add 10 ml of *water R* and evaporate the solution to dryness under reduced pressure. To the resulting clear film add 0.1 ml of *water R* and 0.9 ml of *methanol R*. Centrifuge to separate the amorphous precipitate and dilute the supernatant if necessary to 1 ml with *methanol R*.

Reference solution. Dissolve 10 mg of *arabinose R*, 10 mg of *galactose R*, 10 mg of *rhamnose R* and 10 mg of *xylose R* in 1 ml of *water R* and dilute to 10 ml with *methanol R*.

Apply to the plate as bands 10 µl of each solution. Develop over a path of 10 cm using a mixture of 10 volumes of a 16 g/l solution of *sodium dihydrogen phosphate R*, 40 volumes of *butanol R* and 50 volumes of *acetone R*. Dry the plate in a current of warm air for a few minutes and again develop over a path of 15 cm using the same mobile phase. Dry the plate at 110 °C for 10 min, spray with *anisaldehyde solution R* and dry again at 110 °C for 10 min. The chromatogram obtained with the reference solution shows four clearly separated coloured zones due to galactose (greyish-green to green), arabinose (yellowish-green), xylose (greenish-grey or yellowish-grey) and rhamnose (yellowish-green), in order of increasing R_F value. The chromatogram obtained with the test solution does not show a yellowish-green zone corresponding to the zone of rhamnose in the chromatogram obtained with the reference solution.

Methylcellulose. Examine the chromatograms obtained in the test for acacia. The chromatogram obtained with the test solution does not show a red zone near the solvent front.

Sterculia gum

A. Place 0.2 g of the powdered drug (355) (*2.9.12*) in a 10 ml ground-glass-stoppered cylinder graduated in 0.1 ml. Add 10 ml of *alcohol (60 per cent V/V) R* and shake. Any gel formed occupies not more than 1.5 ml.

B. To 1.0 g of the powdered drug (355) (*2.9.12*) add 100 ml of *water R* and shake. Add 0.1 ml of *methyl red solution R*. Not more than 5.0 ml of *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Foreign matter. Place 2.0 g of the powdered drug (355) (*2.9.12*) in a 250 ml round-bottomed flask and add 95 ml of *methanol R*. Swirl to moisten the powder and add 60 ml of *hydrochloric acid R1*. Add a few glass beads about 4 mm in diameter and heat on a water-bath under a reflux condenser for 3 h, shaking occasionally. Remove the glass beads and filter the hot suspension *in vacuo* through a sintered-glass filter (160) (*2.1.2*). Rinse the flask with a small quantity of *water R* and pass the rinsings through the filter. Wash the residue on the filter with about 40 ml of *methanol R* and dry to constant mass at 110 °C (about 1 h). Allow to cool in a desiccator and weigh. The residue weighs not more than 20 mg (1.0 per cent).

Flow time. Not less than 10 s or, if the substance to be examined is to be used for the preparation of emulsions, not less than 50 s. Place 1.0 g of the powdered drug (125 to 250) (*2.9.12*) in a 1000 ml round bottomed flask with a ground-glass stopper and add 8.0 ml of *alcohol R* and close the flask. Disperse the suspension over the inner surface of the flask by shaking, taking care not to wet the stopper. Open the flask and add in one portion 72.0 ml of *water R*. Stopper the flask and shake vigorously for 3 min. Allow to stand for 24 h and shake vigorously again for 3 min. Eliminate air bubbles by applying vacuum above the mucilage for 5 min. Transfer the mucilage to a 50 ml cylinder. Dip in the mucilage a piece of glass tubing 200 mm long and 6.0 mm in internal diameter and graduated at 20 mm and 120 mm from the lower end; the tubing must not be rinsed with surface-active substances. When the mucilage has reached the upper mark, close the tube with a finger. Withdraw the closed tube, remove the finger and measure with a stop-watch the time needed for the meniscus to reach the lower graduation. Carry out this operation four times and determine the average value of the last three determinations.

Total ash (*2.4.16*). Not more than 4.0 per cent.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^4 micro-organisms per gram, determined by plate count. It complies with the tests for *Escherichia coli* and *Salmonella* (*2.6.13*).

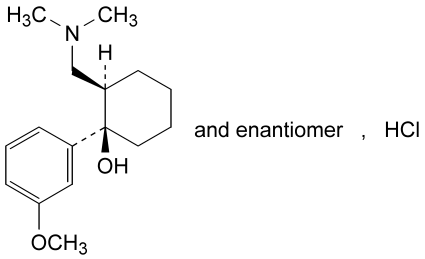
LABELLING

The label states whether or not the contents are suitable for preparing emulsions.

01/2008:1681
corrected 6.0

TRAMADOL HYDROCHLORIDE

Tramadoli hydrochloridum



$C_{16}H_{26}ClNO_2$ M_r 299.8
[36282-47-0]

DEFINITION

(1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol 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. 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 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 in *methanol R* and dilute to 2 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 mg of *tramadol impurity E CRS* in 5 ml of *methanol R*. Dilute 1 ml of the solution to 10 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*, prewashed 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. Saturate the plate for 20 min with *concentrated ammonia R*. For this, add *concentrated ammonia R* to one trough of a twin trough tank. Just before developing, add the mobile phase to the other trough. Place the plate in the chromatographic tank, ensuring that the layer of silica gel is orientated towards the middle of the tank.

Drying: in air.

Detection: expose the plate to iodine vapour for 1 h, examine in ultraviolet light at 254 nm.

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

Limit: in the chromatogram obtained with test solution (a):

– *impurity E*: any spot corresponding to impurity E is not more intense and not greater 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 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 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of *tramadol impurity A CRS* in 4.0 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 R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 270 nm.

Injection: 20 µl.

Run time: 4 times the retention time of tramadol.

Relative retention with reference to tramadol (retention time = about 5 min): impurity A = about 0.85.

System suitability: reference solution (b):

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

Limits:

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

– *any other impurity*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent),

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

Dissolve 2.0 g in *water R* and dilute to 20 ml with the same solvent. 12 ml of this solution complies with limit test A. Prepare the standard using *lead standard solution (2 ppm Pb) R*.

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.000 g.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

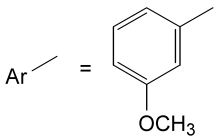
Dissolve 0.180 g in 25 ml of *anhydrous acetic acid R* and add 10 ml of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

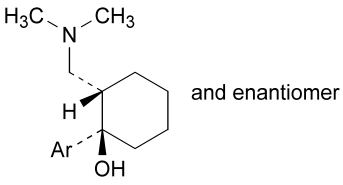
1 ml of *0.1 M perchloric acid* is equivalent to 29.98 mg of $C_{16}H_{26}ClNO_2$.

STORAGE

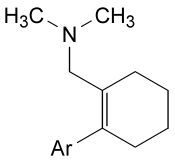
Protected from light.

IMPURITIES

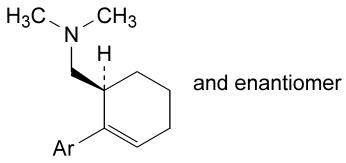




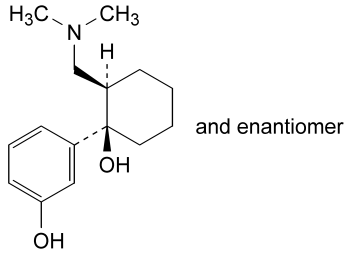
A. (1*RS*,2*SR*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol,



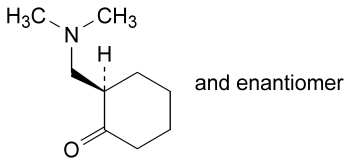
B. [2-(3-methoxyphenyl)cyclohex-1-enyl]-*N*,*N*-dimethylmethanamine,



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



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

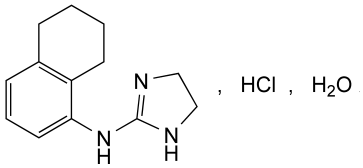


E. (2*RS*)-2-[(dimethylamino)methyl]cyclohexanone.

01/2008:1597

TRAMAZOLINE HYDROCHLORIDE MONOHYDRATE

Tramazolini hydrochloridum monohydricum



$C_{13}H_{18}ClN_3,H_2O$ M_r 269.8
[74195-73-6]

DEFINITION

N-(5,6,7,8-Tetrahydronaphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride monohydrate.

Content: 98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *tramazoline hydrochloride monohydrate CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 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 not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*): 4.9 to 6.3 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R* and dilute to 50.0 ml with the same mixture of solvents.

Reference solution (a). Dissolve 5.0 mg of *tramazoline impurity A CRS* and 5.0 mg of *tramazoline impurity B CRS* in 5 ml of a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R* and add 5 ml of the test solution.

Reference solution (b). Dilute 0.2 ml of reference solution (a) to 100 ml with a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R*.

Column:

– *size*: *l* = 0.125 m, Ø = 4 mm,

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: 2.0 g/l solution of *sodium dodecyl sulphate R* in a mixture of 6 volumes of *2-propanol R*, 42 volumes of *acetonitrile R* and 52 volumes of *water R*.

Flow rate: 1.2 ml/min.

Detection: spectrophotometer at 215 nm.

Injection: 5 µl.

Run time: 3 times the retention time of tramazoline.

Relative retention with reference to tramazoline (retention time = about 6.5 min): impurity A = about 0.71; impurity B = about 0.86.

System suitability: reference solution (a):

– the chromatogram obtained shows 3 clearly separated peaks,

– *resolution*: minimum 1.5 between tramazoline and impurity B.

Limits:

– *impurity A*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

– *impurity B*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

– *any other impurity*: not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.1 per cent),

– *sum of other impurities*: not more than twice the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *disregard limit*: 0.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.02 per cent).

Water (*2.5.12*): 6.2 per cent to 7.2 per cent, determined on 0.500 g.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.