Mobile phase: the upper layer obtained after shaking a mixture of a 50 per cent *V/V* solution of *concentrated ammonia R*, *anhydrous ethanol R* and *di-isopropyl ether R* (10:25:65 *V/V/V*).

Application: 10 µL.

Development: over a path of 12 cm.

Drying: in air.

Detection: spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min.

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

Limit:

– *impurity A*: any spot corresponding to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.1 per cent).

Related substances. Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.10 g in 30 mL of *methanol R* and dilute to 100.0 mL with mobile phase B.

Reference solution (a). Dilute 5.0 mL of the test solution to 100.0 mL with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B. Dilute 1.0 mL of the solution to 25.0 mL with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Reference solution (b). Dissolve 5 mg of *amisulpride impurity B CRS* in 5 mL of the test solution and dilute to 50 mL with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B. Dilute 1 mL of the solution to 10 mL with a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm) with a carbon loading of 16 per cent, a specific surface area of 330 m^2/g and a pore size of 7.5 nm.

Mobile phase:

– *mobile phase A*: *methanol R*,

– *mobile phase B*: 0.7 g/L solution of *sodium octanesulfonate R* in a 0.25 per cent *V/V* solution of *dilute sulfuric acid R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	30 → 36	70 → 64
18 - 35	36 → 52	64 → 48
35 - 45	52	48

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 225 nm.

Injection: 10 µL.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to amisulpride and impurity B.

Limits:

– *any 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 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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).

Chlorides (*2.4.4*): maximum 200 ppm.

Shake 0.5 g with 30 mL of *water R* for 10 min. Filter. 15 mL of the filtrate complies with the test.

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

Dissolve 4.0 g by gently heating in 5 mL of *dilute acetic acid R*. Allow to cool and dilute to 20 mL with *water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (2 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 for 3 h.

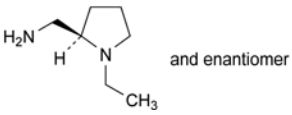
Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g with shaking in a mixture of 5 mL of *acetic anhydride R* and 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

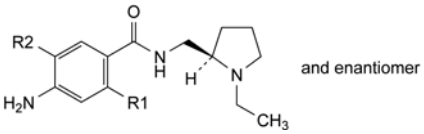
1 mL of *0.1 M perchloric acid* is equivalent to 36.95 mg of $C_{17}H_{27}N_3O_4S$.

IMPURITIES



and enantiomer

A. [(2*RS*)-1-ethylpyrrolidin-2-yl]methanamine,

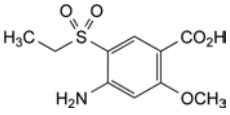


and enantiomer

B. R1 = OH, R2 = SO_2-CH_2-CH_3: 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-hydroxybenzamide,

C. R1 = OCH_3, R2 = I: 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-iodo-2-methoxybenzamide,

D. R1 = OCH_3, R2 = SO_2-CH_3: 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-5-(methylsulfonyl)benzamide,

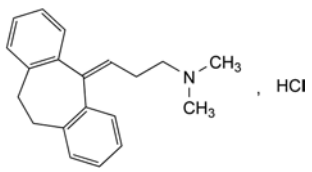


E. 4-amino-5-(ethylsulfonyl)-2-methoxybenzoic acid.

01/2008:0464
corrected 6.3

AMITRIPTYLINE HYDROCHLORIDE

Amitriptylini hydrochloridum



$C_{20}H_{24}ClN$ M_r 313.9
[549-18-8]

DEFINITION

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

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

CHARACTERS

Appearance: white or almost white powder or colourless crystals.

Solubility: freely soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *amitriptyline hydrochloride CRS*.

B. 20 mg gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Dissolve 1.25 g in *water R* and dilute to 25 mL with the same solvent.

Acidity or alkalinity. Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.1 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.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of *dibenzosuberone CRS* (impurity A) and 5.0 mg of *cyclobenzaprine hydrochloride CRS* (impurity B) in 5.0 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);
– *temperature*: 40 °C.

Mobile phase: mix 35 volumes of *acetonitrile R* and 65 volumes of a 5.23 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 7.0 with *phosphoric acid R*.

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Run time: 3 times the retention time of amitriptyline.

Relative retention with reference to amitriptyline (retention time = about 14 min): impurity B = about 0.9; impurity A = about 2.2.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity B and amitriptyline.

Limits:

– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
– *impurity A*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.05 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the peak due to amitriptyline in the chromatogram obtained with reference solution (b) (0.10 per cent);
– *total*: not more than 3 times the area of the peak due to amitriptyline in the chromatogram obtained with reference solution (b) (0.3 per cent);
– *disregard limit*: 0.5 times the area of the peak due to amitriptyline in the chromatogram obtained with reference solution (b) (0.05 per cent).

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

1.0 g complies with test F. Prepare the reference solution using 2 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 for 2 h.

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

ASSAY

Dissolve 0.250 g in 30 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.39 mg of $C_{20}H_{24}ClN$.

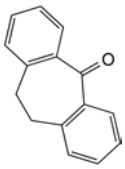
STORAGE

Protected from light.

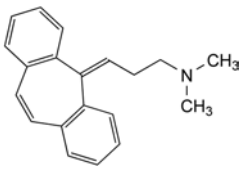
IMPURITIES

Specified impurities: *A, B.*

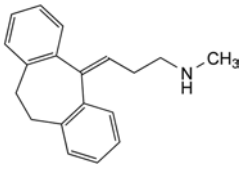
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



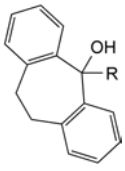
A. 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (dibenzosuberone),



B. 3-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine (cyclobenzaprine),

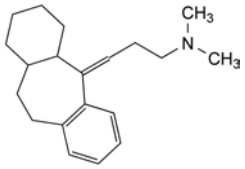


C. 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (nortriptyline),

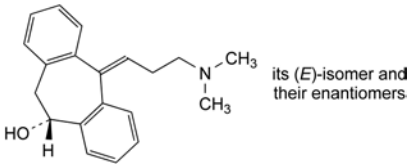


D. R = CH_2-CH_2-CH_2-$N(CH_3)_2$: 5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol,

G. R = H: 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol (dibenzosuberol),



E. *N,N*-dimethyl-3-(1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a*, *d*][7]annulen-5-ylidene)propan-1-amine,

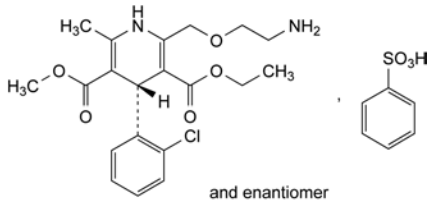


F. (5*EZ*,10*RS*)-5-[3-(dimethylamino)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-10-ol.

04/2010:1491

AMLODIPINE BESILATE

Amlodipini besilas



$C_{26}H_{31}ClN_2O_8S$ M_r 567.1
[111470-99-6]

DEFINITION

3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in 2-propanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *amlodipine besilate CRS*.

TESTS

Optical rotation (*2.2.7*): – 0.10° to + 0.10°.

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution (a). Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Test solution (b). Dilute 5.0 mL of test solution (a) to 100.0 mL with *methanol R*.

Reference solution (a). Dilute 1.0 mL of test solution (a) 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 *amlodipine impurity B CRS* and 5 mg of *amlodipine impurity G CRS* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c). Dissolve 5 mg of *amlodipine for peak identification CRS* (containing impurities D, E and F) in 10 mL of *methanol R*.

Reference solution (d). Dissolve 5.0 mg of *amlodipine impurity A CRS* in *acetonitrile R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (e). Dissolve 50.0 mg of *amlodipine besilate CRS* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *methanol R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 30 °C.

Mobile phase: 2.3 g/L solution of *ammonium acetate R*, *methanol R* (30:70 *V/V*).

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 237 nm.

Injection: 20 µL of test solution (a) and reference solutions (a), (b), (c) and (d).

Run time: twice the retention time of amlodipine.

Identification of impurities: use the chromatogram supplied with *amlodipine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D, E and F; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention with reference to amlodipine (retention time = about 20 min): impurity G = about 0.15; impurity B = about 0.2; impurity D = about 0.5; impurity F = about 0.8; impurity E = about 1.3.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to impurities B and G.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity F = 0.7;
– *impurity D*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
– *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.15 per cent);
– *impurities E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 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). Disregard any peak due to benzene sulfonate (relative retention = about 0.14).

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

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.