Atorvastatin Calcium Tablets

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Posting Date: 25–Jan–2019
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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 5* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 5* was validated using a Zodiac C18 brand of L1 column. The typical retention time for atorvastatin is about 2.2–3.2 min.

The Atorvastatin Calcium Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Edith Chang, Ph.D., Senior Scientific Liaison (301-816-8392 or yec@usp.org).
Atorvastatin Calcium Tablets

**Definition**

Atorvastatin Calcium Tablets contain an amount of atorvastatin calcium (C₂₄H₃₃FN₉O₁₃Ca), 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 900 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 Acetonitrile and Water (50:50) 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: Namely 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: UV 244 nm

Identification A: Diode array; UV 200–400 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System 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 (C₂₄H₃₃FN₉O₁₃Ca) in the portion of Tablets taken:

\[
\text{Result} = (r_0 / r_1) \times (C_0 / C_1) \times [M \times (M_{r1} / M_{r2})] \times 100
\]

- \(r_0\) = peak response of atorvastatin from the Sample solution
- \(r_1\) = peak response of atorvastatin from the Standard solution
- \(C_0\) = concentration of USP Atorvastatin Calcium RS in the Standard solution (mg/mL)
- \(M\) = nominal concentration of atorvastatin in the Sample solution (mg/mL)
- \(M_{r1}\) = 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 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**

<table>
<thead>
<tr>
<th>Label Claim (mg/Tablet)</th>
<th>Cell (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>20 and 40</td>
<td>0.5</td>
</tr>
<tr>
<td>80</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of atorvastatin (C₂₄H₃₃FN₉O₁₃Ca) dissolved:

\[
(A_0 / A_1) \times C_0 \times V \times D \times [M \times (M_{r1} / M_{r2})] \times (1/L) \times 100
\]

- \(A_0\) = absorbance of the Sample solution
- \(A_1\) = absorbance of the Standard solution
- \(C_0\) = concentration of USP Atorvastatin Calcium RS in the Standard solution (mg/mL)
If the product complies with this test, the labeling indicates that it meets USP 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_{37}H_{50}FN_{3}O_{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_{37}H_{50}FN_{3}O_{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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>0.69</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>0.74</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2.73</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2.77</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>5.00</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

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: 4.6-mm x 25-cm; 5-μm packing L1
Column temperature: 30°
Flow rate: 1 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_{37}H_{50}FN_{3}O_{5}) dissolved:

\[ \left( \frac{r_1}{r_2} \right) \times C_S \times V \times [M \times (M_1/M_2)] \times (1/L) \times 100 \]

\( r_1 \) = peak response of atorvastatin from the Sample solution
\( r_2 \) = 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

\( M_1 \) = molecular weight of atorvastatin, 558.64

\( M_2 \) = molecular weight of atorvastatin calcium, 1155.34

\( L \) = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of atorvastatin (C_{37}H_{50}FN_{3}O_{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 x 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_{37}H_{50}FN_{3}O_{5}) dissolved:

\[ \left( \frac{r_1}{r_2} \right) \times C_S \times V \times [M \times (M_1/M_2)] \times (1/L) \times 100 \]

\( r_1 \) = peak response of atorvastatin from the Sample solution
\( r_2 \) = 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

\( M_1 \) = molecular weight of atorvastatin, 558.64

\( M_2 \) = molecular weight of atorvastatin calcium, 1155.34

\( L \) = label claim (mg/Tablet)
If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 5.

**Medium:** Dissolve 6.8 g of monobasic potassium phosphate and 0.9 g of sodium hydroxide in 1 L of water. Adjust with either sodium hydroxide or phosphoric acid to a pH of 6.8, 900 mL.

**Buffer:** Ammonium hydroxide (10% v/v) to a pH of 4.3 ± 0.05.

**Diluent:** Acidic ammonium hydroxide (10% v/v) to a pH of 4.0.

**Sample solution:** Pass the solution through a suitable filter of 0.45-µm pore size, discarding the first few milliliters of the filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 244 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Temperatures**

- Autosampler: 10º
- Column: 30º
- Flow rate: 1.5 mL/min
- Injection volume: 50 µL
- Run time: NLT 2 times the retention time of atorvastatin

**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\(_{48}\)F\(_{2}\)O\(_{4}\)) dissolved:

\[
\text{Result} = \left( \frac{r_0}{r_2} \right) \times C \times V \times \left[ M \times \left( M_1 / M_2 \right) \right] \times \left( 1 / L \right) \times 100
\]

\(r_0\) = peak response of atorvastatin from the Sample solution

\(r_2\) = peak response of atorvastatin from the Standard solution

**Tolerances:** NLT 80% (Q) of the labeled amount of atorvastatin (C\(_{33}\)H\(_{48}\)F\(_{2}\)O\(_{4}\)) is dissolved.

**Uniformity of Dosage Units (905):** Meet the requirements

**Impurities**

**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 (92.5:7.5)

**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 milliliters of the filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 244 nm

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution B (%)</th>
<th>Solution C (%)</th>
<th>Flow Rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>30</td>
<td>100</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>45</td>
<td>25</td>
<td>75</td>
<td>1.5</td>
</tr>
<tr>
<td>50</td>
<td>25</td>
<td>75</td>
<td>1.5</td>
</tr>
<tr>
<td>55</td>
<td>20</td>
<td>80</td>
<td>1.5</td>
</tr>
<tr>
<td>58</td>
<td>100</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>65</td>
<td>100</td>
<td>0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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.

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4 Atorvastatin

**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

**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:

\[
\text{Result} = \left( \frac{r_{i}}{r_{1}} \right) \times \left( C_{i} / C_{0} \right) \times \left[ M \times (M_{1} / M_{2}) \right] \times (1 / F) \times 100
\]

- \( r_{i} \): peak response of each impurity from the Sample solution
- \( r_{1} \): peak response of atorvastatin from the Sample solution
- \( C_{i} \): concentration of USP Atorvastatin Calcium RS in the Standard solution (mg/mL)
- \( C_{0} \): nominal concentration of atorvastatin in the Sample solution (mg/mL)
- \( M \): number of moles of atorvastatin per mole of atorvastatin calcium, 2
- \( M_{1} \): molecular weight of atorvastatin, 558.64
- \( M_{2} \): molecular weight of atorvastatin calcium, 1155.34
- \( F \): relative response factor (see Table 4)

**Acceptance criteria:** See Table 4.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin amide&lt;sup&gt;a&lt;/sup&gt; &lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.44</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound A&lt;sup&gt;a&lt;/sup&gt; &lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.84</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin pyrrolidone analog&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.88</td>
<td>0.68</td>
<td>0.5</td>
</tr>
<tr>
<td>Atorvastatin related compound B&lt;sup&gt;2&lt;/sup&gt; &lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.94</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound C&lt;sup&gt;1&lt;/sup&gt; &lt;sup&gt;5&lt;/sup&gt;</td>
<td>1.09</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin pyrrolidone lactone&lt;sup&gt;h&lt;/sup&gt; &lt;sup&gt;i&lt;/sup&gt;</td>
<td>1.62</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound H&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1.00</td>
<td>1.18</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Table 4 (continued)**

**Name**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin epoxy</td>
<td>1.06</td>
<td>0.53</td>
<td>0.5</td>
</tr>
<tr>
<td>pyrrolodioxazin 6-hydroxy analog&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.12</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin methyl ester&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1.14</td>
<td>0.53</td>
<td>0.5</td>
</tr>
<tr>
<td>pyrrolodioxazin 7-hydroxy analog, if present&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.20</td>
<td>1.12</td>
<td>1.0</td>
</tr>
<tr>
<td>Atorvastatin epoxy THF analog&lt;sup&gt;m&lt;/sup&gt;</td>
<td>1.27</td>
<td>1.12</td>
<td>0.5</td>
</tr>
<tr>
<td>Atorvastatin related compound D&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.49</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin tert-butyl ester&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1.06</td>
<td>1.00</td>
<td>0.2</td>
</tr>
<tr>
<td>Any other unspecified degradation product</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**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**
  - USP Atorvastatin Calcium RS
  - USP Atorvastatin Related Compound B RS

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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-\{(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl\}ethyl\}-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide.
C_{33}H_{33}FN_{2}O_{4} 540.62