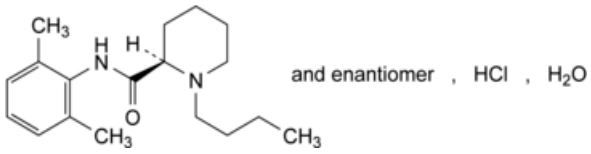
Edition: BP 2025 (Ph. Eur. 11.6 update)

Bupivacaine Hydrochloride

General Notices

(Ph. Eur. monograph 0541)



$C_{18}H_{29}ClN_2O,H_2O$ 342.9 *73360-54-0*

Action and use

Local anaesthetic.

Preparations

Bupivacaine Injection

Bupivacaine Heavy Injection

Bupivacaine and Adrenaline Injection/Bupivacaine and Epinephrine Injection

Bupivacaine and Diamorphine Injection

Bupivacaine and Fentanyl Injection

Ph Eur

DEFINITION

(2*RS*)-1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide hydrochloride monohydrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

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

IDENTIFICATION

First identification: A, C, D.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *bupivacaine hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 25 mg of *bupivacaine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methanol R* (0.1:100 *V/V*).

Application 5 µL.

Development Over a path of 10 cm.

Drying In air.

Detection Spray with *dilute potassium iodobismuthate solution R*.

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

C. It gives reaction (a) of chlorides (2.3.1).
D. Optical rotation (see Tests).

TESTS

Solution S

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

Appearance of solution

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

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of *0.01 M sodium hydroxide*; the pH (2.2.3) is not less than 4.7. Add 0.4 mL of *0.01 M hydrochloric acid*; the pH is not greater than 4.7.

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 1.0 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Gas chromatography (2.2.28).

Internal standard solution Dissolve 25 mg of *methyl behenate R* in *methylene chloride R* and dilute to 500 mL with the same solvent.

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of *water R*, add 2.5 mL of *dilute sodium hydroxide solution R* and extract with 2 quantities, each of 5 mL, of the internal standard solution. Filter the lower layer.

Reference solution (a) Dissolve 10 mg of the substance to be examined, 10 mg of *bupivacaine impurity B CRS* and 10 mg of *bupivacaine impurity E CRS* in 2.5 mL of *water R*, add 2.5 mL of *dilute sodium hydroxide solution R* and extract with 2 quantities, each of 5 mL, of the internal standard solution. Filter the lower layer and dilute to 20 mL with the internal standard solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the internal standard solution.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 10.0 mL with the internal standard solution.

Reference solution (d) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the internal standard solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

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

Carrier gas *helium for chromatography R*.

Flow rate 2.5 mL/min.

Split ratio 1:12.

Temperature:

	Time (min)	Temperature (°C)
	0	180
Column	0 - 10	180 → 230
	10 - 15	230
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and E.

Relative retention With reference to bupivacaine (retention time = about 10 min): impurity B = about 0.7; impurity E = about 1.1; internal standard = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to bupivacaine and impurity E.

Limits:

— *impurity B*: calculate the ratio (R_1) of the area of the principal peak to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (c); from the chromatogram obtained with the test solution, calculate the ratio of the area of the peak due to impurity B to the area of the peak due to the internal standard: this ratio is not greater than R_1 (0.5 per cent);

— *unspecified impurities*: calculate the ratio (R_2) of the area of the principal peak to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (d); from the chromatogram obtained with the test solution, calculate for each impurity the ratio of the area of any peak, apart from the principal peak, the peak

due to impurity B and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than R_2 (0.10 per cent);

— *total*: calculate the ratio (R_3) of the area of the principal peak to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (b); from the chromatogram obtained with the test solution, calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than R_3 (1.0 per cent);

— *disregard limit*: ratio less than 0.05 times R_3 (0.05 per cent).

Impurity F

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 50 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 5.0 mg of *bupivacaine impurity F CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 20 mg of *methyl benzoate R* and 25 mg of *bupivacaine impurity F CRS* in mobile phase A and dilute to 50 mL with mobile phase A. Dilute 3 mL of the solution to 50 mL with mobile phase A. Dilute 1 mL of this solution to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase:

— *mobile phase A*: dissolve 0.23 g of *sodium dihydrogen phosphate monohydrate R* and 3.626 g of *disodium hydrogen phosphate dihydrate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; mix equal volumes of this solution (pH 8.0) and *acetonitrile for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 15	100 → 80	0 → 20
15 - 25	80	20

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 50 µL.

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

Relative retention With reference to bupivacaine (retention time = about 20 min): impurity F = about 0.3; methyl benzoate = about 0.4.

System suitability:

— *resolution*: minimum 4.0 between the peaks due to impurity F and methyl benzoate in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (a).

Limit:

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (10 ppm).

Loss on drying (*2.2.32*)

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

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 20 mL of *water R* and 25 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 32.49 mg of $C_{18}H_{29}ClN_2O$.

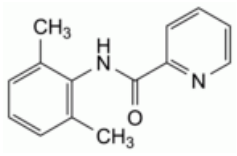
STORAGE

Protected from light.

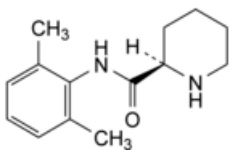
IMPURITIES

Specified impurities *B, F*.

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

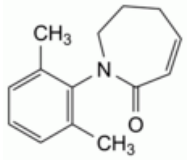


A. *N*-(2,6-dimethylphenyl)pyridine-2-carboxamide,

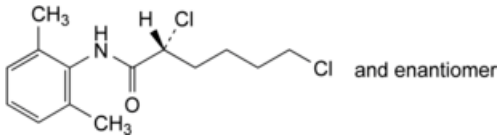


and enantiomer

B. (2*RS*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide,

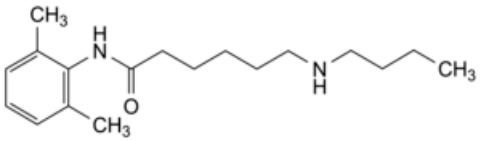


C. 1-(2,6-dimethylphenyl)-1,5,6,7-tetrahydro-2*H*-azepin-2-one,

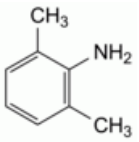


and enantiomer

D. (2*RS*)-2,6-dichloro-*N*-(2,6-dimethylphenyl)hexanamide,



E. 6-(butylamino)-*N*-(2,6-dimethylphenyl)hexanamide,



F. 2,6-dimethylaniline.

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