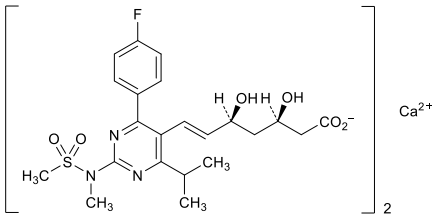
Rosuvastatin Calcium

ロスバスタチンカルシウム



$(C_{22}H_{27}FN_3O_6S)_2Ca$: 1001.14

Monocalcium bis[(3*R*,5*S*,6*E*)-7-{4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoate]

[*147098-20-2*]

Rosuvastatin Calcium contains not less than 97.0% and not more than 102.0% of rosuvastatin calcium $[(C_{22}H_{27}FN_3O_6S)_2Ca]$, calculated on the anhydrous basis.

Description Rosuvastatin Calcium occurs as a white powder.

It is freely soluble in acetonitrile, soluble in methanol, and slightly soluble in water and in ethanol (99.5).

It is hygroscopic.

Identification **(1)** Determine the absorption spectrum of a solution of Rosuvastatin Calcium in methanol (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Rosuvastatin Calcium RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

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

(3) A solution of Rosuvastatin Calcium in a mixture of water and methanol (1:1) (1 in 125) responds to Qualitative Tests *<1.09>* (3) for calcium salt.

Purity **(1)** Inorganic impurities (chloride)—Weigh accurately about 0.15 g of Rosuvastatin Calcium, dissolve in 60 mL of water, add 5 mL of diluted nitric acid (1 in 10), and titrate *<2.50>* with 0.01 mol/L silver nitrate VS (potentiometric titration). Perform a blank determination in the same manner, and make any necessary corrections (not more than 0.2%).

Each mL of 0.01 mol/L silver nitrate VS＝0.3545 mg of Cl

(2) Heavy metals *<1.07>*—Proceed with 1.0 g of Rosuvastatin Calcium according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances—Conduct this procedure using light-resistant vessels. Use the sample solution obtained in the Assay as the sample solution. Separately, pipet 1 mL of the standard solution obtained in the Assay, add a mixture of water and acetonitrile (3:1) to make exactly 10 mL. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (3:1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 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 of related substances, A_T, in the sample solution and the peak area of rosuvastatin, A_S, in the standard solution by the automatic integration method, and calculate the amount of the related substances by the following equation: the amount of the related substance A having the relative retention time of about 0.90 to rosuvastatin is not more than 0.2%, the amount of the related substance B (diastereomer) having the relative retention time of about 1.1 is not more than 0.5%, the amount of the related substance C having the relative retention time of about 1.5 is not more than 0.7%, the amount of the related substance D having the relative retention time of about 1.7 is not more than 0.15%, and each amount of other related substances is not more than 0.1%. Furthermore the total amount of the related substances is not more than 1.1%. For the area of the peak of the related substance C, multiply the relative response factor 1.4.

$$\text{Amount (\%) of related substance} = M_S / M_T \times A_T / A_S \times 1/5$$

M_S: Amount (mg) of Rosuvastatin Calcium RS taken, calculated on the anhydrous basis

M_T: Amount (mg) of Rosuvastatin Calcium taken, calculated on the anhydrous basis

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 2.8 times as long as the retention time of rosuvastatin, beginning after the solvent peak.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 5 mL of the standard solution obtained in the Assay, add 24 mL of acetonitrile, and add water to make exactly 100 mL. Pipet 1 mL of this solution, add 24 mL of acetonitrile, and add water to make

exactly 100 mL. Confirm that the peak area of rosuvastatin obtained with 10 μL of this solution is equivalent to 0.025 to 0.075% of that with 10 μL of the standard solution in the Assay.

System repeatability: When the test is repeated 5 times with 10 μL of the standard solution in the Assay under the above operating conditions, the relative standard deviation of the peak area of rosuvastatin is not more than 2.0%.

(4) Enantiomer — Dissolve 100 mg of Rosuvastatin Calcium in a mixture of water and acetonitrile (3:1) to make exactly 100 mL, and use this solution as the sample solution. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (3:1) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine each peak area by the automatic integration method: the area of related substance E (enantiomer) having the relative retention time of about 0.92 to rosuvastatin from the sample solution is not larger than 1/5 times the peak area of rosuvastatin from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 242 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter) coated with cellulose tris(4-methylbenzoate) for liquid chromatography.

Column temperature: A constant temperature of about 35℃.

Mobile phase: A mixture of diluted trifluoroacetic acid (1 in 1000) and acetonitrile (3:1).

Flow rate: Adjust so that the retention time of rosuvastatin is 26.5 minutes.

Time span of measurement: About 3 times as long as the retention time of rosuvastatin, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution, add a mixture of water and acetonitrile (3:1) to make exactly 50 mL. Confirm that the peak area of rosuvastatin obtained with 10 μL of this solution is equivalent to 7 to 13% of that with the standard solution.

System performance: To 5 mg of rosuvastatin enantiomer add 12 mL of acetonitrile and 10 mL of water, sonicate to dissolve, and add water to make 50 mL. To 1 mL of this solution and 6 mL of acetonitrile add 25 mg of Rosuvastatin Calcium, sonicate to dissolve, and add water to make 25 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, rosuvastatin enantiomer and rosuvastatin are eluted in this order with the resolution between these peaks being not less than 1.5, and the symmetry factor of the peak of rosuvastatin is 1.0 – 1.5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of rosuvastatin is not more than 2%.

Water *<2.48>* Not more than 6% (20 mg, coulometric titration).

Assay Conduct this procedure using light-resistant vessels. Weigh accurately about 35 mg each of Rosuvastatin Calcium and Rosuvastatin Calcium RS (separately determine the water *<2.48>* in the same manner as Rosuvastatin Calcium), dissolve each in a mixture of water and acetonitrile (3:1) to make exactly 50 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S, of rosuvastatin in each solution.

Amount (mg) of rosuvastatin calcium $[(C_{22}H_{27}FN_3O_6S)_2Ca]$
$= M_S \times A_T / A_S$

M_S: Amount (mg) of Rosuvastatin Calcium RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 242 nm).

Column: A stainless steel column 3 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase A: A mixture of water, acetonitrile and diluted trifluoroacetic acid (1 in 100) (70:29:1).

Mobile phase B: A mixture of acetonitrile, water, and diluted trifluoroacetic acid (1 in 100) (75:24:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 — 30	100	0
30 — 50	100 → 60	0 → 40
50 — 60	60 → 0	40 → 100
60 — 70	0	100

Flow rate: 0.75 mL per minute.

System suitability—

System performance: Dissolve 10 mg of Rosuvastatin Calcium in 10 mL of a solution of trifluoroacetic acid in acetonitrile (1 in 100), and allow to stand at 40℃ for 1 hour. After cooling, add 20 mL of water, adjust to pH 6 – 8 with sodium hydroxide TS, and add water to make 50 mL. To 3 mL of this solution, add water to make 50 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, rosuvastatin and the related substance B (diastereomer) are eluted in this order with the resolution between these peaks being not less than 2.5, and the symmetry factor of the peak of rosuvastatin is not more than 1.5.

System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of rosuvastatin is not more than 2.0%.

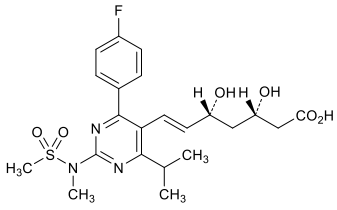
Containers and storage Containers—Tight containers.

Storage—Light-resistant, at a temperature between 2℃ and 8℃.

Others

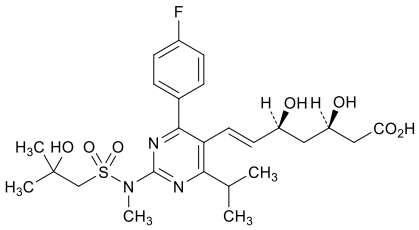
Rosuvastatin enantiomer:

(3*S*,5*R*,6*E*)-7-{4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid



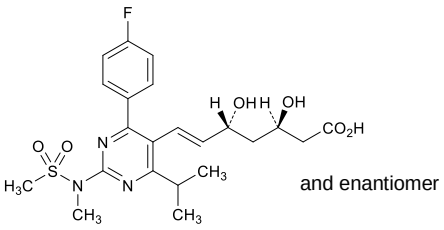
Related substance A:

(3*R*,5*S*,6*E*)-7-[4-(4-Fluorophenyl)-2-{[(2-hydroxy-2-methylpropyl)sulfonyl]methylamino}-6-(1-methylethyl) pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid



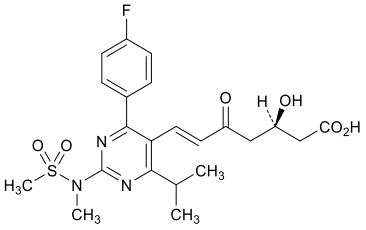
Related substance B (diastereomer):

(3*RS*,5*RS*,6*E*)-7-{4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid



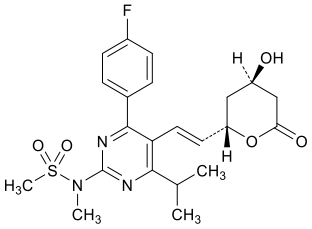
Related substance C:

(3*R*,6*E*)-7-{4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-5-oxohept-6-enoic acid



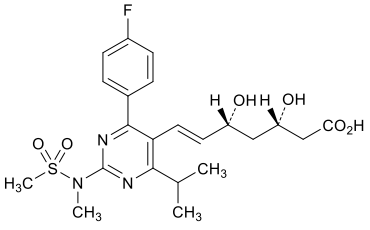
Related substance D:

N-[4-(4-Fluorophenyl)-5-{(1*E*)-2-[(2*S*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethenyl}-6-(1-methylethyl) pyrimidin-2-yl]-*N*-methylmethanesulfonamide



Related substance E (enantiomer):

(3*S*,5*R*,6*E*)-7-{4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid



Add the following to 9.01 Reference Standards (1):

Rosuvastatin Calcium RS

Add the following to 9.41 Reagents, Test Solutions:

Cellulose tris(4-methylbenzoate) for liquid chromatography Prepared for liquid chromatography.

Rosuvastatin enantiomer $C_{22}H_{27}FN_3O_6S$ White powder.

Identification—**(1)** Proceed the test as directed in the system performance of the system suitability in the Purity (4) under Rosuvastatin Calcium: the relative retention time of rosuvastatin enantiomer to rosuvastatin peak is about 0.92.

(2) Determine the ^1H spectrum of a solution of Rosuvastatin enantiomer in deuterated dimethyl sulfoxide for nuclear magnetic resonance spectroscopy(3 in 100) as directed under Nuclear Magnetic Resonance Spectroscopy *<2.21>*, using tetramethylsilane for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits a double triplet signal A at around δ 1.5 ppm, a multiplet signal B at around δ 4.2 ppm, a double doublet signal C at around δ 5.5 ppm, a double doublet signal D at around δ 6.5 ppm, a multiplet signal E at around δ 7.3 ppm, and a multiplet signal F at around δ 7.7 ppm. The ratio of integrated intensity of each signal, A:B:C:D:E:F, is about 1:1:1:1:2:2.