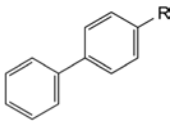
IMPURITIES

Specified impurities: A, B.



A. R = CO-CH_3: 4-acetyl biphenyl,

B. R = H: biphenyl.

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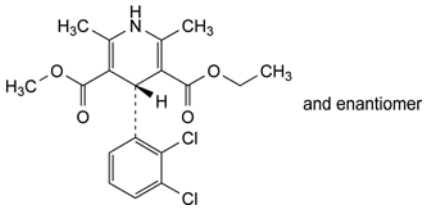
corrected 6.0

FELODIPINE

Felodipinum



$C_{18}H_{19}Cl_2NO_4$ M_r 384.3
[72509-76-3]

DEFINITION

Ethyl methyl (4*RS*)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

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

CHARACTERS

Appearance: white or light yellow, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, in anhydrous ethanol, in methanol and in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

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

Test solution. Dissolve 50 mg in *methanol R* and dilute to 100 mL with the same solvent. Dilute 3 mL of this solution to 100 mL with *methanol R*.

Spectral range: 220-400 nm.

Absorption maxima: at 238 nm and 361 nm.

Absorbance ratio: A_{361} / A_{238} = 0.34 to 0.36.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *felodipine CRS*.

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

Test solution. Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a). Dissolve 10 mg of *felodipine CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b). Dissolve 5 mg of *nifedipine CRS* in reference solution (a) and dilute to 5 mL with reference solution (a).

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

Mobile phase: *ethyl acetate R, cyclohexane R* (40:60 *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 spots.

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

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

Test solution. Dissolve 0.150 g in a mixture of 25 mL of *2-methyl-2-propanol R* and 25 mL of *perchloric acid solution R*. Add 10 mL of *0.1 M cerium sulfate*, allow to stand for 15 min, add 3.5 mL of *strong sodium hydroxide solution R* and neutralise with *dilute sodium hydroxide solution R*. Shake with 25 mL of *methylene chloride R*. Evaporate the lower layer to dryness on a water-bath under nitrogen (the residue is also used in the test for related substances). Dissolve about 20 mg of the residue in *methanol R* and dilute to 50 mL with the same solvent. Dilute 2 mL of this solution to 50 mL with *methanol R*.

Spectral range: 220-400 nm.

Absorption maximum: at 273 nm.

TESTS

Solution S. Dissolve 1.00 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*).

Absorbance (*2.2.25*): maximum 0.10, determined at 440 nm on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

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

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c). Dissolve 50.0 mg of the residue obtained in identification test D (impurity A) and 25.0 mg of *felodipine CRS* in the mobile phase, then dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.125-0.15 m, Ø = 4 mm;

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

Mobile phase: mix 20 volumes of *methanol R*, 40 volumes of *acetonitrile R* and 40 volumes of a phosphate buffer solution pH 3.0 containing 0.8 g/L of *phosphoric acid R* and 8 g/L of *sodium dihydrogen phosphate R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Run time: twice the retention time of felodipine.

Elution order: impurity B, impurity A, felodipine, impurity C.

Retention time: felodipine = about 12 min.

System suitability: reference solution (c):

– *resolution*: minimum 2.5 between the peaks due to impurity A and felodipine.

Limits:

– *sum of impurities B and C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

– *sum of impurities other than B and C*: 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*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent).

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 0.160 g in a mixture of 25 mL of *2-methyl-2-propanol R* and 25 mL of *perchloric acid solution R*. Add 0.05 mL of *ferroin R*. Titrate with *0.1 M cerium sulfate* until the pink colour disappears. Titrate slowly towards the end of the titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 19.21 mg of $C_{18}H_{19}Cl_2NO_4$.

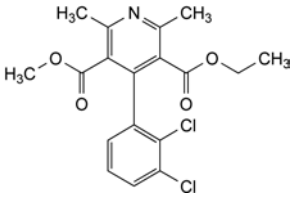
STORAGE

Protected from light.

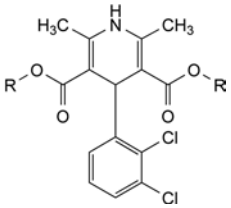
IMPURITIES

Specified impurities: B, C.

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*): *A.*



A. ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate,



B. R = CH_3: dimethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,

C. R = C_2H_5: diethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

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corrected 7.0

FELYPRESSIN

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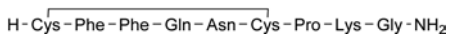

$C_{46}H_{65}N_{13}O_{11}S_2$ M_r 1039
[56-59-7]

DEFINITION

L-Cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysylglycinamide cyclic (1,6)-disulfide.

Synthetic nonapeptide having a vasoconstricting activity. It is available as an acetate.

Content: 95.0 per cent to 102.0 per cent (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance: white or almost white, powder or flakes.

Solubility: freely soluble in water, practically insoluble in acetone and ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.
Results: the principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

B. Amino acid analysis (*2.2.56*). For hydrolysis use Method 1 and for analysis use Method 1.
Express the content of each amino acid in moles. Calculate the relative proportions of amino acids, taking one-seventh of the sum of the number of moles of glutamic acid, aspartic acid, proline, lysine, glycine and phenylalanine as equal to one. The values fall within the following limits: aspartic acid: 0.9 to 1.1; glutamic acid: 0.9 to 1.1; proline: 0.9 to 1.1; glycine: 0.9 to 1.1; phenylalanine: 1.8 to 2.2; half-cystine: 1.8 to 2.2; lysine: 0.9 to 1.1.

TESTS

Specific optical rotation (*2.2.7*): – 35 to – 29, determined at 25 °C (anhydrous and acetic acid-free substance).

Dissolve 20.0 mg in a 1 per cent *V/V* solution of *glacial acetic acid R* and dilute to 10.0 mL with the same solution.

Related substances. Liquid chromatography (*2.2.29*); use the normalisation procedure. *The solutions are stable for 24 h at room temperature or for 1 week at 2-8 °C.*

Test solution (a). Dissolve 5.0 mg of the substance to be examined in 5.0 mL of mobile phase A.

Test solution (b). Dilute 1.0 mL of test solution (a) to 5.0 mL with mobile phase A.

Reference solution. Dissolve the contents of a vial of *felypressin CRS* in mobile phase A to obtain a concentration of 0.2 mg/mL.

Column:
– *size*: *l* = 0.15 m, Ø = 3.9 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),
– *temperature*: 50 °C.

Mobile phase:
– *mobile phase A*: dissolve 3.62 g of *tetramethylammonium hydroxide R* in 900 mL *water R*; adjust to pH 2.5 with *phosphoric acid R* and dilute to 1000 mL with *water R*;
– *mobile phase B*: dissolve 1.81 g of *tetramethylammonium hydroxide R* in 450 mL of a 50 per cent *V/V* solution of *acetonitrile for chromatography R*; adjust to pH 2.5 with *phosphoric acid R* and dilute to 500 mL with a 50 per cent *V/V* solution of *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	80 → 50	20 → 50
20 - 25	50	50

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µL of test solution (a) and 50 µL of the reference solution.