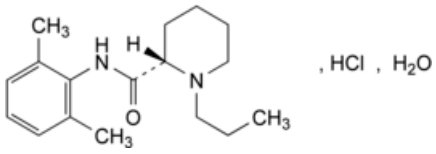
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ropivacaine Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 2335)



$C_{17}H_{27}ClN_2O,H_2O$ 328.9 *132112-35-7*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

(-)-(2*S*)-*N*-(2,6-Dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water and in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

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

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ropivacaine hydrochloride monohydrate CRS*.

B. Specific optical rotation (2.2.7): -74.0 to -64.0 (anhydrous substance).

Mix 2 mL of a 200 g/L solution of *sodium hydroxide R* and 30 mL of *water R* and dilute to 100.0 mL with *ethanol (96 per cent) R* (solution A). Dissolve 0.500 g of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

C. It gives reaction (a) of chlorides (2.3.1).
D. Enantiomeric purity (see Tests).

TESTS

Solution S

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1).

pH (2.2.3)

4.5 to 6.0 for solution S.

Absorbance (2.2.25)

Maximum 0.030 at 405 nm and maximum 0.025 at 436 nm, determined on solution S prepared immediately before use, with a path length of 5 cm and using *water R* as the compensation liquid.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 55 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase.

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

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *bupivacaine hydrochloride CRS* (impurity A) in the mobile phase and dilute to 5 mL with the mobile phase. Dilute 1 mL of this solution to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase Mix 1.3 mL of a 138 g/L solution of *sodium dihydrogen phosphate R* and 32.5 mL of an 89 g/L solution of *disodium hydrogen phosphate dodecahydrate R* and dilute to 1000 mL with *water R*; mix equal volumes of this solution (pH 8.0) and *acetonitrile R*.

Flow rate 1.0 mL/min.

Injection 20 µL.

Detection Spectrophotometer at 240 nm.

Run time 2.5 times the retention time of ropivacaine.

Relative retention With reference to ropivacaine (retention time = about 6 min): impurity A = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 6.0 between the peaks due to ropivacaine and impurity A.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

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

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

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

Impurity H

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

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 13.0 mg of *2,6-dimethylaniline hydrochloride R* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Retention time Impurity H = about 2-3 min.

Limit:

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

Enantiomeric purity

Capillary electrophoresis (2.2.47): use the normalisation procedure.

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 25 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with *water R*.

Reference solution (b) Dissolve 1.5 mg of the substance to be examined and 1.5 mg of *ropivacaine impurity G CRS* in *water R* and dilute to 100 mL with the same solvent.

Capillary:

— *material*: fused silica;

— *size*: effective length = about 72 cm, total length = 80 cm, Ø = 50 µm.

Temperature 30 °C.

CZE buffer Prepare a 13.3 g/L solution of *dimethyl-β-cyclodextrin R* in an 11.5 g/L solution of *phosphoric acid R* previously adjusted to pH 3.0 with *triethanolamine R*. The CZE buffer is prepared and filtered through a membrane filter (nominal pore size 0.45 µm) immediately before use.

Detection Spectrophotometer at 206 nm.

Preconditioning of the capillary Rinse the capillary at 100 kPa with *water R* for 1 min, with *0.1 M sodium hydroxide* for 10 min and with *water R* for 3 min. If the capillary is new or dry, increase the sodium hydroxide rinse to 30 min.

Between-run rinsing Rinse the capillary at 100 kPa with *water R* for 1 min, with *0.1 M sodium hydroxide* for 4 min, with *water R* for 1 min and with the CZE buffer for 4 min.

Injection Under pressure (5 kPa) for 5 s.

Migration Apply a field strength of 375 V/cm with an initial ramp of 500 V/s and a positive polarity corresponding to a current of 40-45 µA.

Run time 30 min.

System suitability:

— *resolution*: minimum 3.7 between the peaks due to impurity G (1st peak) and (*S*)-ropivacaine in the electropherogram obtained with reference solution (b); if necessary, increase the dimethyl-β-cyclodextrin concentration in the CZE buffer or vary the pH between 2.9 and 3.1 or lower the temperature;

— *signal-to-noise ratio*: minimum 10 for the principal peak in the electropherogram obtained with reference solution (a).

Limit:

— *impurity G*: maximum 0.5 per cent.

Water (*2.5.12*)

5.0 per cent to 6.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

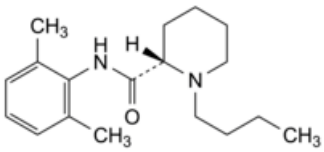
Dissolve 0.250 g in a mixture of 10 mL of *water R* and 40 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.09 mg of $C_{17}H_{27}ClN_2O$.

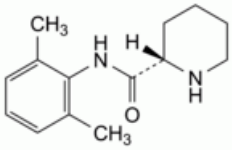
IMPURITIES

Specified impurities *A, G, H.*

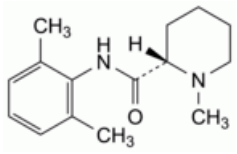
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) *B, C, D, E, F.*



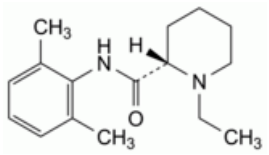
A. (*S*)-bupivacaine,



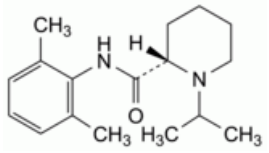
B. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide,



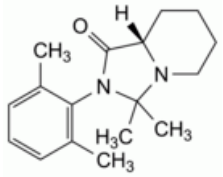
C. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)-1-methylpiperidine-2-carboxamide ((*S*)-mepivacaine),



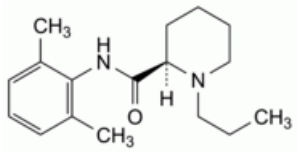
D. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)-1-ethylpiperidine-2-carboxamide,



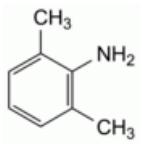
E. (-)-(2*S*)-*N*-(2,6-dimethylphenyl)-1(1-methylethyl)piperidine-2-carboxamide,



F. (8a*S*)-2-(2,6-dimethylphenyl)-3,3-dimethylhexahydroimidazo[1,5-*a*]pyridin-1(5*H*)-one (acetone adduct),



G. (+)-(2*R*)-*N*-(2,6-dimethylphenyl)-1-propylpiperidine-2-carboxamide ((*R*)-ropivacaine),



H. 2,6-dimethylaniline.

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