– angle of oscillation of about 10°,

– oscillation radius of about 10 cm.

Shake for 10 s and record the time between the end of the shaking and the instant the 1st portion of foam-free liquid surface appears.

This duration is not longer than 15 s.

Mineral oils. Place 2.0 g in a test-tube and examine in ultraviolet light at 365 nm. The fluorescence is not more intense than that of a solution containing 0.1 ppm of *quinine sulphate R* in *0.005 M sulphuric acid* examined in the same conditions.

Phenylated compounds: the corrected absorbance (*2.2.25*) is not greater than 0.2.

Test solution. Dissolve 5.0 g with shaking in 10.0 ml of *cyclohexane R*.

Spectral range: 200-350 nm.

Calculate the corrected absorbance using the following expression:

$$B - C$$

B = absorbance at the absorption maximum between 250 nm and 270 nm,

C = absorbance at 300 nm.

Heavy metals: maximum 5 ppm.

Mix 1.0 g with *methylene chloride R* and dilute to 20 ml with the same solvent. Add 1.0 ml of a freshly prepared 0.02 g/l solution of *dithizone R* in *methylene chloride R*, 0.5 ml of *water R* and 0.5 ml of a mixture of 1 volume of *dilute ammonia R2* and 9 volumes of a 2 g/l solution of *hydroxylamine hydrochloride R*. At the same time, prepare the reference solution as follows: to 20 ml of *methylene chloride R* add 1.0 ml of a freshly prepared 0.02 g/l solution of *dithizone R* in *methylene chloride R*, 0.5 ml of *lead standard solution (10 ppm Pb) R* and 0.5 ml of a mixture of 1 volume of *dilute ammonia R2* and 9 volumes of a 2 g/l solution of *hydroxylamine hydrochloride R*. Immediately shake each solution vigorously for 1 min. Any red colour in the test solution is not more intense than that in the reference solution.

Volatile matter: maximum 1.0 per cent, determined on 1.00 g by heating in an oven at 150 °C for 2 h. Carry out the test using a dish 60 mm in diameter and 10 mm deep.

ASSAY

Silica. Heat not less than 20.0 mg to 800 °C increasing the temperature by 20 °C/min under a current of *nitrogen R* at a flow rate of 200 ml/min and weigh the residue (silica).

Poly(dimethylsiloxane). Infrared absorption spectrophotometry (*2.2.24*).

Test solution. Place about 50 mg (*E*) in a screw-capped 125 ml cylindrical tube, add 25.0 ml of *toluene R*, swirl manually to disperse and add 50 ml of *dilute hydrochloric acid R*, close the tube and place on a vortex mixer; shake for 5 min. Transfer the contents of the tube to a separating funnel, allow to settle and transfer 5 ml of the upper layer to a screw-capped test tube containing 0.5 g of *anhydrous sodium sulphate R*. Cap and shake vigorously manually. Centrifuge to obtain a clear solution.

Reference solution. Introduce about 0.20 g of *dimeticone CRS* (poly(dimethylsiloxane)) into 100.0 ml of *toluene R*. Prepare the reference solution in the same way as for the test solution, using 25.0 ml of the dimeticone solution obtained above.

Blank solution. Shake 10 ml of *toluene R* with 1 g of *anhydrous sodium sulphate R*. Centrifuge the resulting suspension.

Record the infrared absorption spectra for the test solution and the reference solution in 0.5 mm cells, from 1330 cm^{-1} to 1180 cm^{-1}. Determine the absorbance of the band at 1260 cm^{-1}.

Calculate the percentage content of poly(dimethylsiloxane) using the following expression:

$$\frac{25 \times C \times A_M \times 100}{A_E \times E}$$

A_M = absorbance of the test solution,

A_E = absorbance of the reference solution,

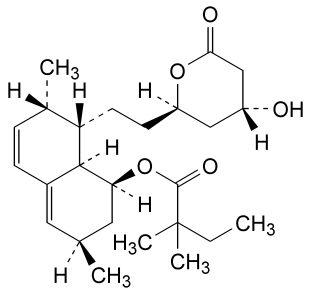
C = concentration of the reference solution, in milligrams per millilitre,

E = mass of the substance to be examined, in milligrams.

01/2008:1563

SIMVASTATIN

Simvastatinum



$C_{25}H_{38}O_5$ M_r 418.6

[79902-63-9]

DEFINITION

Simvastatin contains not less than 97.0 per cent and not more than the equivalent of 102.0 per cent of (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate, calculated with reference to the dried substance. A suitable antioxidant may be added.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, very soluble in methylene chloride, freely soluble in alcohol.

IDENTIFICATION

A. It complies with the test for specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *simvastatin CRS*. Examine the substances prepared as discs.

TESTS

Appearance of solution. Dissolve 0.200 g in *methanol R* and dilute to 20 ml with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*). Dissolve 0.125 g in *acetonitrile R* and dilute to 25.0 ml with the same solvent. The specific optical rotation is + 285 to + 300, calculated with reference to the dried substance.

Related substances. Examine by liquid chromatography (*2.2.29*) as prescribed under Assay.

Inject 5 µl of reference solution (b). Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained is at least 20 per cent of the full scale of the recorder. Inject 5 µl of test solution (a) and continue the chromatography for five times the retention time of simvastatin. When the chromatograms are recorded under the prescribed conditions the relative retentions are: impurity A about 0.45, lovastatin (impurity E) and epilovastatin (impurity F) about 0.60, impurity G about 0.80, impurity B about 2.38, impurity C about 2.42 and impurity D about 3.80 (retention time of simvastatin: about 2.6 min). In the chromatogram obtained with test solution (a): the area of the peak due to lovastatin and epilovastatin is not greater than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent); the area of any peak apart from the principal peak and the peak due to lovastatin and epilovastatin is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent); the sum of the areas of all peaks, apart from the principal peak and the peak due to lovastatin and epilovastatin, is not greater than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Heavy metals (*2.4.8*). 1.0 g complies with limit test C for heavy metals (20 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in a desiccator under high vacuum at 60 °C for 3 h.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Examine by liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture. Prepare a mixture of 40 volumes of a solution of a 1.4 g/l solution of *potassium dihydrogen phosphate R*, adjusted to pH 4.0 with *phosphoric acid R*, and 60 volumes of *acetonitrile R*. Filter.

Test solution (a). Dissolve 75.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Test solution (b). Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). Dissolve 1.0 mg of *simvastatin CRS* and 1.0 mg of *lovastatin CRS* in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (b). Dilute 0.5 ml of test solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). Dissolve 40.0 mg of *simvastatin CRS* in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.033 m long and 4.6 mm in internal diameter packed with *end-capped octadecylsilyl silica gel for chromatography R* (3 µm),

– as mobile phase at a flow rate of 3.0 ml/min:

Mobile phase A. Mix 50 volumes of *acetonitrile R* and 50 volumes of a 0.1 per cent *V/V* solution of *phosphoric acid R*,

Mobile phase B. A 0.1 per cent *V/V* solution of *phosphoric acid R* in *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0 - 4.5	100	0	isocratic
4.5 - 4.6	100 → 95	0 → 5	linear gradient
4.6 - 8.0	95 → 25	5 → 75	linear gradient
8.0 - 11.5	25	75	isocratic
11.5 - 11.6	25 → 100	75 → 0	linear gradient
11.6 - 13	100	0	re-equilibration

– as detector a spectrophotometer set at 238 nm.

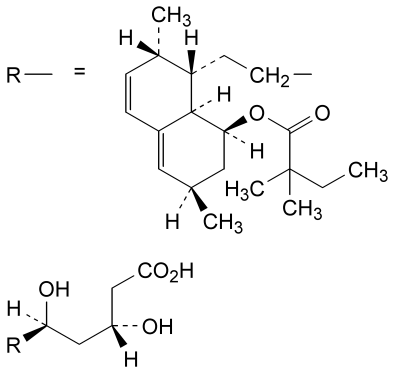
Inject 5 µl of reference solution (a). The test and the assay are not valid unless, in the chromatogram obtained, the resolution between the peak corresponding to lovastatin and epilovastatin and the peak corresponding to simvastatin is at least 5.0. When the chromatograms are recorded under the prescribed conditions the retention times are: lovastatin and epilovastatin about 1.6 min and simvastatin about 2.6 min. Inject 5 µl of reference solution (c). Adjust the sensitivity of the system so that the height of the principal peak is at least 50 per cent of the full scale of the recorder. Inject 5 µl of test solution (b).

Calculate the content of simvastatin from the peak areas in the chromatograms obtained with test solution (b) and reference solution (c) and the declared content of *simvastatin CRS*.

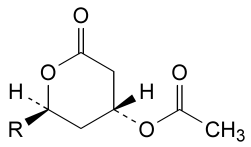
STORAGE

Store under nitrogen, in an airtight container, protected from light.

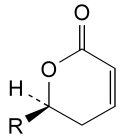
IMPURITIES



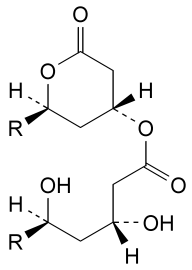
A. (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid (hydroxy acid),



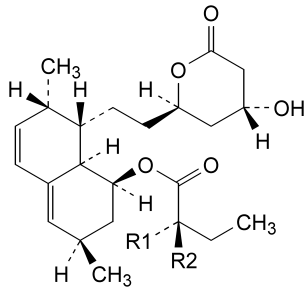
B. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-(acetyloxy)-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate (acetate ester),



C. (1*S*,3*R*,7*S*,8*S*,8a*R*)-3,7-dimethyl-8-[2-[(2*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate (anhydrosimvastatin),

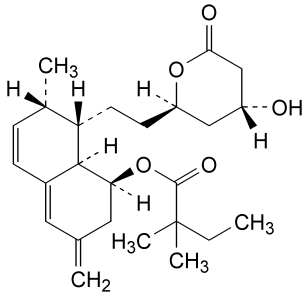


D. (2*R*,4*R*)-2-[[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]ethyl]-6-oxotetrahydro-2*H*-pyran-4-yl (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoate (dimer),



E. R1 = CH_3, R2 = H: (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate (lovastatin),

F. R1 = H, R2 = CH_3: (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*R*)-2-methylbutanoate (epilovastatin),

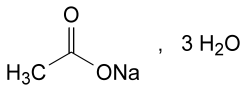


G. (1*S*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-7-methyl-3-methylene-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate.

01/2008:0411

SODIUM ACETATE TRIHYDRATE

Natrii acetas trihydricus



$C_2H_3NaO_2,3H_2O$ M_r 136.1
[6131-90-4]

DEFINITION

Sodium ethanoate trihydrate.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: colourless crystals.

Solubility: very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. 1 ml of solution S (see Tests) gives reaction (b) of acetates (*2.3.1*).

B. 1 ml of solution S gives reaction (a) of sodium (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Solution S. Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 7.5 to 9.0.

Dilute 5 ml of solution S to 10 ml with *carbon dioxide-free water R*.

Reducing substances. Dissolve 5.0 g in 50 ml of *water R*, then add 5 ml of *dilute sulphuric acid R* and 0.5 ml of *0.002 M potassium permanganate*. The pink colour persists for at least 1 h. Prepare a blank in the same manner but without the substance to be examined.

Chlorides (*2.4.4*): maximum 200 ppm.

Dilute 2.5 ml of solution S to 15 ml with *water R*.

Sulphates (*2.4.13*): maximum 200 ppm.

Dilute 7.5 ml of solution S to 15 ml with *distilled water R*.