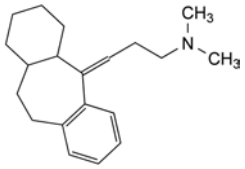
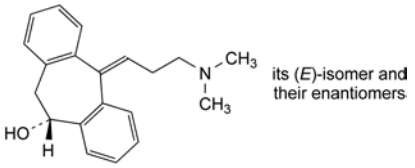


E. *N,N*-dimethyl-3-(1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a*, *d*][7]annulen-5-ylidene)propan-1-amine,

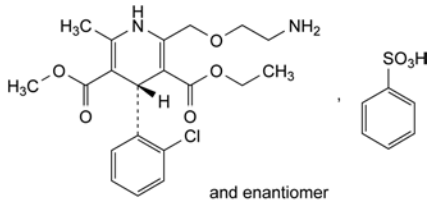


F. (5*EZ*,10*RS*)-5-[3-(dimethylamino)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-10-ol.

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.

Injection: test solution (b), reference solution (e).

Calculate the percentage content of $C_{26}H_{31}ClN_20_8S$ from the declared content of *amlodipine besilate CRS*.

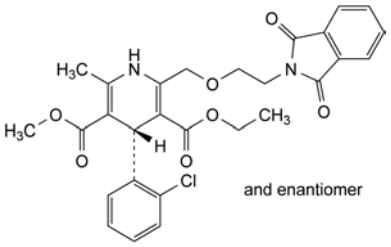
STORAGE

In an airtight container, protected from light.

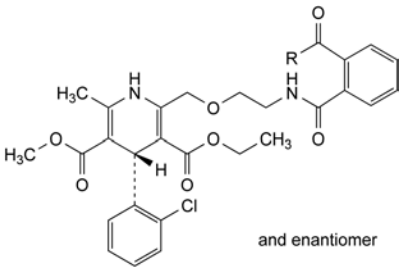
IMPURITIES

Specified impurities: A, D, E, F.

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, G, H.*

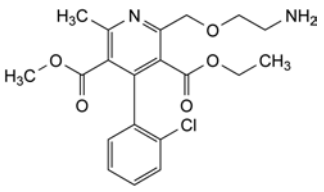


A. 3-ethyl 5-methyl (4*RS*)-4-(2-chlorophenyl)-2-[[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethoxy]methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate,

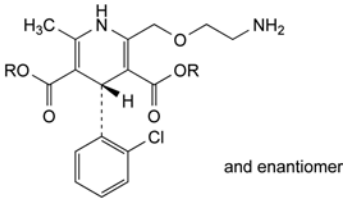


B. R = $NHCH_3$: 3-ethyl 5-methyl (4*RS*)-4-(2-chlorophenyl)-6-methyl-2-[[2-[[2-(methylcarbamoyl)benzoyl]amino]-ethoxy]methyl]-1,4-dihydropyridine-3,5-dicarboxylate,

H. R = OH: 2-[[2-[[(4*RS*)-4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]ethyl]carbamoyl]benzoic acid,

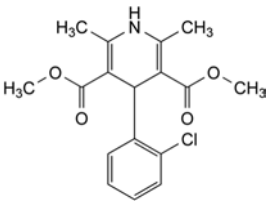


D. 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate,



E. R = C_2H_5: diethyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate,

F. R = CH_3: dimethyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate,



G. dimethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

01/2008:0877

AMMONIA SOLUTION, CONCENTRATED

Ammoniae solutio concentrata

NH_3 M_r 17.03

DEFINITION

Content: 25.0 per cent *m/m* to 30.0 per cent *m/m*.

CHARACTERS

Appearance: clear, colourless liquid, very caustic.

Solubility: miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Relative density (*2.2.5*): 0.892 to 0.910.

B. It is strongly alkaline (*2.2.4*).

C. To 0.5 mL add 5 mL of *water R*. Bubble air through the solution and lead the gaseous mixture obtained over the surface of a solution containing 1 mL of *0.1 M hydrochloric acid* and 0.05 mL of *methyl red solution R*. The colour changes from red to yellow. Add 1 mL of *sodium cobaltinitrite solution R*. A yellow precipitate is formed.

TESTS

Solution S. Evaporate 220 mL almost to dryness on a water-bath. Cool, add 1 mL of *dilute acetic acid R* and dilute to 20 mL with *distilled water R*.

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

To 2 mL add 8 mL of *water R*.

Oxidisable substances. Cautiously add, whilst cooling, 8.8 mL to 100 mL of *dilute sulfuric acid R*. Add 0.75 mL of *0.002 M potassium permanganate*. Allow to stand for 5 min. The solution remains faintly pink.

Pyridine and related substances: maximum 2 ppm, calculated as pyridine.

Measure the absorbance (*2.2.25*) at 252 nm using *water R* as the compensation liquid. The absorbance is not greater than 0.06.

Carbonates: maximum 60 ppm.

To 10 mL in a test-tube with a ground-glass neck add 10 mL of *calcium hydroxide solution R*. Stopper immediately and mix. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of a 0.1 g/L solution of *anhydrous sodium carbonate R*.

Chlorides (*2.4.4*): maximum 1 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*): maximum 5 ppm.

Dilute 3 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*): maximum 0.25 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Heavy metals (*2.4.8*): maximum 1 ppm.

Dilute 4 mL of solution S 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*.