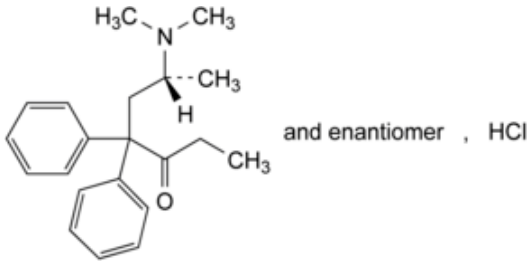
Edition: BP 2025 (Ph. Eur. 11.6 update)

Methadone Hydrochloride

General Notices

(Ph. Eur. monograph 0408)



$C_{21}H_{28}ClNO$ 345.9 *1095-90-5*

Action and use

Opioid receptor agonist; analgesic; treatment of opioid dependence.

Preparations

Methadone Concentrate for Oral Solution

Methadone Injection

Methadone Oral Solution (1 mg per ml)

Methadone Tablets

Ph Eur

DEFINITION

(6*RS*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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

IDENTIFICATION

First identification: A, C, D.

Second identification: A, B, D.

A. Optical rotation (see Tests).
B. Melting point (2.2.14): 233 °C to 236 °C.
C. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of methadone hydrochloride*.

D. Dilute 1 mL of solution S (see Tests) to 5 mL with *water R* and add 1 mL of *dilute ammonia R1*. Mix, allow to stand for 5 min and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 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

Dilute 10 mL of solution S to 25 mL with *carbon dioxide-free water R*. To 10 mL of the solution add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Optical rotation (2.2.7)

-0.05° to + 0.05°, determined on solution S in a 2 dm tube.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *imipramine hydrochloride CRS* and 5 mg of *cyclobenzaprine hydrochloride CRS* in 100.0 mL of *methanol R*.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, *Ø* = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 1.05 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.2 mL/min.

Injection liner Packed with deactivated glass wool to wipe the needle.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 4	150 → 250
	4 - 35	250
Injection port		200
Detector		250

Detection Flame ionisation.

Injection 2 µL.

Run time 1.5 times the retention time of methadone.

Relative retention With reference to methadone (retention time = about 25 min): impurity E = about 0.44; impurity C = about 0.81; impurity B = about 0.89; impurity D = about 0.98; impurity A = about 1.14; imipramine = about 1.19; cyclobenzaprine = about 1.24.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to imipramine and cyclobenzaprine.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 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 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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).

Loss on drying (*2.2.32*)

Maximum 0.5 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 5 mL of *0.01 M hydrochloric acid* and 50 mL of *anhydrous ethanol 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. Carry out a blank titration.

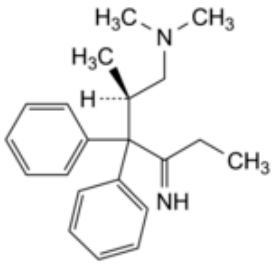
1 mL of *0.1 M sodium hydroxide* is equivalent to 34.59 mg of $C_{21}H_{28}ClNO$.

STORAGE

Protected from light.

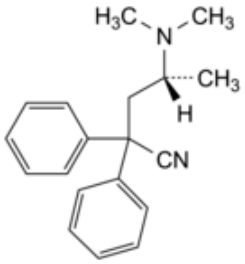
IMPURITIES

Specified impurities *A, B, C, D, E.*



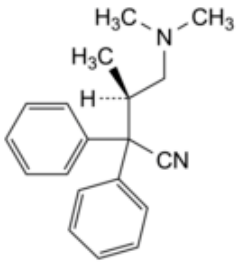
and enantiomer

A. (2*RS*)-4-imino-*N*,*N*,2-trimethyl-3,3-diphenylhexan-1-amine (isomethadone ketimine),



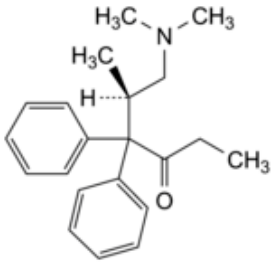
and enantiomer

B. (4*RS*)-4-(dimethylamino)-2,2-diphenylpentanenitrile (didiavalo),



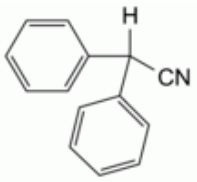
and enantiomer

C. (3*RS*)-4-(dimethylamino)-3-methyl-2,2-diphenylbutanenitrile (isodidiavalo),



and enantiomer

D. (5*RS*)-6-(dimethylamino)-5-methyl-4,4-diphenylhexan-3-one (isomethadone),



E. diphenylacetonitrile.

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