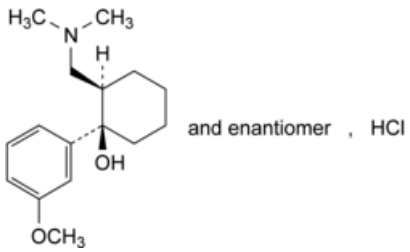
Edition: BP 2025 (Ph. Eur. 11.6 update)

Tramadol Hydrochloride

General Notices

(Ph. Eur. monograph 1681)



$C_{16}H_{26}ClNO_2$ 299.8 *36282-47-0*

Action and use

μ-Opioid receptor (OP3, MOR) agonist and noradrenaline reuptake inhibitor; analgesic.

Preparations

Tramadol Capsules

Tramadol Prolonged-release Capsules

Tramadol Injection

Tramadol Oral Drops

Tramadol Prolonged-release Tablets

Ph Eur

DEFINITION

(1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, very slightly soluble in acetone.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 180 °C to 184 °C.
B. Infrared absorption spectrophotometry (2.2.24).

Comparison tramadol hydrochloride CRS.

C. Examine the chromatograms obtained in the test for impurity E.

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

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

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

Appearance of solution

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

Acidity

To 10 mL of solution S, add 0.2 mL of methyl red solution R and 0.2 mL of 0.01 M hydrochloric acid. The solution is red. Not more than 0.4 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to yellow.

Optical rotation (2.2.7)

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

Impurity E

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.10 g of the substance to be examined in methanol R and dilute to 2.0 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with methanol R.

Reference solution (a) Dissolve 25 mg of tramadol hydrochloride CRS in methanol R and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 5.0 mg of tramadol impurity E CRS in methanol R and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with methanol R.

Reference solution (c) Dissolve 5 mg of tramadol impurity A CRS in 1 mL of reference solution (a).

Plate TLC silica gel F_{254} plate R.

Pretreatment Wash the plate with *methanol R*.

Mobile phase *concentrated ammonia R*, *2-propanol R*, *toluene R* (1:19:80 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate. Add *concentrated ammonia R* to one trough of a twin trough tank then saturate the plate for 20 min. Just before developing, add the mobile phase to the other trough. Place the plate in the trough, ensuring that the layer of silica gel faces the middle of the tank.

Drying In air.

Detection Expose to iodine vapour for 1 h, then examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (c) shows 2 clearly separated spots.

Limit Test solution (a):

— *impurity E*: any spot due to impurity E is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.15 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *tramadol impurity A CRS* in 4 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

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

Mobile phase 295 volumes of *acetonitrile R* and 705 volumes of a mixture of 0.2 mL of *trifluoroacetic acid R* and 100 mL of *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL.

Run time 4 times the retention time of tramadol.

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

Relative retention With reference to tramadol (retention time = about 6 min): impurity A = about 0.85.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and tramadol.

Calculation of percentage contents:

— for each impurity, use the concentration of tramadol hydrochloride in reference solution (a).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.02 per cent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 50 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M ethanolic sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 29.98 mg of $C_{16}H_{26}ClNO_2$.

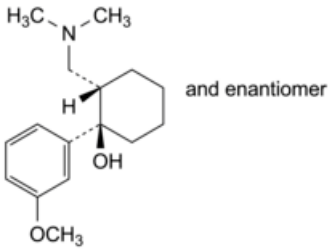
STORAGE

Protected from light.

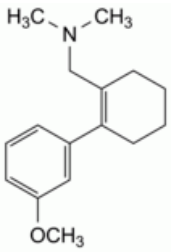
IMPURITIES

Specified impurities *A, E.*

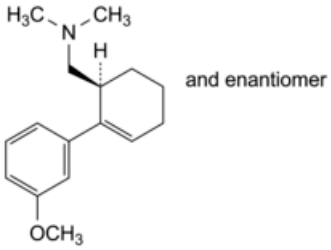
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



A. (1*RS*,2*SR*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol,

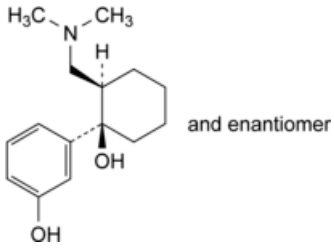


B. [2-(3-methoxyphenyl)cyclohex-1-en-1-yl]-*N*,*N*-dimethylmethanamine,



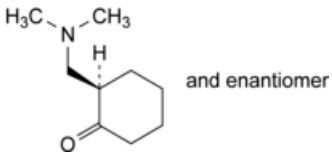
and enantiomer

C. [(1*RS*)-2-(3-methoxyphenyl)cyclohex-2-en-1-yl]-*N*,*N*-dimethylmethanamine,



and enantiomer

D. (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-hydroxyphenyl)cyclohexan-1-ol,



and enantiomer

E. (2*RS*)-2-[(dimethylamino)methyl]cyclohexan-1-one.

Ph Eur