Simvastatin Tablet

Dissolution *<6.10>* Perform the test with 1 tablet of Simvastatin Tablets at 50 revolutions per minute according to the Paddle method, using 900 mL of a solution, prepared by adding 1000 mL of water to 3 g of polysorbate 80, as the dissolution medium. Start the test, withdraw not less than 10 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 5.6 μg of simvastatin ($C_{25}H_{38}O_5$) according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 22 mg of Simvastatin RS (separately, determine the loss on drying *<2.41>*, previously dried under reduced pressure not exceeding 0.67 kPa at 60ºC for 3 hours), and dissolve in acetonitrile to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with exactly 20 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 simvastatin of both solutions.

The requirements are met if Simvastatin Tablet conforms to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of simvastatin ($C_{25}H_{38}O_5$)

$= M_S \times A_T/A_S \times V'/V \times 1/C \times 45/2$

M_S: Amount (mg) of Simvastatin RS, calculated on the anhydrous basis

C: Labeled amount (mg) of simvastatin ($C_{25}H_{38}O_5$) in 1 tablet

Operating conditions−

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column 3.9 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 50ºC.

Mobile phase: A mixture of methanol and 0.02 mol/L potassium dihydrogen phosphate TS (4:1).

Flow rate: Adjust the flow rate so that the retention time of simvastatin is about 4 minutes.

System suitability−

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of simvastatin are not less than 3000 and not more than 2.0, 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 simvastatin is not more than 1.0%.

Dissolution Requirements

Labeled amount	Specified minute	Dissolution rate
5 mg	30 minutes	Not less than 70%
10 mg	45 minutes	Not less than 70%
20 mg	45 minutes	Not less than 70%

Simvastatin RS $C_{25}H_{38}O_5$: 418.57 (+)-(1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl]-1-naphtyl 2,2-dimethylbutanoate. It meets the following requirements. Purify according to the following method if needed.

Purification method−Dissolve 5 g of simvastatin in 70 mL of methanol, and filter. Warm the filtrate to a temperature of about 35ºC, add 30 mL of water, cool to about 15 ºC and allow to stand for several hours, and filter. Wash the crystals so obtained with a mixture of water and methanol (1:1), and dry at 40ºC for 3 hours under reduced pressure.

Description−Simvastatin RS occurs as a white, crystals or crystalline powder.

Identification−Determine the infrared absorption spectrum of Simvastatin RS as directed in the potassium bromide disk method under Infrared Spectrophotometry *<2.25>*: it exhibits absorption at the wave numbers of about 3550cm^{-1}, 3010cm^{-1}, 1720cm^{-1}, 1695 cm^{-1}, 1465 cm^{-1}, and 1390cm^{-1}.

Optical rotation <2.49>: $[\alpha]_D^{25}$: + 288 - + 295° (0.05 g, calculated on the dried basis, 10 mL of acetonitrile, 100 mm).

Related substances−Dissolve 30 mg of Simvastatin RS in a mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate TS, pH 4.0 (3:2) to make exactly 20 mL, and use this solution as the sample solution. Perform the test with 5 μL of the sample solution as directed under Liquid chromatography *<2.01>* according to the following conditions, and determine each peak area by the automatic integration method: the total area of the peaks of related substances other than simvastatin is not more than 1.0%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 33 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

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

Mobile phase B: A solution of phosphoric acid in acetonitrile (1 in 1000).

Flowing of the 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 − 4.5	100	0
4.5 − 4.6	100 → 95	0 → 5
4.6 − 8.0	95 → 25	5 → 75
8.0 − 11.5	25	75

Flow rate: 3.0 mL per minute.

Time span of measurement: About 5 times as long as the retention time of simvastatin beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 0.5 mL of the sample solution, add a mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate TS, pH 4.0 (3:2) to make exactly 100 mL, and use this solution as the solution for system suitability test. Pipet 2 mL of the solution for system suitability test, and add a mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate TS, pH 4.0 (3:2) to make exactly 10 mL. Confirm that the peak area of simvastatin obtained from 5 μL of this solution is equivalent to 16 to 24% of that from 5 μL of the solution for system suitability test.

System performance: Dissolve 3 mg of lovastatin in 2 mL of the sample solution. When the procedure is run with 5 μL of this solution under the above operating conditions, lovastatin and simvastatin are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 5 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of simvastatin is not more than 10%.

Loss on drying <*2.41*>: not more than 0.2% (2 g, reduced pressure not exceeding 0.67 kPa, 60ºC, 3 hours).

Potassium Dihydrogen Phosphate TS, 0.01 mol/L Dissolve 1.36 g of potassium dihydrogen phosphate, pH 4.0 in 1000 mL of water, and adjust the pH to 4.0 with phosphoric acid.

Lovastatin $C_{24}H_{36}O_5$ White, crystals or crystalline powder. Soluble in acetonitrile and in methanol, sparingly soluble in ethanol, and practically insoluble in water.

Optical rotation *<2.49>*: $[\alpha]_D^{25}$: +325 − +340° (50 mg, calculated on the dried basis, 10 mL of acetonitrile, 100 mm).

Loss on drying *<2.41>*: not more than 1.0% (1 g, reduced pressure not exceeding 0.67 kPa, 60ºC, 3 hours).