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

Simvastatin Oral Suspension

General Notices

Action and use

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

DEFINITION

Simvastatin Oral Suspension is a suspension of Simvastatin in a suitable flavoured vehicle.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Simvastatin. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

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

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *dichloromethane*.
(1) Shake a quantity of the oral suspension containing 25 mg of Simvastatin with 10 mL of *dichloromethane* for 10 minutes. Allow to separate and use the lower layer.
(2) 0.25% w/v of *simvastatin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

12 volumes of *propan-2-ol*, 23 volumes of *dichloromethane* and 65 volumes of *cyclohexane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

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

45 volumes of a 0.14% w/v solution of *potassium dihydrogen phosphate*, adjusted to pH 4.0 with *orthophosphoric acid*, and 55 volumes of *acetonitrile* (solution A).

(1) Mix with the aid of ultrasound a quantity of the oral suspension containing 16 mg of Simvastatin with 30 mL of solution A. Add a sufficient volume of solution A to produce 50 mL and mix. Centrifuge and filter (0.45-µm PVDF syringe filter is suitable).
(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 5 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
34-37	0	100	isocratic
37-38	0→100	100→0	linear gradient
38-45	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 area of any peak corresponding to impurities A and I is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (6%);

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 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 half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

45 volumes of a 0.14% w/v solution of *potassium dihydrogen phosphate*, adjusted to pH 4.0 with *orthophosphoric acid*, and 55 volumes of *acetonitrile*. Mix and filter (solvent B).

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

(1) Mix with the aid of ultrasound a weighed quantity of the oral suspension containing 16 mg of Simvastatin with 30 mL of solution B. Add a sufficient volume of solution B to produce 50 mL and mix. Centrifuge and filter (0.45-µm PVDF syringe filter is suitable). Dilute 5 volumes to 200 volumes.
(2) 0.0008% w/v of *simvastatin BPCRS*.
(3) 0.002% w/v of each of *simvastatin BPCRS* and *lovastatin EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used. Inject 50 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to simvastatin and lovastatin (impurity E) is at least 3.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{25}H_{38}O_5$, weight in volume, 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.