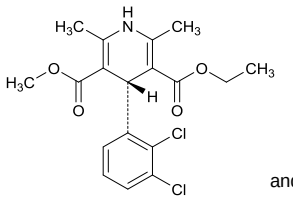
Felodipine

フェロジピン



and enantiomer

$C_{18}H_{19}Cl_2NO_4$: 384.25

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

[*72509-76-3*]

Felodipine contains not less than 99.0% and not more than 101.0% of felodipine ($C_{18}H_{19}Cl_2NO_4$), calculated on the dried basis.

Description Felodipine occurs as pale yellow-white to light yellow-white, crystals or crystalline powder.

It is freely soluble in methanol and in ethanol (99.5), and practically insoluble in water.

A solution of Felodipine in methanol (1 in 20) shows no optical rotation.

Identification **(1)** Determine the absorption spectrum of a solution of Felodipine in methanol (1 in 62,500) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Felodipine as directed in the potassium bromide disk method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Heavy metals—Being specified separately when the drug is granted approval based on the Law.

(2) Related substances—Dissolve 25 mg of Felodipine in 50 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method: the area of the peak other than felodipine, the related substance B, having the relative retention time of about 0.7 to felodipine, and the related substance C, having the relative retention time of about 1.4, obtained from the sample solution is not larger than the peak area of felodipine from the standard solution. Furthermore, the total area of the peaks of rerated substances B and C is not larger than 10 times the peak area of felodipine from the standard solution, and the total area of the peaks other than felodipine and related substances mentioned above is not larger than 3 times the peak area of felodipine from the standard solution. For this calculation the peak area less than 1/5 times the peak area of felodipine from the standard solution is excluded.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25℃.

Mobile phase: Dissolve 3.2 g of sodium dihydrogen phosphate dihydrate in 400 mL of water, adjust to pH 3.0 with phosphoric acid, and add 200 mL of methanol and 400 mL of acetonitrile.

Flow rate: Adjust so that the retention time of felodipine is about 12 minutes.

Time span of measurement: About 2 times as long as the retention time of felodipine, beginnig after the solvent peak.

System suitability—

Test for required detectability: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the SN ratio of the peak of felodipine is not less than 30.

System performance: Dissolve 25 mg of Felodipine in 50 mL of the mobile phase. To 1 mL of this solution add the mobile phase to make 100 mL. To 1 mL of this solution add the mobile phase to make 10 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of felodipine are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of felodipine is not more than 2.0%.

Loss on drying *<2.41>* Not more than 0.2% (1 g, 105℃, 3 hours).

Residue on ignition *<2.44>* Not more than 0.1% (1 g).

Assay Weigh accurately about 0.16 g of Felodipine, dissolve in 25 mL of *t*-butyl alcohol and 25 mL of diluted perchloric acid (17 in 200), and titrate with 0.1 mol/L cerium

(IV) sulfate VS <2.50> (indicator: 50 μL of 1,10-phenanthroline TS) until the color of the solution changes from orange to colorless. Perform a blank determination in the same manner, and make any necessary correction.

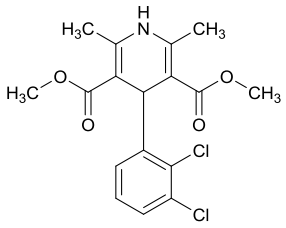
Each mL of 0.1 mol/L cerium sulfate (IV) VS
＝19.21 mg of $C_{18}H_{19}Cl_2NO_4$

Containers and storage Containers—Well-closed containers.

Others

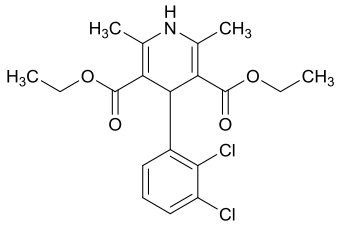
Related substance B:

Dimethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Related substance C:

Diethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Add the following to 9.21 Standard Solutions for Volumetric Analysis:

Cerium (IV) Sulfate, 0.1 mol / L

1000 mL of this solution contains 40.43 g of cerium (IV) sulfate tetrahydrate ($Ce(SO_4)_2.4H_20$: 404.30).

Preparation—Dissolve 40.43 g of cerium sulfate (IV) tetrahydrate in water to make 1000 mL, and standardize the solution as follows:

Standardization—Weigh accurately about 0.2 g of sodium oxalate (standard reagent), previously dried at 150 to 200℃ for 1 to 1.5 hours, and allowed to cool in a desiccator (silica gel), and dissolve in 75 mL of water. Add a mixture of 5 mL of water and 2 mL of sulfuric acid with stirring, add 10 mL of hydrochloric acid. Warm to 70 – 75℃, and titrate <2.50> the solution with 0.1 mol/L cerium (IV) sulfate VS until the solution shows a persistent slightly yellow color, and calculate the molarity factor.

Each mL of 0.1 mol/L cerium sulfate (IV) VS
＝6.700 mg of $Na_2C_2O_4$