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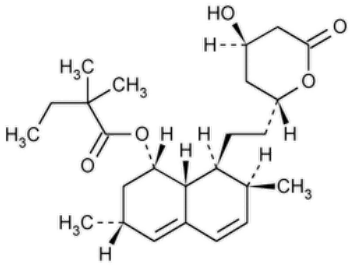
Simvastatin



$C_{25}H_{38}O_5$ 418.57

Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),8aβ]].

2,2-Dimethylbutyric acid, 8-ester with (4*R*,6*R*)-6-2-[(1*S*,2*S*,6*R*,8*S*,8α*R*)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one CAS RN®: 79902-63-9; UNII: AGG2FN16EV.

» Simvastatin contains not less than 98.0 percent and not more than 102.0 percent of $C_{25}H_{38}O_5$, calculated on the dried basis. It may contain a suitable antioxidant.

Packaging and storage—Preserve in well-closed containers. Store between 15° and 30°, or under refrigeration.

USP Reference standards ⟨11⟩—

USP Lovastatin RS
USP Simvastatin RS

Identification—

Change to read:

A: ▲*Spectroscopic Identification Tests* ⟨197⟩*, Infrared Spectroscopy: 197M*▲ (CN 1-May-2020) ·

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Specific rotation ⟨781S⟩**:** between +285° and +298°.

Test solution: 5 mg per mL, in acetonitrile.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Chromatographic purity—[Note—The Simvastatin solutions are stable for up to 3 days when stored at 4°. Without refrigeration, they should be injected immediately after preparation.]

Mobile phase, Diluent, and *Chromatographic system*—Proceed as directed in the *Assay*.

Test solution—Use the *Assay preparation*.

Procedure—Inject about 5 µL of the *Test solution* into the chromatograph, record the chromatogram, identify the specified impurities listed in *Table 1,* and measure the areas for all the peaks. Calculate the percentage of each impurity in the portion of Simvastatin taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak area for each impurity; and r_s is the sum of the areas of all the peaks. Reporting level for impurities is 0.05%.

Table 1

Name	Relative Retention Time	Limit %
Simvastatin hydroxyacid[1]	0.45	0.4
Epilovastatin[2] and Lovastatin	0.60	1.0[3]
Methylene simvastatin[4]	0.80	0.4
Simvastatin	1.0	n/a
Acetyl simvastatin[5]	2.38	0.4
Anhydro simvastatin[6]	2.42	0.4
Simvastatin dimer[7]	3.80	0.4
Any other individual impurity	—	0.1
Total impurities other than lovastatin and epilovastatin	—	1.0

[1] (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.

[2] (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.

[3] If present, lovastatin and epilovastatin may not be completely resolved by the method. These peaks are integrated together to determine conformance.

[4] (1*S*,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-dimethylbut-3-enoate.

[5] (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.

[6] (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.

[7] (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.

Assay—[NOTE—The Simvastatin solutions are stable for up to 3 days when stored at 4°. Without refrigeration, they should be injected immediately after preparation.]

Dilute phosphoric acid—Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with water to volume.

Solution A—Prepare a mixture of acetonitrile and *Dilute phosphoric acid* (50:50).

Solution B—Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with acetonitrile to volume.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B,* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Buffer solution—Prepare a solution containing 1.4 g of monobasic potassium phosphate per L, and adjust with phosphoric acid to a pH of 4.0.

Diluent—Prepare a mixture of acetonitrile and *Buffer solution* (3:2).

System suitability preparation—Dissolve accurately weighed quantities of USP Simvastatin RS and USP Lovastatin RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 1.5 mg per mL of USP Simvastatin RS and 0.015 mg per mL of USP Lovastatin RS.

Standard preparation—Dissolve an accurately weighed quantity of USP Simvastatin RS in *Diluent* to obtain a solution having a known concentration of about 1.5 mg per mL.

Assay preparation—Transfer about 75 mg of Simvastatin, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *CHROMATOGRAPHY ⟨621⟩*)—The liquid chromatograph is equipped with a 238-nm detector and a 4.6- × 33-mm column that contains packing L1. The flow rate is about 3.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
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

Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.60 for lovastatin and 1.0 for simvastatin; and the resolution, *R,* between simvastatin and lovastatin is greater than 3. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{38}O_5$ in the portion of Simvastatin taken by the formula:

$$VC(r_U/r_S)$$

in which V is the volume, in mL, of the *Assay preparation; C* is the concentration, in mg per mL, of USP Simvastatin RS in the *Standard preparation;* and r_U and r_S are the responses of the simvastatin peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
SIMVASTATIN	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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