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Simvastatin Tablets

DEFINITION
Simvastatin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of simvastatin ($C_{25}H_{38}O_5$).

IDENTIFICATION
- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **Procedure**

Buffer solution: Dissolve 3.9 g of monobasic sodium phosphate in 900 mL of water. Adjust, if necessary, with either sodium hydroxide or phosphoric acid to a pH of 4.5. Dilute with water to 1000 mL and mix.

Mobile phase: Acetonitrile and *Buffer solution* (65:35)

Solution A: Add 3.0 mL of glacial acetic acid to 900 mL of water. Adjust with 5 N sodium hydroxide to a pH of 4.0 and dilute with water to 1 L.

Diluent: Acetonitrile and *Solution A* (8:2)

Standard solution: 0.1 mg/mL of USP Simvastatin RS in *Diluent*

Sample solution: Nominally 0.1 mg/mL of simvastatin from Tablets in *Diluent* as follows. Crush NLT 20 Tablets into a fine powder and transfer the powder equivalent to 100 mg of simvastatin to a suitable volumetric flask. Add *Diluent* to fill 70% of the volume of the flask, and sonicate with intermittent swirling for 10 min. Equilibrate to room temperature and dilute with *Diluent* to volume. Centrifuge a portion of the mixture, and pass the clear supernatant through a filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate.

Chromatographic system
(See *Chromatography (621), System Suitability*.)

Mode: LC

Detector: UV 238 nm. For *Identification B*, use a diode array detector in the range of 190–300 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of simvastatin ($C_{25}H_{38}O_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of simvastatin from the *Sample solution*

r_S = peak area of simvastatin from the *Standard solution*

C_S = concentration of USP Simvastatin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of simvastatin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Medium: Prepare a pH 7.0 buffer solution containing 0.5% sodium dodecyl sulfate in 0.01 M sodium phosphate as follows. Dissolve 30 g of sodium dodecyl sulfate and 8.28 g of monobasic sodium phosphate in 6000 mL of water and adjust with 50% (w/v) sodium hydroxide solution to a pH of 7.0; 900 mL.

Apparatus 2: 50 rpm

Time: 30 min

Prewashed manganese dioxide: Transfer 10 g of manganese dioxide to a suitable container, and treat as follows. Add 50 mL of *Medium*, and shake vigorously for 5 min. Centrifuge, decant the supernatant layer, and discard. Repeat twice, first with *Medium* and then with water. Dry the solid at 100° for 1 h before use.

Standard solution: ▲USP Simvastatin RS in *Medium*. Transfer a portion of the solution to a centrifuge tube containing about 10 mg of *Prewashed manganese dioxide* per milliliter of transferred solution under test, and mix. Allow the mixture to stand for 30 min with occasional shaking, centrifuge, and use a portion of the clear supernatant.▲ (ERR 1-Dec-2019)

Sample solution: Pass a portion of the solution under test through a suitable filter. Transfer a portion of the solution to a centrifuge tube containing about 10 mg of *Prewashed manganese dioxide* per milliliter of transferred solution under test, and mix. Allow the mixture to stand for 30 min with occasional shaking, centrifuge, and use a portion of the clear supernatant.

Instrumental conditions

Mode: UV

Analytical wavelengths: 247 and 257 nm

Blank: Prepare as directed for the *Sample solution*, except use the *Medium*.

Analysis: Calculate the percentage of the labeled amount of simvastatin ($C_{25}H_{38}O_5$) dissolved from the difference between the UV absorbances at the wavelengths of maximum and minimum absorbances at about 247 and 257 nm, respectively, of the *Sample solution*, in comparison with the *Standard solution*.

Tolerances: NLT 75% (*Q*) of the labeled amount of simvastatin ($C_{25}H_{38}O_5$) is dissolved.

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Solution A: Prepare a mixture of acetonitrile and dilute phosphoric acid (1 mL in 1 L of water) (45:55).

Solution B: Prepare a mixture of acetonitrile and dilute phosphoric acid (1 mL in 1 L of water) (90:10).

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
38	100	0
40	65	35
50	65	35
70	0	100
90	0	100
92	100	0
100	100	0

Solution C: 1.4 g/L of monobasic potassium phosphate in water. Adjust with diluted ammonia solution to a pH of 7.0.

Diluent: Acetonitrile and *Solution C* (60:40)

System suitability stock solution: 0.2 mg/mL each of USP Simvastatin RS and USP Lovastatin RS in *Diluent*. Sonicate if necessary.

System suitability solution: 0.02 mg/mL each of USP Simvastatin RS and USP Lovastatin RS in *Diluent* from *System suitability stock solution*

Standard solution: 7.5 µg/mL of USP Simvastatin RS and equivalent to 0.015 mg/mL of tenivastatin from USP Tenivastatin Calcium RS in *Diluent*

Sample solution: Nominally 1.5 mg/mL of simvastatin in *Diluent* prepared as follows. Transfer a suitable amount of powdered Tablets (NLT 20) to a volumetric flask. Add *Diluent* to fill 60% of the volume of the flask, and sonicate with intermittent swirling for 5 min. Dilute with *Diluent* to volume. Pass the solution through a filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 238 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of simvastatin

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 8.0 between simvastatin and lovastatin, *System suitability solution*

Tailing factor: NMT 1.5 for simvastatin, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tenivastatin in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of tenivastatin from the *Sample solution*

r_S = peak response of tenivastatin from the *Standard solution*

C_S = concentration of USP Tenivastatin Calcium RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of simvastatin in the *Sample solution* (mg/mL)

Calculate the percentage of any unspecified impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of any unspecified impurity from the *Sample solution*

r_S = peak response of simvastatin from the *Standard solution*

C_S = concentration of USP Simvastatin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of simvastatin in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Tenivastatin[a]	0.43	1.0

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Lovastatin[b,c]	0.63	—
Epilovastatin[b,d]	0.66	—
Methylene simvastatin[b,e]	0.80	—
Simvastatin	1.00	—
Tenivastatin methyl ester[b,f]	1.14	—
Acetyl simvastatin[b,g]	1.54	—
Anhydro simvastatin[b,h]	1.59	—
Simvastatin related compound D[b,i]	2.30	—
Individual unspecified impurity	—	0.5
Total impurities[j]	—	2.0

[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.

[b] Process impurity included in the table for identification purposes only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

[c] (*S*)-(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-methylbutanoate.

[d] (*R*)-(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-methylbutanoate.

[e] (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-dimethylbut-3enoate.

[f] Methyl (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.

[g] (1*S*,3*R*,8*S*,8a*R*)-8-{2-[(2*R*,4*R*)-4-Acetoxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate.

[h] (1*S*,3*R*,7*S*,8*S*,8a*R*)-3,7-Dimethyl-8-{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.

[i] (3*R*,5*R*)-(2*R*,4*R*)-2-(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 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.

[j] Excluding lovastatin.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **USP Reference Standards** ⟨11⟩

USP Lovastatin RS

(*S*)-(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-methylbutanoate.

$C_{24}H_{36}O_5$ 404.54

USP Simvastatin RS

USP Tenivastatin Calcium RS

Calcium (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 (1:2) monohydrate.

$C_{50}H_{78}CaO_{12} \cdot H_2O$ 929.24

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

Topic/Question	Contact	Expert Committee
SIMVASTATIN TABLETS	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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