Rosuvastatin Tablets

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Posting Date	27–July–2018
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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Rosuvastatin Tablets monograph. The purpose for the revision is to add *Dissolution Test 3* to accommodate drug products that were approved with different conditions and tolerances.

The Rosuvastatin Tablets Revision Bulletin supersedes the Rosuvastatin Tablets monograph that is becoming official in the *First Supplement to USP 41–NF 36*.

Should you have any questions, please contact Donald Min**,** Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@usp.org).

Add the following:

▲Rosuvastatin Tablets

DEFINITION

Rosuvastatin Tablets contain NLT 90% and NMT 110% of the labeled amount of rosuvastatin ($C_{22}H_{28}FN_3O_6S$).

IDENTIFICATION

- **A.** The UV absorption spectra of the rosuvastatin peak of the *Sample solution* exhibit maxima and minima at the same wavelengths as those of the corresponding peak of the *Standard solution*, as obtained in the *Assay*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Protect all solutions containing rosuvastatin from light.

Solution A: 1% trifluoroacetic acid in water

Mobile phase: Acetonitrile, *Solution A*, and water (37:1:62)

Diluent: Acetonitrile and water (25:75)

Standard stock solution: 1 mg/mL of USP Rosuvastatin Calcium RS prepared as follows. To a suitable amount of USP Rosuvastatin Calcium RS in a suitable volumetric flask, add water equal to about 50% of the flask volume. Vigorously mix or sonicate the flask to dissolve the material. Add acetonitrile equal to about 25% of the total volume and then dilute with water to volume.

Standard solution: 25 µg/mL of USP Rosuvastatin Calcium RS in *Diluent* from the *Standard stock solution*

Sample solution: Nominally 25 µg/mL of rosuvastatin prepared as follows. Transfer a suitable number of Tablets, NLT 5 Tablets for 80-mg Tablet strength and NLT 10 Tablets for all other Tablet strengths, into a suitable extraction flask. Add water and vigorously mix to disintegrate the Tablets. Add acetonitrile and mix vigorously. Add more water to obtain a 25:75 composition of acetonitrile and water. Pass the solution through a suitable filter. Dilute the filtrate with *Diluent*, if necessary, to the desired concentration.

Chromatographic system

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

Mode: LC

Detector: UV 242 nm. For *Identification A*, use a diode array detector in the range of 200–440 nm.

Column: 3.2-mm × 25-cm; 5-µm packing L1. [NOTE—A suitable guard column may be used.]

Column temperature: 40°

Flow rate: 0.75 mL/min

Injection volume: 10 µL

Run time: NLT 1.3 times the retention time of rosuvastatin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.8

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M \times (M_{r1}/M_{r2})] \times 100$$

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

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

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

C_U = nominal concentration of rosuvastatin in the *Sample solution* (µg/mL)

M = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2

M_{r1} = molecular weight of rosuvastatin, 481.54

M_{r2} = molecular weight of rosuvastatin calcium, 1001.14

Acceptance criteria: 90%–110%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**

Protect all solutions containing rosuvastatin from light.

Test 1

Medium: Citrate buffer, pH 6.6 (prepare a solution of 14.7 g/L of sodium citrate dihydrate and 0.33 g/L of anhydrous citric acid; adjust if necessary with sodium citrate or citric acid to a pH of 6.6); 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Diluent: Acetonitrile and water (25:75)

Mobile phase: Acetonitrile, water, and phosphoric acid (400:600:1)

Standard stock solution: 1 mg/mL of USP Rosuvastatin Calcium RS in *Diluent*

Standard solution: A solution of concentration similar to the *Sample solution* in *Medium* from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 242 nm

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

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 2.5 times the retention time of rosuvastatin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times [M \times (M_{r1}/M_{r2})] \times 100$$

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

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

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

M = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2

M_{r1} = molecular weight of rosuvastatin, 481.54

M_{r2} = molecular weight of rosuvastatin calcium, 1001.14

Tolerances: NLT 75% (*Q*) of the labeled amount of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets *Dissolution Test 2*.

Medium: 0.05 M citrate buffer pH 6.6 (to a solution of 10.5 g/L of citric acid monohydrate, add 5.9 g/L of sodium hydroxide and mix; adjust with 0.2 M sodium hydroxide or 0.2 M hydrochloric acid to a pH of 6.6); 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer: Dissolve 2.72 g of potassium dihydrogen phosphate in 1 L of water and add 2 mL of triethylamine. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Standard stock solution: 0.5 mg/mL of USP Rosuvastatin Calcium RS in *Medium*. Sonication may be necessary for complete dissolution.

Standard solution: (*L*/900) mg/mL of USP Rosuvastatin Calcium RS in *Medium* from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 10-cm; 5-µm packing L1
Flow rate: 2 mL/min
Injection volume: 20 µL
Run time: NLT 1.5 times the retention time of rosuvastatin

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 rosuvastatin ($C_{22}H_{28}FN_3O_6S$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times [M \times (M_{r1}/M_{r2})] \times 100$$

r_U = peak response of rosuvastatin from the *Sample solution*
r_S = peak response of rosuvastatin from the *Standard solution*
C_S = concentration of USP Rosuvastatin Calcium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
M = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2
M_{r1} = molecular weight of rosuvastatin, 481.54
M_{r2} = molecular weight of rosuvastatin calcium, 1001.14

Tolerances: NLT 80% (*Q*) of the labeled amount of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) is dissolved.

▲**Test 3:** If the product complies with this test, the labeling indicates that it meets *Dissolution Test 3*.

Medium: 0.05 M citrate buffer pH 6.6 (dissolve 63.0 of citric acid monohydrate and 35.2 g of sodium hydroxide into 6 L of water and mix; adjust if necessary with sodium hydroxide or citric acid to a pH of 6.6); 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Standard stock solution: 0.044 mg/mL of USP Rosuvastatin Calcium RS in *Medium*. Sonication may be necessary for complete dissolution.

Standard solution: (*L*/900) mg/mL of USP Rosuvastatin Calcium RS in *Medium* from the *Standard stock solution*, where *L* is the label claim in mg/Tablet. [NOTE—The *Standard stock solution* is the *Standard solution* for 40-mg Tablets.]

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Instrumental conditions
Mode: UV
Analytical wavelength: 241 nm
Cell: 1.0 cm (for 5-mg and 10-mg Tablets) and 0.2 cm (for 20-mg and 40-mg Tablets)
Blank: *Medium*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times [M \times (M_{r1}/M_{r2})] \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Rosuvastatin Calcium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
M = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2
M_{r1} = molecular weight of rosuvastatin, 481.54
M_{r2} = molecular weight of rosuvastatin calcium, 1001.14

Tolerances: NLT 80% (*Q*) of the labeled amount of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) is dissolved.▲ (RB 1-Aug-2018)

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**

Protect all solutions containing rosuvastatin calcium from light.

Mobile phase and **Diluent:** Prepare as directed in the *Assay*.

System suitability stock solution: 50 µg/mL each of USP Rosuvastatin Calcium RS and rosuvastatin diastereomers in acidic water prepared as follows. To a suitable amount of USP Rosuvastatin Calcium RS in a suitable volumetric flask, add water equal to about 50% of the flask volume. Add 1 M hydrochloric acid equal to about 10% of the total volume. Heat in a water bath at 60° for 2 h and neutralize by adding 1 M sodium hydroxide. Cool to room temperature and add acetonitrile equal to about 25% of the total volume. Dilute with water to volume.

System suitability solution: 25 µg/mL each of USP Rosuvastatin Calcium RS and rosuvastatin diastereomers prepared by mixing *System suitability stock solution* and *Diluent* (1:1)

Standard solution: 10 µg/mL of USP Rosuvastatin Calcium RS in *Diluent*

Sample solution: Nominally 1 mg/mL of rosuvastatin prepared as follows. Transfer a number of Tablets per *Table 1* into a suitable extraction flask. Add water, and mix vigorously to disintegrate the Tablets. Add acetonitrile and mix vigorously followed by an additional amount of water to obtain a final composition of

acetonitrile and water (1:3). Pass the solution through a suitable filter.

Table 1

Tablet Strength (mg)	Number of Tablets	Volumetric Flask Size (mL)	Water (mL)	Acetonitrile (mL)
2.5	40	100	50	25
5	20	100	50	25
10	10	100	50	25
20	10	200	100	50
40	12	500	250	125
80	6	500	250	125

Chromatographic system: Proceed as directed in the *Assay*, except for *Run time*.
Run time: NLT 2.5 times the retention time of rosuvastatin
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.5 between rosuvastatin and rosuvastatin diastereomers, *System suitability solution*
Tailing factor: NMT 1.8, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M \times (M_{r1}/M_{r2})] \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of rosuvastatin from the *Standard solution*
C_S = concentration of USP Rosuvastatin Calcium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of rosuvastatin in the *Sample solution* (mg/mL)
M = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2
M_{r1} = molecular weight of rosuvastatin, 481.54
M_{r2} = molecular weight of rosuvastatin calcium, 1001.14
F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Rosuvastatin related compound A	0.9	—	—
Rosuvastatin	1.0	—	—
Rosuvastatin diastereomers[a, b]	1.1	—	—
Rosuvastatin ketone[c]	1.6	0.71	2.1
Rosuvastatin lactone[d]	2.3	1.0	1.5
Rosuvastatin ethyl ester (if present)[e]	3.8	1.0	0.5
Any unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	3.6

[a] (3*RS*,5*RS*,*E*)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid.
[b] Process impurity controlled in the drug substance monograph. Provided for information only; the content is not calculated, not reported, and not included in the total impurities.
[c] (*R*,*E*)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido) pyrimidin-5-yl]-3-hydroxy-5-oxohept-6-enoic acid.
[d] *N*-[4-(4-Fluorophenyl)-5-{(*E*)-2-[(2*S*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]vinyl}-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide.
[e] Ethyl (3*R*,5*S*,*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS ⟨11⟩**
USP Rosuvastatin Calcium RS▲ 1S (USP41)