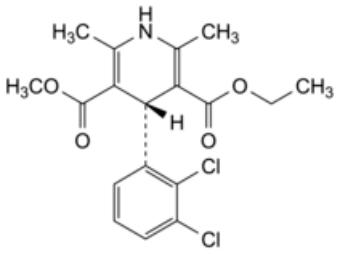
Edition: BP 2025 (Ph. Eur. 11.6 update)

Felodipine

General Notices

(Ph. Eur. monograph 1013)



and enantiomer

$C_{18}H_{19}Cl_2NO_4$ 384.3 *72509-76-3*

Action and use

Calcium channel blocker.

Preparation

Felodipine Prolonged-release Tablets

Ph Eur

DEFINITION

3-Ethyl 5-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 anhydrous ethanol, in methanol and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, 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 the solution to 100 mL with methanol R.

Spectral range 220-400 nm.

Absorption maxima 238 nm and 361 nm.

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

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.250 g in a mixture of 40 mL of 2-methyl-2-propanol R and 25 mL of perchloric acid solution R. Add 20 mL of 0.1 M cerium sulfate, allow to stand for 15 min, add 6 mL of strong sodium hydroxide solution R and neutralise with dilute sodium hydroxide solution R. Shake with 50 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 273 nm.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison felodipine CRS.

D. 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).

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. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50 mg of the residue obtained in identification test B (impurity A) and 25 mg of *felodipine CRS* in the mobile phase, then dilute to 50 mL with the mobile phase. Dilute 1 mL of the solution to 100 mL with the mobile phase. Dilute 1 mL of this solution to 10 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *felodipine for peak identification CRS* (containing impurities B and C) in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *end-capped 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 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time Twice the retention time of felodipine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram supplied with *felodipine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B and C.

Relative retention With reference to felodipine (retention time = about 6 min): impurity B = about 0.7; impurity A = about 0.9; impurity C = about 1.4.

System suitability Reference solution (b):

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

Calculation of percentage contents:

— for each impurity, use the concentration of felodipine in reference solution (a).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurity C*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 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 $C_{18}H_{19}Cl_2NO_4$.

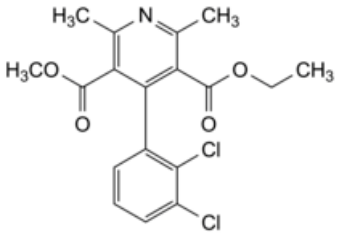
STORAGE

Protected from light.

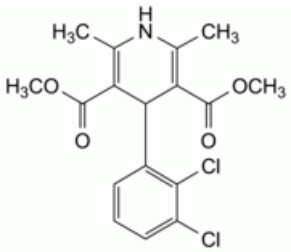
IMPURITIES

Specified impurities *B, C.*

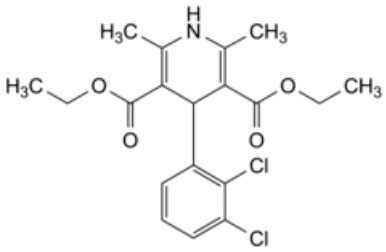
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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. dimethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,



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

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