Atorvastatin Calcium Tablets

Type of Posting	Revision Bulletin
Posting Date	27–Apr–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 Atorvastatin Calcium Tablets monograph. The purpose for the revision is to add *Dissolution Test 4* to accommodate drug products that were approved with different dissolution conditions and acceptance criteria.

- *Dissolution Test 4* was validated using the Inertsil ODS 3V brand of L1 packing column. The typical retention time for the atorvastatin peak is between 5.4 and 6.6 min.

Additionally, the acceptance criteria for the following two impurities in *Table 4* have been revised:

- Atorvastatin related compound D has been widened from NMT 0.35% to NMT 0.5%.
- Atorvastatin epoxy THF analog has been widened from NMT 0.25% to NMT 1.0%.

The Atorvastatin Calcium Tablets Revision Bulletin supersedes the monograph that will be official in *USP 41–NF 36*. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Sujatha Ramakrishna, Principal Scientific Liaison (301-816-8349 or sxr@usp.org).

Add the following:

▲ Atorvastatin Calcium Tablets

DEFINITION

Atorvastatin Calcium Tablets contain an amount of atorvastatin calcium [$(C_{33}H_{34}FN_2O_5)_2Ca$], equivalent to NLT 94.5% and NMT 105.0% of the labeled amount of atorvastatin.

IDENTIFICATION

- **A.** The UV absorption spectrum of the major peak of the *Sample solution* corresponds to that 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**

Buffer: 0.05 M ammonium citrate buffer pH 4.0 prepared as follows. Dissolve 9.62 g of anhydrous citric acid in 950 mL of water, adjust with ammonium hydroxide to a pH of 4.0, and dilute with water to 1000 mL.

Mobile phase: Acetonitrile, stabilizer-free tetrahydrofuran, and *Buffer* (27:20:53)

Solution A: Dissolve 9.62 g of anhydrous citric acid in 900 mL of water, adjust with ammonium hydroxide to a pH of 7.4, and dilute with water to 1000 mL.

Diluent: Acetonitrile and *Solution A* (1:1)

System suitability solution: 0.1 mg/mL of USP Atorvastatin Calcium RS and 0.01 mg/mL of USP Atorvastatin Related Compound H RS in *Diluent*. Shake mechanically for 30 min or until dissolved.

Standard solution: 0.1 mg/mL of USP Atorvastatin Calcium RS in *Diluent*. Shake mechanically for 15 min or until dissolved.

Sample stock solution: Prepare a known nominal concentration of atorvastatin by transferring NLT 10 Tablets to an appropriate volumetric flask. Add *Diluent* to about 50% of the final volume of the flask, and shake the mixture mechanically for 15 min or until dissolved. Dilute with *Diluent* to volume. Centrifuge or pass through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally equivalent to 0.1 mg/mL of atorvastatin in *Diluent* from the *Sample stock solution*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector
Assay: UV 244 nm
Identification A: Diode array; UV 200–400 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 5.0 between atorvastatin and atorvastatin related compound H, *System suitability solution*
Tailing factor: NMT 1.5 for atorvastatin, *System suitability solution*
Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) 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 atorvastatin from the *Sample solution*
r_S = peak response of atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of atorvastatin in the *Sample solution* (mg/mL)
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, 1155.34

Acceptance criteria: 94.5%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**

Test 1
Buffer: 0.05 M phosphate buffer prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 900 mL of water. Adjust with 6 N sodium hydroxide to a pH of 6.8 and dilute with water to 1 L.
Medium: *Buffer*; 900 mL
Apparatus 2: 75 rpm
Time: 15 min
Diluent: Acetonitrile and water (50:50)
Standard stock solution: 1 mg/mL of USP Atorvastatin Calcium RS in *Diluent*. Shake mechanically for 10 min or until dissolved.
Standard solution: (*L*/900) mg/mL in *Medium* from *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 or centrifuge prior to analysis.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelength: 244 nm
Cell: See *Table 1* or make appropriate dilutions of the solutions with *Medium* to be within the validated linearity range of the suitable spectrophotometer.

Table 1

Label Claim (mg/Tablet)	Cell (cm)
10	1.0
20 and 40	0.5
80	0.2

Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) dissolved:

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
D = dilution factor for the *Sample solution*, if applicable
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, 1155.34
L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. *Dissolution Test 2* is suitable for products labeled to contain 80 mg of atorvastatin.
Medium and **Apparatus 2:** Proceed as directed in *Test 1*.
Time: 30 min
Diluent, Standard solution, Sample solution, Instrumental conditions, and **Blank:** Proceed as directed in *Test 1*.
Tolerances: NLT 85% (Q) of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Buffer: Combine 250 mL of 0.2 M monobasic potassium phosphate, 112 mL of 0.2 N sodium hydroxide, and 638 mL of water. Adjust with either 0.02 N sodium hydroxide or phosphoric acid to a pH of 6.8.
Solution A: Acetonitrile, methanol, and 0.1% trifluoroacetic acid (5:5:90)
Solution B: Acetonitrile, methanol, and 0.1% trifluoroacetic acid (45:45:10)
Solution C: Dissolve 50 g of Tween 80 in 1 L of *Buffer*.
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0.00	30	70
0.69	30	70
0.74	0	100
2.73	0	100
2.77	30	70
5.00	30	70

Medium: *Solution C* and *Buffer* (6:94); 900 mL
Apparatus 2: 75 rpm
Time: 30 min
Standard stock solution: 0.96 mg/mL of USP Atorvastatin Calcium RS in methanol
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (L/900) mg/mL, 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 248 nm
Column: 2.1-mm × 5-cm; 2.6-µm packing L1
Column temperature: 40°
Flow rate: 0.7 mL/min
Injection volume: 2 µL
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 atorvastatin ($C_{33}H_{35}FN_2O_5$) dissolved:

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

r_U = peak response of atorvastatin from the *Sample solution*
r_S = peak response of atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, 1155.34
L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) is dissolved.

▲**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: Dissolve 6.8 g of monobasic potassium phosphate and 0.89 g of sodium hydroxide in 1 L of water. Adjust with either 1 N sodium hydroxide or phosphoric acid to a pH of 6.8; 900 mL.
Apparatus 2: 75 rpm
Time: 15 min
Buffer: Dissolve about 6.8 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 0.5 N potassium hydroxide solution to a pH of 6.0.
Mobile phase: Acetonitrile and *Buffer* (55:45)
Standard stock solution: 0.225 mg/mL of atorvastatin from USP Atorvastatin Calcium RS prepared as follows. To a suitable amount of USP Atorvastatin Calcium RS, add 5% of total volume of methanol, sonicate to dissolve, and cool. Dilute with *Medium* to volume.
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (L/900) mg/mL, 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 248 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 20 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 atorvastatin ($C_{33}H_{35}FN_2O_5$) dissolved:

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

r_U = peak response of atorvastatin from the *Sample solution*
r_S = peak response of atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, 1155.34
L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) is dissolved. ▲ (RB 1-May-2018)

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

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Rinse glassware with *Diluent* before preparing solutions containing atorvastatin calcium.

Buffer: 5.75 g/L of monobasic ammonium phosphate in water. Adjust with dilute acetic acid (10% v/v) or dilute ammonium hydroxide (10% v/v) to a pH of 4.3 ± 0.05.

Solution A: Acetonitrile and stabilizer-free tetrahydrofuran (925:75)

Solution B: *Solution A* and *Buffer* (42:58)

Solution C: Methanol, *Solution A*, and *Buffer* (60:20:20)

Diluent: *N,N*-Dimethylformamide

System suitability solution: 60 µg/mL of USP Atorvastatin Calcium RS, 50 µg/mL of USP Atorvastatin Related Compound B RS, 10 µg/mL of USP Atorvastatin Related Compound H RS, and 0.5 µg/mL of USP Atorvastatin Related Compound D RS in *Diluent*

Standard solution: 5 µg/mL of USP Atorvastatin Calcium RS in *Diluent*. Sonication may be necessary for complete dissolution.

Sample solution: Nominally equivalent to 1 mg/mL of atorvastatin, prepared as follows. Crush and finely powder NLT 20 Tablets. Transfer the amount of powder, equivalent to about 50 mg of atorvastatin, to a 50-mL volumetric flask. Add 30 mL of *Diluent* and shake mechanically for 15 min. Dilute with *Diluent* to volume and pass the solution through a suitable filter of 0.45-µm pore size, discarding the first few mL of the filtrate.

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution B (%)	Solution C (%)	Flow Rate (mL/min)
0	100	0	1.8
30	100	0	1.8
45	25	75	1.5
50	25	75	1.5
55	20	80	1.5
58	100	0	1.8
65	100	0	1.8

For the *Standard solution*, the run time is only 30 min. For the *System suitability solution* and *Sample solution*, the run time is 65 min.

Chromatographic system

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

Mode: LC

Detector: UV 244 nm

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

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: See *Table 3*.

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times of all peaks eluting before atorvastatin related compound H as given in *Table 4* are calculated with respect to the atorvastatin peak. The relative retention times for all peaks eluting after atorvastatin related compound H are calculated with respect to atorvastatin related compound H.]

Suitability requirements

Resolution: NLT 1.4 between atorvastatin related compound B and atorvastatin

Tailing factor: NMT 1.5 for the atorvastatin peak

Relative standard deviation: NMT 5% for the atorvastatin peak

Signal-to-noise ratio: NLT 10 for atorvastatin related compound D

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 atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of atorvastatin in the *Sample solution* (mg/mL)
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, 1155.34
F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atorvastatin amide[a, b]	0.44	—	—

Table 4 *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atorvastatin related compound A[b, c]	0.84	—	—
Atorvastatin pyrrolidone analog[d]	0.88	0.68	0.5
Atorvastatin related compound B[b, e]	0.94	—	—
Atorvastatin	1.00	—	—
Atorvastatin related compound C[b, f]	1.09	—	—
Atorvastatin pyrrolidone lactone[b, g]	1.62	—	—
Atorvastatin related compound H[h]	1.00	1.18	1.0
Atorvastatin epoxy pyrrolooxazin 6-hydroxy analog[i]	1.06	0.53	0.5
Atorvastatin methyl ester[b, j]	1.12	—	—
Atorvastatin epoxy pyrrolooxazin 7-hydroxy analog, if present[k]	1.14	0.53	0.5
Atorvastatin epoxy THF analog[l, m]	1.20	1.12	▲1.0 ▲ (RB 1-May-2018)
Atorvastatin related compound D[n]	1.27	1.12	▲0.5 ▲ (RB 1-May-2018)
Atorvastatin *tert*-butyl ester[b, o]	1.49	—	—
Any other unspecified degradation product	—	1.00	0.2
Total degradation products	—	—	4.0

[a] (3*R*,5*R*)-7-{(3*R*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanamido}-3,5-dihydroxyheptanoic acid.
[b] Process impurity included in the table for identification 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] (3*R*,5*R*)-7-[2-Isopropyl-4,5-diphenyl-3-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
[d] (3*R*,5*R*)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-oxo-4-phenyl-3-(phenylcarbamoyl)-2,3-dihydro-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
[e] (3*S*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
[f] (3*R*,5*R*)-7-[2,3-Bis(4-fluorophenyl)-5-isopropyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
[g] 5-(4-Fluorophenyl)-1-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-3-isopropyl-2-oxo-*N*,4-diphenyl-2,3-dihydro-1*H*-pyrrole-3-carboxamide.
[h] 5-(4-Fluorophenyl)-1-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide.
[i] 4-{6-(4-Fluorophenyl)-7,8-epoxy-6-hydroxy-8a-isopropyl-7-phenyl-8-(phenylcarbamoyl)hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-2-yl}-3-hydroxybutanoic acid.
[j] (3*R*,5*R*)-Methyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate.
[k] (3*R*)-4-(1b-(4-Fluorophenyl)-7-hydroxy-7-isopropyl-1a-phenyl-7a-(phenylcarbamoyl)hexahydro-1a*H*-oxireno[2′,3′:3,4]pyrrolo[2,1-*b*][1,3]oxazin-3-yl)-3-hydroxybutanoic acid.
[l] 4-(4-Fluorophenyl)-2,4-dihydroxy-2-isopropyl-*N*,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide.
[m] Atorvastatin related compound D can undergo transformation equilibrium to the atorvastatin epoxy THF analog. The equilibrium can be shifted under slightly acidic conditions and therefore some products could have a combined specification reported under atorvastatin related compound D.
[n] 3-(4-Fluorobenzoyl)-2-isobutyryl-*N*,3-diphenyloxirane-2-carboxamide.
[o] (3*R*,5*R*)-*tert*-Butyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used, only if *Test 1* is not used.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Atorvastatin Calcium RS

USP Atorvastatin Related Compound B RS
Calcium (3*S*,5*R*)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate (1:2).
$C_{66}H_{68}CaF_2N_4O_{10}$ 1155.34

USP Atorvastatin Related Compound D RS
3-(4-Fluorobenzoyl)-2-isobutyryl-*N*,3-diphenyloxirane-2-carboxamide.
$C_{26}H_{22}FNO_4$ 431.46

USP Atorvastatin Related Compound H RS
5-(4-Fluorophenyl)-1-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide.
$C_{33}H_{33}FN_2O_4$ 540.62▲ USP41