ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Polydimethylsiloxane RS

Simethicone Oral Suspension

» Simethicone Oral Suspension is a suspension of Simethicone in Water. It contains an amount of polydimethylsiloxane ($[–(CH_3)_2SiO–]_n$) that is not less than 85.0 percent and not more than 115.0 percent of the labeled amount of simethicone.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩**—**
USP Polydimethylsiloxane RS

Identification, *Infrared Absorption* ⟨197S⟩—[NOTE—Use the procedural blank, prepared as directed in the *Assay,* to set the instrument.]

Test solution—Prepare as directed for the *Assay preparation* in the *Assay.*

Standard solution—Prepare as directed for the *Standard preparation* in the *Assay.*

Cell size: 0.5 mm.

pH ⟨791⟩**:** between 3.5 and 4.6.

Assay—

Standard preparation—Transfer about 60 mg of USP Polydimethylsiloxane RS, accurately weighed, to a 25-mL volumetric flask, add 15 mL of hexanes, and sonicate for 3 minutes. Allow to cool, dilute with hexanes to volume, and mix. Transfer 10 mL of this solution to a capped test tube, add about 1 g of anhydrous sodium sulfate, mix for about 1 minute, and centrifuge. Use the clear supernatant as the *Standard preparation.* The *Standard preparation* has a concentration of about 2.4 mg of USP Polydimethylsiloxane RS per mL.

Assay preparation—Transfer an accurately measured quantity of Oral Suspension, equivalent to about 240 mg of simethicone, to a glass-stoppered centrifuge tube. Add 5 mL of methanol, and mix for about 15 seconds. Add 30.0 mL of hexanes, and mix for about 10 seconds. Loosen the stopper, and heat the tube for about 10 minutes in a water bath at 65 ± 1°. Mix for 1 minute, and centrifuge. Using a glass syringe, transfer the upper hexanes layer to a 100-mL volumetric flask. Repeat the extraction with two 30.0-mL portions of hexanes, combining the hexanes extracts in the 100-mL volumetric flask. [NOTE—If an emulsion forms during any of the extractions, as much as 2 mL of methanol may be added to disperse the emulsion.] Allow the combined extracts to cool, dilute with hexanes to volume, and mix. Transfer 10 mL of this solution to a capped test tube, add about 1 g of anhydrous sodium sulfate, mix for about 1 minute, and centrifuge. Use the clear supernatant as the *Assay preparation.*

Dry hexanes—Mix 100 mL of hexanes and 10 g of anhydrous sodium sulfate, allow to settle, and centrifuge. Use the clear supernatant.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* at the wavelength of maximum absorption at about 7.9 µm, using *Dry hexanes* as the blank to set the instrument. Calculate the quantity, in mg, of $[–(CH_3)_2SiO–]_n$ in each mL of the Oral Suspension taken by the formula:

$$(100C/V)(A_U / A_S)$$

in which C is the concentration, in mg per mL, of USP Polydimethylsiloxane RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.

Simethicone Tablets

» Simethicone Tablets contain an amount of polydimethylsiloxane ($[–(CH_3)_2SiO–]_n$) that is not less than 85.0 percent and not more than 115.0 percent of the labeled amount of simethicone.

Packaging and storage—Preserve in well-closed containers.

Labeling—Tablets that are gelatin-coated are so labeled.

USP Reference standards ⟨11⟩**—**
USP Polydimethylsiloxane RS

Identification, *Spectrophotometric Identification Tests, Infrared Absorption* ⟨197⟩—
[NOTE—Use the procedural blank, prepared as directed in the *Assay,* to set the instrument.]

Test solution—Prepare as directed for the *Assay preparation* in the *Assay.*

Standard solution—Prepare as directed for the *Standard preparation* in the *Assay.*

Cell size: 0.5 mm.

Disintegration ⟨701⟩**:** 30 minutes in water; 60 minutes in water for plain-coated Tablets; and 45 minutes in simulated gastric fluid for Tablets labeled as gelatin-coated.

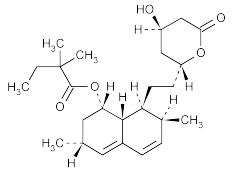
Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Assay—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of simethicone, to a round, narrow-mouth, screw-capped, 120-mL bottle, and proceed as directed in the *Assay* under *Simethicone,* beginning with "add 25.0 mL of toluene," except that for Tablets labeled as gelatin-coated, shake for 30 minutes instead of 5 minutes. Calculate the quantity, in mg, of $[–(CH_3)_2SiO–]_n$ in the portion of Tablets taken by the formula:

$$25C(A_U / A_S)$$

in which C is the concentration, in mg per mL, of USP Polydimethylsiloxane RS in the Standard solution, and A_U and A_S are the absorbances of the solution from the Tablets and the Standard solution, respectively.

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**),8a*β*]].

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 [79902-63-9].

» 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—

A: *Infrared Absorption* ⟨197M⟩.

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%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

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

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

Simvastatin Tablets

» Simvastatin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of simvastatin ($C_{25}H_{38}O_5$).

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Simvastatin RS

Identification—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*.

Dissolution ⟨711⟩**—**

Medium: pH 7.0 buffer solution containing 0.5% sodium dodecyl sulfate in 0.01 M sodium phosphate prepared by dissolving 30 g of sodium dodecyl sulfate and 8.28 g of monobasic sodium phosphate in 6000 mL of water, and adjusting with 50% (w/v) sodium hydroxide solution to a pH of 7.0; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

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

Test solution—Transfer a filtered portion of the solution under test to a centrifuge tube containing about 10 mg of *Prewashed manganese dioxide* per mL of transferred solution under test, and mix. Allow the mixture to stand for 30 minutes with occasional shaking, centrifuge, and use a portion of the clear supernatant as the *Test solution*.

Blank—Proceed as directed for *Test solution*, except to use the *Dissolution Medium*.

Procedure—Determine the amount of $C_{25}H_{38}O_5$ dissolved from the difference between the UV absorbances at the wavelengths of maximum and minimum absorbance at about 247 nm and 257 nm, respectively, on filtered portions of the *Test solution*, in comparison with a Standard solution having a known concentration of USP Simvastatin RS in the same *Medium* treated in the same way as the solution under test, each solution corrected for the *Blank*.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{25}H_{38}O_5$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Diluting solution—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 1000 mL. To 200 mL of this solution, add 800 mL of acetonitrile, and mix.

Buffer solution—Dissolve 3.9 g of monobasic sodium phosphate in 900 mL of water. Adjust, if necessary, with either 50% sodium hydroxide or 85% phosphoric acid to a pH of 4.5, dilute with water to 1000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (65:35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Simvastatin RS in *Diluting solution*, and dilute quantitatively, and stepwise if necessary, with *Diluting solution* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Transfer 10 Tablets to a 250-mL volumetric flask. Add a small volume of water (not more than 10 mL), and swirl to disintegrate the Tablets. Dilute with *Diluting solution* to volume, sonicate for 15 minutes, and cool to room temperature. If necessary, dilute with *Diluting solution* to volume. Centrifuge a portion of the mixture, and dilute a portion of the clear supernatant with *Diluting solution* to obtain a solution having a concentration of about 0.1 mg of simvastatin per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 238-nm detector and a 4.6-mm × 25-cm column containing packing L1 and maintained at a temperature of 45°. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 3.0; the column efficiency is not less than 4500 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas of the major peaks. Calculate the quantity, in mg, of simvastatin ($C_{25}H_{38}O_5$) in each Tablet taken by the formula:

$$(L / D)C(r_U / r_S)$$

in which L is the labeled quantity, in mg, of simvastatin in each Tablet; D is the concentration, in mg per mL, of simvastatin in 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 peak areas of simvastatin obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Sincalide for Injection

» Sincalide for Injection is a sterile, synthetically prepared C-terminal octapeptide of cholecystokinin and sodium chloride. It contains not less than 85.0 percent and not more than 125.0 percent of the labeled amount of sincalide ($C_{49}H_{62}N_{10}O_{16}S_3$).

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass.

Labeling—Label it to state that it is to be used within 24 hours after constitution.