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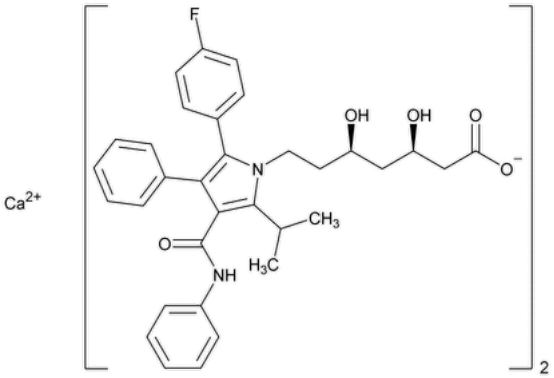
Atorvastatin Calcium



$C_{66}H_{68}CaF_2N_4O_{10}$ 1155.36

1*H*-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylami no)carbonyl]-, calcium salt (2:1), [*R*-(*R**,*R**)]-;

Calcium (β*R*,δ*R*)-2-(*p*-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoate (1:2);

[(3*R*,5*R*)-7-[3-(Phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, calcium salt]

Anhydrous CAS RN®: 134523-03-8; UNII: C0GEJ5QCSO.

$C_{66}H_{68}CaF_2N_4O_{10} \cdot 3H_2O$ 1209.41

Trihydrate CAS RN®: 344423-98-9; UNII: 48A5M73Z4Q.

$C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$

Propylene glycol solvate 1231.46

DEFINITION

Atorvastatin Calcium contains NLT 98.0% and NMT 102.0% of atorvastatin calcium ($C_{66}H_{68}CaF_2N_4O_{10}$), calculated on the anhydrous and solvent-free basis. If labeled as a propylene glycol solvate, it contains NLT 98.0% and NMT 102.0% of atorvastatin calcium ($C_{66}H_{68}CaF_2N_4O_{10}$), calculated on the anhydrous, propylene glycol-free, and solvent-free basis. It may contain a suitable antioxidant.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

[Note—If a difference appears in the IR spectra of the analyte and the standard, separately dissolve equal portions of the sample specimen and the USP Reference Standard in equal volumes of methanol, evaporate the solution to dryness in similar containers under identical conditions, and repeat the test on the residues.]

• **B. Calcium**

Diluent: Methanol, water, and hydrochloric acid (75:25:2)

Sample solution: 0.05 mg/mL of Atorvastatin Calcium in *Diluent*

Blank: *Diluent*

Analysis

Samples: *Sample solution* and *Blank*

Instrumental conditions

(See *Atomic Absorption Spectroscopy ⟨852⟩*.)

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Calcium emission line at 422.7 nm

Flame: Air–acetylene

Acceptance criteria: The *Sample solution* exhibits a significant absorption at the calcium emission line at 422.7 nm.

ASSAY

• **Procedure**

Buffer: 3.9 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 5.0 ± 0.1.

Solution A: Acetonitrile, stabilizer-free tetrahydrofuran, and *Buffer* (21:12:67)

Solution B: Acetonitrile, stabilizer-free tetrahydrofuran, and *Buffer* (61:12:27)

Mobile phase: See *Table 1*. [Note—If necessary, adjust the *Mobile phase* by increasing or decreasing the percentage of acetonitrile or the pH of the ammonium acetate solution to achieve a retention time of 26–34 min for the atorvastatin peak.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
40	100	0
70	20	80
85	0	100
100	0	100
105	100	0
115	100	0

Diluent: *N,N*-dimethylformamide

System suitability solution: 0.05 mg/mL of USP Atorvastatin Calcium RS and 0.06 mg/mL of USP Atorvastatin Related Compound B RS in *Diluent*

Standard solution: 0.4 mg/mL of USP Atorvastatin Calcium RS in *Diluent*. [Note—Use sonication if necessary.]

Sample solution: 0.4 mg/mL of Atorvastatin Calcium in *Diluent*. [Note—Use sonication if necessary.]

Chromatographic system

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

[Note—If significant fronting of the peaks for atorvastatin related compound B and atorvastatin is observed, use the following diluent to prepare the *Sample solution*, the *Standard solution*, and the *System suitability solution*: acetonitrile, stabilizer-free tetrahydrofuran, and water (1:1:2).]

Mode: LC

Detector: UV 244 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between the peaks for atorvastatin related compound B and atorvastatin, *System suitability solution*

Tailing factor: NMT 1.6, *Standard solution*

Relative standard deviation: NMT 0.6%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of atorvastatin calcium ($C_{66}H_{68}CaF_2N_4O_{10}$) in the portion of Atorvastatin Calcium taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

C_U = concentration of Atorvastatin Calcium in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis. If labeled as a propylene glycol solvate, 98.0%–102.0% on the anhydrous, propylene glycol-free, and solvent-free basis.

OTHER COMPONENTS

• **Content of Propylene Glycol** (if labeled as a propylene glycol solvate)

Diluent: Dimethylsulfoxide

Standard solution: 0.125 mg/mL of propylene glycol in *Diluent*

Sample solution: 2.5 mg/mL of Atorvastatin Calcium (as propylene glycol solvate) in *Diluent*. Use sonication as needed to achieve a complete dissolution.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 75-m; 3-µm coating of G43

Temperatures

Injection port: 230°

Detector: 250°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	0	100	1
100	10	140	5
140	30	225	3

Carrier gas: Helium

Flow rate: 6.0 mL/min

Injection volume: 1 µL

Injection type: Splitless, using a suitable inlet liner

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of propylene glycol in the portion of Atorvastatin Calcium as propylene glycol solvate taken:

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

r_U = peak response of propylene glycol from the *Sample solution*

r_S = peak response of propylene glycol from the *Standard solution*

C_S = concentration of propylene glycol in the *Standard solution* (mg/mL)

C_U = concentration of Atorvastatin Calcium (as propylene glycol solvate) in the *Sample solution* (mg/mL)

Acceptance criteria: 5.4%–7.3%

IMPURITIES

• **Organic Impurities, Procedure 1:** [Note—On the basis of the synthetic route or of the solid state nature of the drug substance, perform either *Procedure 1* or *Procedure 2*. *Procedure 2* may be suitable when atorvastatin lactone, atorvastatin epoxy tetrahydrofuran analog, and atorvastatin acetonide are possible related compounds, and it may be suitable for an amorphous form of the drug substance.]

Buffer, Solution A, Solution B, Mobile phase, Diluent, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 1.5 µg/mL each of USP Atorvastatin Related Compound A RS, USP Atorvastatin Related Compound B RS, USP Atorvastatin Related Compound C RS, and USP Atorvastatin Related Compound D RS in *Diluent*

Sample solution: 1 mg/mL of Atorvastatin Calcium in *Diluent*. [Note—Use sonication if necessary.]

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between the peaks for atorvastatin related compound B and atorvastatin

Analysis

Samples: *Standard solution* and *Sample solution*

Chromatograph the *Standard solution,* and identify the components based on their relative retention times, given in *Table 3*.

Calculate the percentage of each of the atorvastatin related compounds A, B, C, and D in the portion of Atorvastatin Calcium taken:

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

r_U = peak response of the relevant atorvastatin related compound from the *Sample solution*

r_S = peak response of the relevant atorvastatin related compound from the *Standard solution*

C_S = concentration of the relevant atorvastatin related compound in the *Standard solution* (mg/mL)

C_U = concentration of Atorvastatin Calcium in the *Sample solution* (mg/mL)

Calculate the percentage of any other individual impurity in the portion of Atorvastatin Calcium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 3*. Disregard any peak observed in the blank; the reporting level for impurities is 0.05%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Atorvastatin related compound A[a]	0.8	0.3
Atorvastatin related compound B[b]	0.9	0.3
Atorvastatin	1.0	—
Atorvastatin related compound C[c]	1.2	0.3
Atorvastatin related compound D[d,e]	2.1	0.2
Any other individual impurity	—	0.1
Total impurities[f]	—	1.0

[a] Desfluoro impurity.

[b] 3*S*,5*R* Isomer.

[c] Difluoro impurity.

[d] Epoxide impurity.

[e] Atorvastatin related compound D may undergo a conversion to its cyclic hemiketal, which is a specified impurity listed in *Table 5* in *Organic Impurities, Procedure 2*, as "atorvastatin epoxy tetrahydrofuran analog". The cyclic hemiketal of atorvastatin related compound D elutes about 1–2 min before atorvastatin related compound D. Use the sum of the areas of the two peaks as a peak response for atorvastatin related compound D in the *Standard solution* and the *Sample solution*.

[f] This total does not include atorvastatin related compound E, as determined in the *Enantiomeric Purity* test.

- **Organic Impurities, Procedure 2**

Buffer: pH 5.0 mixture of 0.045 M ammonium formate and 0.0045 M ammonium acetate solutions, prepared as follows. Weigh 2.84 g of ammonium formate and 0.35 g of ammonium acetate, and dissolve in 950 mL of water. Adjust with 20% formic acid to a pH of 5.0, and dilute with water to 1 L.

Solution A: Acetonitrile and *Buffer* (33:67)

Solution B: Acetonitrile

Solution C: Stabilizer-free tetrahydrofuran

Mobile phase: See *Table 4*. Return to original conditions, and re-equilibrate the system.

Table 4

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	91	0	9
15	91	6	3
20	82	16	2
25	82	16	2
50	32	66	2
55	32	66	2

Diluent: Acetonitrile, stabilizer-free tetrahydrofuran, and *Buffer* (60:5:35)

Peak identification solution: 0.5 mg/mL of USP Atorvastatin Calcium RS and 2.5 µg/mL each of USP Atorvastatin Related Compound A RS, USP Atorvastatin Related Compound B RS, USP Atorvastatin Related Compound H RS, and USP Atorvastatin Related Compound I RS in *Diluent*

Sample solution: 0.5 mg/mL of Atorvastatin Calcium in *Diluent*. Use sonication to dissolve. [NOTE—The solution is stable for 3 h at room temperature and for 24 h when stored at 2°–8°, protected from light.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 4-µm packing L11

Temperatures

Column: 40°

Autosampler: 4°

Flow rate: 1.1 mL/min

Injection volume: 15 µL

System suitability

Sample: *Peak identification solution*

Suitability requirements

Peak-to-valley ratio: NLT 2 between the peaks for atorvastatin related compound B and atorvastatin

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Atorvastatin Calcium taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

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

r_T = sum of all the peak responses, each divided by the corresponding value of the relative response factor from *Table 5*

F = relative response factor for the impurity (see *Table 5*)

Acceptance criteria: See *Table 5*. Disregard any peak eluting before 2 min and any peak observed in the blank; the reporting level for impurities is 0.05%.

Table 5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atorvastatin diamino[a]	0.58	0.74	0.15
Atorvastatin related compound A[b]	0.86	1.0	0.3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atorvastatin related compound B[c]	0.94	1.0	0.3
Atorvastatin	1.0	—	—
Atorvastatin related compound C[d] (if present)	1.1	1.0	0.3
Atorvastatin 3-deoxyhept-2-enoic acid[e]	1.45	1.0	0.10
Atorvastatin related compound H[f]	1.90	1.0	0.15
Atorvastatin epoxy tetrahydrofuran analog[g]	2.00	0.71	0.15
Atorvastatin ethyl ester[h]	2.08	1.0	0.15
Atorvastatin related compound D[i]	2.18	1.3	0.15
Atorvastatin related compound I[j]	2.75	1.0	0.15
Any other individual impurity	—	1.0	0.10
Total impurities[k]	—	—	1.0

[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] Desfluoro impurity.

[c] 3*S*,5*R* Isomer.

[d] Difluoro impurity.

[e] (*S*,*E*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-5-hydroxyhept-2-enoic acid.

[f] Lactone impurity.

[g] 4-(4-Fluorophenyl)-2,4-dihydroxy-2-isopropyl-*N*,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide.

[h] (3*R*,5*R*)-Ethyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate.

[i] Epoxide impurity.

[j] Acetonide impurity.

[k] This total does not include atorvastatin related compound E, as determined in the *Enantiomeric Purity* test.

- **Enantiomeric Purity**

Mobile phase: Hexane, dehydrated alcohol, and trifluoroacetic acid (940:60:1)

System suitability stock solution: 5 mg/mL of USP Atorvastatin Calcium RS and 37.5 µg/mL of USP Atorvastatin Related Compound E RS in methanol. [Note—Atorvastatin related compound E is the 3*S*,5*S* enantiomer of atorvastatin.]

System suitability solution: Transfer 2.0 mL of the *System suitability stock solution* to a 10-mL volumetric flask, add 2.0 mL of dehydrated alcohol, and dilute with hexane to volume.

Sample solution: Transfer 10 mg of Atorvastatin Calcium to a 10-mL volumetric flask, dissolve in 2.0 mL of methanol, add 2.0 mL of dehydrated alcohol, and dilute with hexane to volume.

Chromatographic system

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

Mode: LC

Detector: UV 244 nm

Column: 4.6-mm × 25-cm; packing L51

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—The elution order of the peaks is atorvastatin related compound E followed by atorvastatin.]

Resolution: NLT 2.0 between the peaks for atorvastatin related compound E and atorvastatin

Analysis

Sample: *Sample solution*

Calculate the percentage of atorvastatin related compound E in the portion of Atorvastatin Calcium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for atorvastatin related compound E

r_T = sum of the peak responses for atorvastatin related compound E and atorvastatin

Acceptance criteria: NMT 0.3% of atorvastatin related compound E

SPECIFIC TESTS

• **WATER DETERMINATION,** *Method Ia* ⟨921⟩**:** 3.5%–5.5% for the trihydrate form. If labeled as amorphous or as semicrystalline, NMT 6.0%. If labeled as a propylene glycol solvate, NMT 1.0%.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve the trihydrate form in well-closed containers, and store at room temperature. If labeled as amorphous or semicrystalline or as a propylene glycol solvate, store as per labeling instructions. Possible packaging and storage conditions could include the following: Preserve in well-closed containers protected from light and moisture, or in tight containers; store at room temperature, at controlled room temperature, or at 2°–8°; store under nitrogen atmosphere or packed with an oxygen absorber; and store under nitrogen atmosphere, packed with silica gel and an oxygen absorber.

• **LABELING:** Where it is an amorphous form, the label so indicates. Where it is a semicrystalline form, the label so indicates. Where it is a propylene glycol solvate form, the label so indicates. If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies. Label it to indicate the name and quantity of any added antioxidant.

Change to read:

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Atorvastatin Calcium RS

USP Atorvastatin Related Compound A RS

Calcium (3*R*,5*R*)-7-[2-isopropyl-4,5-diphenyl-3-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate (1:2);
Also known as Desfluoro impurity, or (3*R*,5*R*)-7-[3-(phenylcarbamoyl)-2-isopropyl-4,5-diphenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoicacid, calcium salt.

$C_{66}H_{70}CaN_4O_{10}$ 1119.38

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); also known as 3*S*,5*R* Isomer, or (3*S*,5*R*)-7-[3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, calcium salt.

$C_{66}H_{68}CaF_2N_4O_{10}$ 1155.34

USP Atorvastatin Related Compound C RS

Calcium (3*R*,5*R*)-7-[2,3-Bis(4-fluorophenyl)-5-isopropyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate (1:2); Also known as Difluoro impurity, or (3*R*,5*R*)-7-[3-(phenylcarbamoyl)-4,5-bis(4-fluorophenyl)-2-isopropyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, calcium salt.

$C_{66}H_{66}CaF_4N_4O_{10}$ 1191.34

USP Atorvastatin Related Compound D RS

3-(4-Fluorobenzoyl)-2-isobutyryl-*N*,3-diphenyloxirane-2-carboxamide; Also known as Epoxide impurity, or 3-(4-fluorobenzoyl)-2-isobutyryl-3-phenyl-oxirane-2-carboxylic acid phenylamide.

$C_{26}H_{22}FNO_4$ 431.46

USP Atorvastatin Related Compound E RS

Calcium (3*S*,5*S*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate (1:2); Also known as 3*S*,5*S* Enantiomer, or (3*S*,5*S*)-7-[3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, calcium salt.

$C_{66}H_{68}CaF_2N_4O_{10}$ 1155.36

▲ USP Atorvastatin Related Compound H RS

Also known as Lactone impurity;

▲ (ERR 1-Jun-2023)

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.

$C_{33}H_{33}FN_2O_4$ 540.64

▲ USP Atorvastatin Related Compound I RS

Also known as Acetonide impurity;

▲ (ERR 1-Jun-2023)

tert-Butyl 2-((4*R*,6*R*)-6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]ethyl}-2,2-dimethyl-1,3-dioxan-4-yl)acetate.

$C_{40}H_{47}FN_2O_5$ 654.82

Topic/Question	Contact	Expert Committee
ATORVASTATIN CALCIUM	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

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