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Simvastatin Tablets

General Notices

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

DEFINITION

Simvastatin Tablets contain Simvastatin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of simvastatin, $C_{25}H_{38}O_5$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Simvastatin with 20 mL of *dichloromethane*, filter through a glass fibre filter (Whatman GF/C is suitable) and evaporate the filtrate to dryness under a stream of *nitrogen*. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of simvastatin *(RS 423)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.01M *sodium dihydrogen orthophosphate* containing 0.5% w/v of *sodium dodecyl sulfate* and adjusted to pH 7.0 with 1M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a 20-mL sample of the medium, filter and transfer 10 mL of the filtrate into a centrifuge tube containing 0.1 g of *manganese(IV) oxide, pre-washed*. Shake the tube for 30 minutes, or until the manganese(IV) oxide is completely dispersed and centrifuge. Measure the *absorbance* of the clear supernatant liquid, suitably diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.001% w/v of Simvastatin, at the maximum at 247 nm and at the minimum at 257 nm, Appendix II B using dissolution medium that has been similarly treated with *manganese(IV) oxide, pre-washed* in the reference cell.
(2) Measure the *absorbance* of a 0.001% w/v solution of *simvastatin BPCRS* prepared by dissolving *simvastatin BPCRS* in the dissolution medium and treating with *manganese(IV) oxide, pre-washed* as described for solution (1), at 247 nm and

at 257 nm, using dissolution medium that has been similarly treated with *manganese(IV) oxide, pre-washed* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of simvastatin, $C_{25}H_{38}O_5$, in the medium using the differences in *absorbance* at 247 nm and at 257 nm and using the declared content of $C_{25}H_{38}O_5$ in *simvastatin BPCRS*.

LIMITS

The amount of simvastatin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in solution A.

Mix 40 volumes of a 0.14% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 4.0 with *orthophosphoric acid*, and 60 volumes of *acetonitrile* (solution A).

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Simvastatin with 20 mL of solution A. Add sufficient solution A to produce 50 mL, mix and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.2% w/v of *simvastatin for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Zorbax Eclipse XDB-C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.4 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 238 nm.
(f) Use an autosampler temperature of 8°
(g) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A 40 volumes of *acetonitrile* and 60 volumes of a 0.1% v/v solution of *orthophosphoric acid*.

Mobile phase B 5 volumes of a 0.1% v/v solution of *orthophosphoric acid* and 95 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	100	0	isocratic
4-5	100→80	0→20	linear gradient
5-33	80→60	20→40	linear gradient
33-34	60→0	40→100	linear gradient
34-48	0	100	isocratic
48-49	0→100	100→0	linear gradient
50-55	100	0	re-equilibration

Use the chromatogram supplied with *simvastatin for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B C, D, E, F, G, I and J.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to simvastatin (retention time about 19 minutes) are: impurity I, about 0.67; impurity A, about 0.69; impurity E, about 0.81; impurity F, about 0.83; impurity G, about 0.9; impurity B, about 1.69; impurity J, about 1.74; impurity C, about 1.8 and impurity D, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3):

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity E;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity J.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to impurities A and I is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity B, C, E or F is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity D or G is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks*, other than any peaks corresponding to impurities A + I, B, C, D, E, F and G, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Add 3 mL of *glacial acetic acid* to 900 mL of *water*, adjust the pH to 4.0 with 1M *sodium hydroxide* and add sufficient *water* to produce 1000 mL. Mix 1 volume of this solution with 4 volumes of *acetonitrile* (solution B).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution B.

(1) Mix, with the aid of ultrasound and shaking, a quantity of whole tablets containing 0.16 g of Simvastatin in a minimum volume of *water* until completely dispersed. Add a sufficient volume of solution B to produce 75 mL, mix with the aid of ultrasound and shaking for 15 minutes, allow to cool to room temperature, dilute to produce 100 mL and centrifuge. Dilute 1.5 volumes of the clear supernatant solution to 25 volumes.
(2) 0.01% w/v of *simvastatin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 238 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

7 volumes of a buffer solution prepared as described below and 13 volumes of *acetonitrile*.

To prepare the buffer solution dissolve 5.1 g of *sodium dihydrogen orthophosphate* in 900 mL of *water*, adjust the pH to 4.5 with either *orthophosphoric acid* or 1M *sodium hydroxide* and add sufficient *water* to produce 1000 mL.

When the chromatograms are recorded using the prescribed conditions the retention time of simvastatin is about 7 minutes.

SYSTEM SUITABILITY

The test is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{38}O_5$ in the tablets using the declared content of $C_{25}H_{38}O_5$ in *simvastatin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Simvastatin.