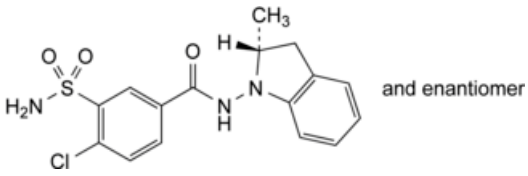
Edition: BP 2025 (Ph. Eur. 11.6 update)

Indapamide

General Notices

(Ph. Eur. monograph 1108)



$C_{16}H_{16}ClN_3O_3S$ 365.8 *26807-65-8*

Action and use

Thiazide-like diuretic.

Preparations

Indapamide Tablets

Indapamide Prolonged-release Tablets

Ph Eur

DEFINITION

4-Chloro-*N*-[(2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-yl]-3-sulfamoylbenzamide.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

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

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in ethanol (96 per cent) R and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with ethanol (96 per cent) R.

Spectral range 220-350 nm.

Absorption maximum At 242 nm.

Shoulders At 279 nm and 287 nm.

Specific absorbance at the absorption maximum 590 to 630.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison indapamide CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in ethanol (96 per cent) R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of indapamide CRS in ethanol (96 per cent) R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of indometacin R in 5 mL of reference solution (a) and dilute to 10 mL with ethanol (96 per cent) R.

Plate TLC silica gel GF_{254} plate R.

Mobile phase glacial acetic acid R, acetone R, toluene R (1:20:79 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Optical rotation (2.2.7)

-0.02° to + 0.02°.

Dissolve 0.250 g in anhydrous ethanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use or maintain them at 4 °C.*

Solvent mixture acetonitrile R, methanol R (50:50 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 7 mL of the solvent mixture and dilute to 20.0 mL with a 0.2 g/L solution of sodium edetate R.

Reference solution (a) Dissolve 3.0 mg of *indapamide impurity B CRS* in 3.5 mL of the solvent mixture and dilute to 10.0 mL with a 0.2 g/L solution of *sodium edetate R*. To 1.0 mL of the solution add 35 mL of the solvent mixture and dilute to 100.0 mL with a 0.2 g/L solution of *sodium edetate R*.

Reference solution (b) To 1.0 mL of the test solution add 17.5 mL of the solvent mixture and dilute to 50.0 mL with a 0.2 g/L solution of *sodium edetate R*. To 1.0 mL of this solution add 7 mL of the solvent mixture and dilute to 20.0 mL with a 0.2 g/L solution of *sodium edetate R*.

Reference solution (c) Dissolve 20.0 mg of *indapamide CRS* in 7 mL of the solvent mixture and dilute to 20.0 mL with a 0.2 g/L solution of *sodium edetate R*.

Reference solution (d) Dissolve 25 mg of *indapamide CRS* and 45 mg of *methylnitrosoindoline CRS* (impurity A) in 17.5 mL of the solvent mixture and dilute to 50 mL with a 0.2 g/L solution of *sodium edetate R*.

Column:

— *size*: *l* = 0.20 m, Ø = 4.6 mm;

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

— *temperature*: 40 °C.

Mobile phase *glacial acetic acid R*, *acetonitrile R*, *methanol R*, 0.2 g/L solution of *sodium edetate R* (0.1:17.5:17.5:65 *V/V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

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

Run time 2.5 times the retention time of indapamide.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A, use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to indapamide (retention time = about 11 min): impurity A = about 1.4; impurity B = about 1.7.

System suitability:

— *resolution*: minimum 4.0 between the peaks due to indapamide and impurity A in the chromatogram obtained with reference solution (d).

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

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

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity A

Liquid chromatography (*2.2.29*). *Carry out the test protected from light*.

Test solution Dissolve 25.0 mg of the substance to be examined in 1 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*. Shake for 15 min. Allow to stand at 4 °C for 1 h and filter.

Reference solution Dissolve 25.0 mg of the substance to be examined in 1.0 mL of a 0.125 mg/L solution of *methylnitrosoindoline CRS* (impurity A) in *acetonitrile R* and dilute to 10.0 mL with *water R*. Shake for 15 min. Allow to stand at 4 °C for 1 h and filter.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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

— *temperature*: 30 °C.

Mobile phase Mix 7 volumes of *acetonitrile R*, 20 volumes of *tetrahydrofuran R* and 73 volumes of a 1.5 g/L solution of *triethylamine R* adjusted to pH 2.8 with *phosphoric acid R*.

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 305 nm.

Injection 0.1 mL.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 3 for the peak due to impurity A appearing just before the peak due to indapamide;

— *peak-to-valley-ratio*: minimum 6.7, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to indapamide.

Limit:

— *impurity A*: the area of the peak due to impurity A in the chromatogram obtained with the test solution is not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with the reference solution and the area of the peak due to impurity A in the chromatogram obtained with the test solution (5 ppm).

Impurity C

Liquid chromatography (*2.2.29*). *Maintain the solutions at 10 °C after preparation.*

Solution A Dissolve 0.20 g of *sodium edetate R* in *water for chromatography R*, add 1.5 mL of *anhydrous acetic acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 75.0 mg of the substance to be examined in 7.5 mL of *acetonitrile R* and dilute to 25.0 mL with *water R*.

Reference solution (a) Dissolve 9.0 mg of *indapamide impurity C CRS* in 1.0 mL of *water R*, add 6.0 mL of *acetonitrile R* and dilute to 20.0 mL with *water R*. To 1.0 mL of the solution add 7.5 mL of *acetonitrile R* and dilute to 25.0 mL with *water R*.

Reference solution (b) To 1.0 mL of reference solution (a) add 3.0 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*.

Reference solution (c) To 1 mL of reference solution (a) add 3 mL of *acetonitrile R* and dilute to 10 mL with the test solution.

Column:

— *size*: *l* = 0.05 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (1.8 µm);

— *temperature*: 50 °C.

Mobile phase *acetonitrile for chromatography R*, solution A (30:70 *V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 2 µL of the test solution and reference solutions (b) and (c).

Run time 3 times the retention time of indapamide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to indapamide (retention time = about 1.3 min): impurity C = about 0.5.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to impurity C and indapamide;

— *signal-to-noise ratio*: minimum 20 for the peak due to impurity C.

Calculation of content:

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

Limit:

— *impurity C*: maximum 600 ppm.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

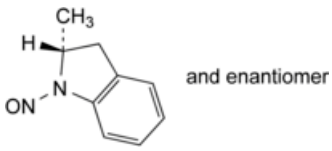
Calculate the percentage content of $C_{16}H_{16}ClN_3O_3S$ taking into account the assigned content of *indapamide CRS*.

STORAGE

Protected from light.

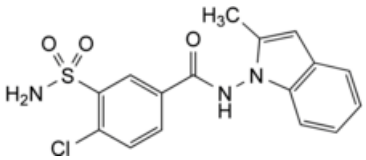
IMPURITIES

Specified impurities *A, B, C.*

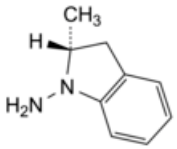


and enantiomer

A. (2*RS*)-2-methyl-1-nitroso-2,3-dihydro-1*H*-indole,



B. 4-chloro-*N*-(2-methyl-1*H*-indol-1-yl)-3-sulfamoylbenzamide,



and enantiomer

C. (2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-amine.

Ph Eur