Simvastatin Tablets

**General Notices**

Details for the public consultation of this monograph are as follows:

<table>
<thead>
<tr>
<th>EAG: MC2</th>
<th>Medicinal Chemistry 2</th>
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</thead>
</table>
| **Contact Details** | helen.coms@mhra.gov.uk  
Stephen.maddock@mhra.gov.uk |
| **Deadline for Comment** | 30th September 2019 |
| **Target Publication Date (subject to change)** | BP 2021 |
| **Notes:** | Monograph Revision  
Related Substances: Revision to method conditions to identify and limit specific impurities.  
If current limits are too tight, please provide relevant batch/stability data to the BP. |

**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, C₂₅H₃₈O₅  
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 glass fibre filter (Whatman GF/C is suitable) and evaporate the filtrate to dryness using a rotary evaporator and a water bath at 40°. 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°C, 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 pre-washed manganese(IV) oxide. Shake the tube for 30 minutes, or until the manganese(IV) oxide is completely dispersed, centrifuge and measure the absorbance of the clear supernatant liquid, suitably diluted with the dissolution medium if necessary, 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 pre-washed manganese(IV) oxide 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 pre-washed manganese(IV) oxide as described above, at 247 nm and at 257 nm, using dissolution medium that has been similarly treated with pre-washed manganese(IV) oxide 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 the solvent mixture.

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

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 100 mg of Simvastatin with 20 mL of solvent mixture. Add sufficient solvent mixture to produce 50 mL, mix and filter.

(2) Dilute 1 volume of solution (1) to 200 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 °C.

(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.

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

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 0.8; 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 $H_p$ is the height above the baseline of the peak due to impurity F and $H_v$ 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 $H_p$ is the height above the baseline of the peak due to impurity C and $H_v$ 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 twice 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 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 0.8 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 twice 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 A).

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Mix a quantity of whole tablets containing 0.16 g of Simvastatin in water and mix with the aid of ultrasound and shaking until completely dispersed. Add sufficient of solution A to produce about 75 mL, mix with the aid of ultrasound and shaking for 15 minutes, allow to cool to room temperature, add sufficient of solution A to produce 100 mL and centrifuge. Dilute 15 volumes of the clear supernatant solution to 25 volumes with solution A.

(2) 0.01% w/v of simvastatin BPCRS in solution A.

**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.

**SYSTEM SUITABILITY**

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

**DETERMINATION OF CONTENT**

Calculate the content of C23H38O5 in the tablets using the declared content of C23H38O5 in simvastatin BPCRS.
IMPURITIES

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