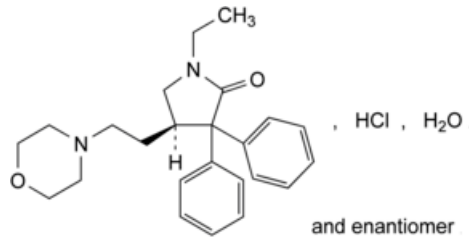
Edition: BP 2025 (Ph. Eur. 11.6 update)

Doxapram Hydrochloride

General Notices

(Ph. Eur. monograph 1201)



$C_{24}H_{31}ClN_2O_2,H_2O$ 433.0 *7081-53-0*

Action and use

Respiratory stimulant.

Preparation

Doxapram Injection

Ph Eur

DEFINITION

(4*RS*)-1-Ethyl-4-[2-(morpholin-4-yl)ethyl]-3,3-diphenylpyrrolidin-2-one hydrochloride monohydrate.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *doxapram hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

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

Reference solution Dissolve 10 mg of *doxapram hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase Solution of *ammonia R* containing 17 g/L of NH_3, *2-propanol R*, *2-methylpropanol R* (10:10:80 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *dilute potassium iodobismuthate solution R* and examine immediately.

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).

TESTS

Solution S

Dissolve 1.000 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dilute 10 mL of solution S to 25 mL with *water R*.

pH (2.2.3)

3.5 to 5.0.

Dilute 5 mL of solution S to 25 mL with *carbon dioxide-free water R*.

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Related substances

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

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

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

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 5.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *doxapram impurity B CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase. To 1.0 mL of the solution, add 1.0 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase Mix 50 volumes of *acetonitrile R* and 50 volumes of a 0.82 g/L solution of *sodium acetate R* adjusted to pH 4.5 with *glacial acetic acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Run time 4 times the retention time of doxapram.

Retention time Doxapram = about 6 min.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to doxapram and impurity B.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),

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

Loss on drying (*2.2.32*)

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

Sulfated ash (*2.4.14*)

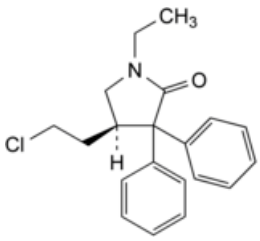
Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 10 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*) using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

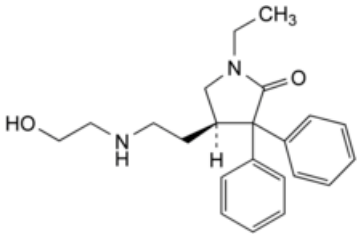
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.50 mg of $C_{24}H_{31}ClN_2O_2$.

IMPURITIES



and enantiomer

A. (4*RS*)-4-(2-chloroethyl)-1-ethyl-3,3-diphenylpyrrolidin-2-one,



and enantiomer

B. (4*RS*)-1-ethyl-4-[2-[(2-hydroxyethyl)amino]ethyl]-3,3-diphenylpyrrolidin-2-one.

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