ethanol (96%)* to produce 200 mL.

(1) 0.25% w/v solution of the substance being examined in solvent A.

(2) Dilute 1 volume of solution (1) to 400 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} plate* (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 4 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, allow it to dry in air, spray with a mixture of equal volumes of *sulfuric acid* and *absolute ethanol*, heat at 110° for 5 minutes and examine under *ultraviolet light (365 nm)* immediately.

MOBILE PHASE

2 volumes of *water*, 10 volumes of 13.5M *ammonia*, 20 volumes of *butan-1-ol* and 65 volumes of *acetone*.

LIMITS

In the chromatogram obtained with solution (1) any *secondary spot* of the same colour and at an Rf value lower than that of the principal spot is not more intense than the spot in the chromatogram obtained solution (2) (0.25%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Solution A 18 volumes of *acetonitrile* and 82 volumes of *water*.

(1) Dissolve 20 mg of the substance being examined in 200 mL of solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and further dilute 1 volume of this solution to 10 volumes with solution A.

(3) Dilute 3 volumes of solution (1) to 100 volumes with solution A.

(4) 0.002% w/v each of *zuclopenthixol hydrochloride BPCRS* and *trans*-clopenthixol hydrochloride BPCRS (impurity B) in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Symmetry Shield RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature 40°.

(e) Use a detection wavelength of 270 nm.

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(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *trifluoroacetic acid* and 25 volumes of *water*.

Mobile phase B 1 volume of *trifluoroacetic acid* and 25 volumes of *acetonitrile*.

Mobile phase C *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-8	82	18	0	isocratic
8-17	82→5	18→10	0→85	linear gradient
17-19	5→82	10→18	85→0	linear gradient
19-30	82	18	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to zuclopenthixol (retention time about 6 minutes) are: impurity A, about 0.1; impurity B, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to zuclopenthixol and impurity B is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

The area of any peak due to *trans*-zuclopenthixol is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

The area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

The sum of the areas of any *secondary peak*, excluding *trans*-clopenthixol hydrochloride, is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Water

Not more than 2.5%, determined on 0.5 g, Appendix IX C.

Sulfated ash

Not more than 0.1%, Appendix IX A.

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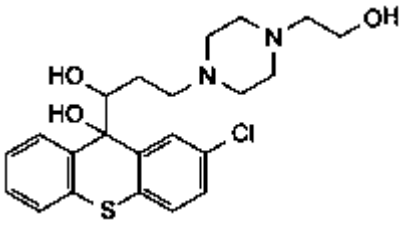
ASSAY

Dissolve 0.5 g in 50 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 23.70 mg of $C_{22}H_{25}ClN_2OS,2HCl$.

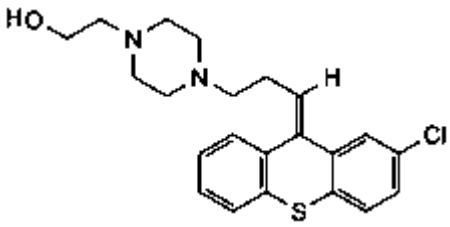
STORAGE

Zuclopenthixol Hydrochloride should be protected from light.

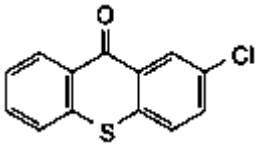
IMPURITIES



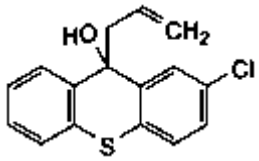
A. 2-chloro-9-(1-hydroxy-3-(4-(2-hydroxyethyl)]piperazin-1-ylpropyl)thioxanthen9-ol,



B. *trans*-clopenthixol,



C. 2-chlorothioxanthone,



D. 9-allyl-2-chlorothioxanthen-9-ol,

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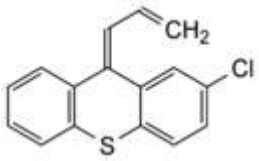
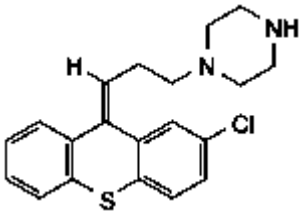


E. 9-allylidene-2-chlorothioxanthene,



F. 2-chloro-9-(3-piperazin-1-ylpropylidene)thioxanthene.

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Zuclopenthixol Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Zuclopenthixol Tablets contain Zuclopenthixol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of zuclopenthixol, $C_{22}H_{25}ClN_2OS$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing the equivalent of 20 mg of zuclopenthixol add 40 mL of 0.1M hydrochloric acid, heat on a water bath for 30 minutes, shaking occasionally, cool, dilute to 200 mL with water and shake thoroughly. Centrifuge a portion of the resulting solution and dilute 20 mL of the supernatant liquid to 200 mL with water. Measure the absorbance, Appendix II B at 230 nm using 0.002M hydrochloric acid in the reference cell. The light absorption, Appendix II B, in the range 205 to 350 nm of a 0.0015% w/v solution in ethanol (96%) exhibits maxima at 230, 268 and 325 nm.
B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1. *Carry out the procedure protected from light.*

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.01M hydrochloric acid, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions

(1) After 30 minutes withdraw a sample of the medium, filter and dilute with the dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.0002% w/v of zuclopenthixol.

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(2) 0.00024% w/v of *zuclopenthixol hydrochloride BPCRS* in the dissolution medium.

(3) 0.002% w/v each of *zuclopenthixol hydrochloride BPCRS* and *trans-clopenthixol hydrochloride BPCRS* (impurity B) in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *octylsilyl silica gel for chromatography* (3.5 µm) (Symmetry Shield RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature maintained at 40°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 250 µL of each solution.

(g) allow the chromatography to proceed for 1.5 times the retention time of zuclopenthixol (retention time about 6 miuntes).

MOBILE PHASE

2 volumes of trifluoroacetic acid, 9 volumes of acetonitrile and 41 volumes of water.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to zuclopenthixol and trans-clopenthixol hydrochloride is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of zuclopenthixol, $C_{22}H_{25}ClN_2OS$, in the medium from the chromatograms obtained and the declared content of $C_{22}H_{25}ClN_2OS$, in zuclopenthixol hydrochloride BPCRS.

LIMITS

The amount of zuclopenthixol released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Solution A 18 volumes of acetonitrile and 82 volumes of water.

(1) Shake a quantity of the powdered tablets containing the equivalent of 25 mg of zuclopenthixol with 5 mL of Solution A with the aid of ultrasound. Add 15 mL of Solution A, place in a water bath for 20 minutes, allow to cool and dilute to 25 mL with solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A, further dilute 1 volume of this solution to 5 volumes with solution A.

(3) Dilute 3 volumes of solution (1) to 100 volumes with solution A.

(4) 0.002% w/v each of *zuclopenthixol hydrochloride BPCRS* and *trans-clopenthixol hydrochloride BPCRS* (impurity B) in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Symmetry Shield RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 ml per minute.

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(d) Use a column temperature 40°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *trifluoroacetic acid* and 25 volumes of water.

Mobile phase B 1 volume of trifluoroacetic acid and 25 volumes of acetonitrile.

Mobile phase C *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-8	82	18	0	isocratic
8-17	82→5	18→10	0→85	linear gradient
17-19	5→82	10→18	85→0	linear gradient
19-30	82	18	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to zuclopenthixol (retention time about 6 minutes) are: impurity A, about 0.1; trans-clopenthixol hydrochloride, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to zuclopenthixol and trans-clopenthixol hydrochloride is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

The area of any peak due to trans-zuclopenthixol is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%).

The area of any peak due to zuclopenthixol impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

The area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

The sum of the areas of any secondary peak, excluding trans-clopenthixol hydrochloride, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area of less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions protected from light.

Solution A 18 volumes of acetonitrile and 82 volumes of water.

(1) To a quantity of the powdered tablets containing the equivalent of 25 mg of zuclopenthixol add 50 mL of solution A and mix with the aid of ultrasound. Add 150 mL of solution A and place in a water bath for 20 minutes, allow to cool and dilute to 250 mL with solution A.

(2) 0.012% w/v of zuclopenthixol hydrochloride BPCRS in solution A.

(3) 0.002% w/v each of *zuclopenthixol hydrochloride BPCRS* and *trans-clopenthixol hydrochloride BPCRS* (impurity B) in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Dissolution may be used, with an injection volume of 5µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to zuclopenthixol and trans-clopenthixol hydrochloride is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of zuclopenthixol, $C_{22}H_{25}ClN_2OS$, in the medium from the chromatograms obtained and the declared content of $C_{22}H_{25}ClN_2OS$, in zuclopenthixol hydrochloride BPCRS.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of zuclopenthixol.

IMPURITIES

The impurities limited by the requirements of this monograph include those shown under Zuclopenthixol Hydrochloride.

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