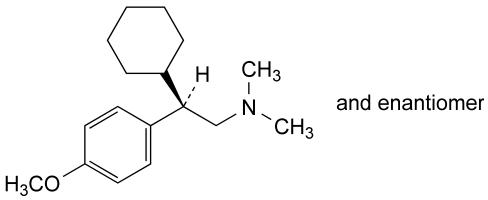
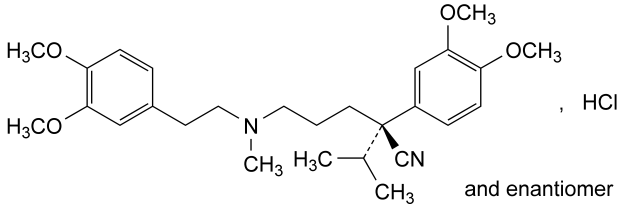



G. (2*RS*)-2-cyclohexyl-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine.

**01/2008:0573**
**corrected 6.0**

# VERAPAMIL HYDROCHLORIDE

## Verapamili hydrochloridum




$C_{27}H_{39}ClN_2O_4$ $M_r$ 491.1
[152-11-4]

DEFINITION

(2*RS*)-2-(3,4-Dimethoxyphenyl)-5-[[2-(3,4-dimethoxyphenyl)-ethyl](methyl)amino]-2-(1-methylethyl)pentanenitrile 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 methanol, sparingly soluble in ethanol (96 per cent).

mp: about 144 °C.

IDENTIFICATION

*First identification: B, D.*

*Second identification: A, C, D.*

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

*Test solution.* Dissolve 20.0 mg in *0.01 M hydrochloric acid* and dilute to 100.0 ml with the same acid. Dilute 5.0 ml of this solution to 50.0 ml with *0.01 M hydrochloric acid.*

*Spectral range*: 210-340 nm.

*Absorption maxima*: at 229 nm and 278 nm.

*Shoulder*: at 282 nm.

*Absorbance ratio*: $A_{278}/A_{229}$ = 0.35 to 0.39.

B. Infrared absorption spectrophotometry (*2.2.24*).

*Preparation*: discs.

*Comparison*: *verapamil hydrochloride CRS.*

C. Thin-layer chromatography (*2.2.27*).

*Test solution.* Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 5 ml with the same solvent.

*Reference solution (a).* Dissolve 20 mg of *verapamil hydrochloride CRS* in *methylene chloride R* and dilute to 10 ml with the same solvent.

*Reference solution (b).* Dissolve 5 mg of *papaverine hydrochloride CRS* in reference solution (a) and dilute to 5 ml with reference solution (a).

*Plate*: *TLC silica gel $F_{254}$ plate R.*

*Mobile phase*: *diethylamine R, cyclohexane R* (15:85 *V/V*).

*Application*: 5 µl.

*Development*: over a path of 15 cm.

*Drying*: in air.

*Detection*: examine in ultraviolet light at 254 nm.

*System suitability*: reference solution (b):

– the chromatogram shows 2 clearly separated principal spots.

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

D. It gives reaction (b) of chlorides (*2.3.1*).

TESTS

**Solution S**. Dissolve 1.0 g in *carbon dioxide-free water R* while gently heating 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*).

**pH** (*2.2.3*): 4.5 to 6.0 for solution S.

**Optical rotation** (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution.* Dissolve 25.0 mg of the substance to be examined in the initial mobile phase composition and dilute to 10.0 ml with the initial mobile phase composition.

*Reference solution (a).* Dissolve 5 mg of *verapamil hydrochloride CRS*, 5 mg of *verapamil impurity I CRS* and 5 mg of *verapamil impurity M CRS* in the initial mobile phase composition and dilute to 20 ml with the initial mobile phase composition. Dilute 1 ml of this solution to 10 ml with the initial mobile phase composition.

*Reference solution (b).* Dilute 1.0 ml of the test solution to 100.0 ml with the initial mobile phase composition. Dilute 1.0 ml of this solution to 10.0 ml with the initial mobile phase composition.

*Column*:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

*Mobile phase*:

– *mobile phase A*: 6.97 g/l solution of *dipotassium hydrogen phosphate R* adjusted to pH 7.20 with *phosphoric acid R*;

– *mobile phase B*: *acetonitrile R*;

| Time (min) | Mobile phase A (per cent *V/V*) | Mobile phase B (per cent *V/V*) |
|---|---|---|
| 0 - 22 | 63 | 37 |
| 22 - 27 | 63 → 35 | 37 → 65 |
| 27 - 35 | 35 | 65 |
| 35 - 36 | 35 → 63 | 65 → 37 |
| 36 - 50 | 63 | 37 |

*Flow rate*: 1.5 ml/min.

*Detection*: spectrophotometer at 278 nm.

Monographs T-Z

*Equilibration*: with the mobile phase at the initial composition for about 60 min.

*Injection*: 10 µl.

*Retention time*: verapamil = about 16 min; impurity I = about 21 min; impurity M eluting as a doublet = about 32 min.

*System suitability*: reference solution (a):

– *resolution*: minimum 5.0 between the peaks due to verapamil and impurity I;

– impurity M elutes from the column.

*Limits*:

– *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

**Heavy metals** (*2.4.8*): maximum 10 ppm.

1.0 g complies with test C. Prepare the reference solution using 1 ml of *lead standard solution (10 ppm Pb) R*.

**Loss on drying** (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

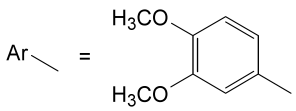
Dissolve 0.400 g in 50 ml of *anhydrous ethanol R* and add 5.0 ml of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Measure the volume added between the 2 points of inflexion.

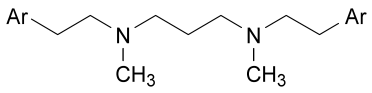
1 ml of *0.1 M sodium hydroxide* is equivalent to 49.11 mg of $C_{27}H_{39}ClN_2O_4$.

STORAGE

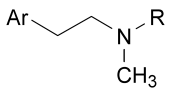
Protected from light.

IMPURITIES





A. *N,N′*-bis[2-(3,4-dimethoxyphenyl)ethyl]-*N,N′*-dimethylpropane-1,3-diamine,

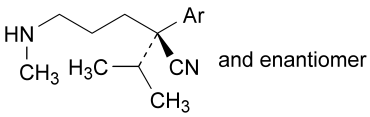


B. R = H: 2-(3,4-dimethoxyphenyl)-*N*-methylethanamine,

C. R = $CH_3$: 2-(3,4-dimethoxyphenyl)-*N,N*-dimethylethanamine,

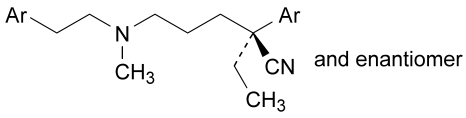
D. R = $CH_2$-$CH_2$-$CH_2$-Cl: 3-chloro-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylpropan-1-amine,

E. Ar-$CH_2$OH: (3,4-dimethoxyphenyl)methanol,

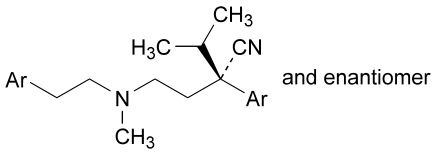


F. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-(methylamino)-2-(1-methylethyl)pentanenitrile,

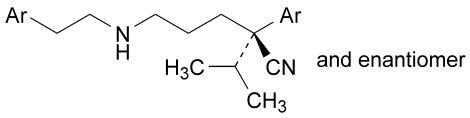
G. Ar-CHO: 3,4-dimethoxybenzaldehyde,



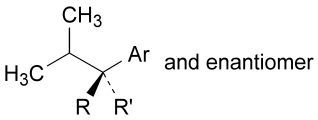
H. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]-2-ethylpentanenitrile,



I. (2*RS*)-2-(3,4-dimethoxyphenyl)-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]ethyl]-3-methylbutanenitrile,

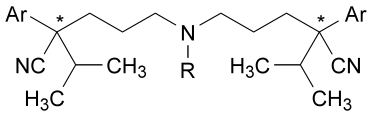


J. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-(1-methylethyl)pentanenitrile (*N*-norverapamil),



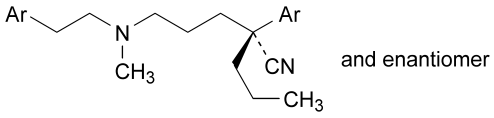
K. R = H, R′ = CN: (2*RS*)-2-(3,4-dimethoxyphenyl)-3-methylbutanenitrile,

L. R+ R′ = O: 1-(3,4-dimethoxyphenyl)-2-methylpropan-1-one,

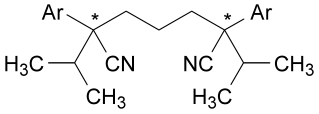


M. R = $CH_2$-$CH_2$-Ar: 5,5′-[[2-(3,4-dimethoxyphenyl)ethyl]-imino]bis[2-(3,4-dimethoxyphenyl)-2-(1-methylethyl)-pentanenitrile],

N. R = $CH_3$: 5,5′-(methylimino)bis[2-(3,4-dimethoxyphenyl)-2-(1-methylethyl)pentanenitrile],



O. (2*RS*)-2-(3,4-dimethoxyphenyl)-5-[2-[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]- 2-propylpentanenitrile,



P. 2,6-bis(3,4-dimethoxyphenyl)-2,6-bis(1-methylethyl)-heptane-1,7-dinitrile.