## Rosuvastatin Tablets

| | |
|---|---|
| **Type of Posting** | Revision Bulletin |
| **Posting Date** | 29–Mar–2019 |
| **Official Date** | 01–April–2019 |
| **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 4* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using the Waters XBridge C18 brand of column with L1 packing. The typical retention time for rosuvastatin is about 2.1 min.

The Rosuvastatin Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Yanyin Yang**,** Associate Scientific Liaison (301-692-3623 or yanyin.yang@usp.org).

# 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.

▲**Test 4:** If the product complies with this test, the labeling indicates that it meets *Dissolution Test 4*.
**Medium:** 0.05 M sodium 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 10% w/v sodium citrate dihydrate solution or 10% w/v anhydrous citric acid solution to a pH of 6.6); 900 mL
**Apparatus 1:** 100 rpm
**Time:** 30 min
**Solution A:** Acetonitrile and water (25:75)
**Mobile phase:** Acetonitrile, phosphoric acid, and water (40: 0.1: 60)
**Standard stock solution:** 1.04 mg/mL of USP Rosuvastatin Calcium RS in *Solution A*. 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
**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 242 nm
**Column:** 4.6-mm × 5-cm; 3.5-µm packing L1
**Flow rate:** 1.0 mL/min
**Injection volume:** 20 µL
**Run time:** NLT 3.5 times the retention time of rosuvastatin
**System suitability**
**Sample:** *Standard solution*

**Suitability requirements**
**Tailing factor:** NMT 1.5
**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. ▲ (RB 1-Apr-2019)

- **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 |

**Table 2** *(continued)*

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| 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