Amlodipine and Atorvastatin Tablets

**Type of Posting**  
Revision Bulletin

**Posting Date**  
26–Nov–2019

**Official Date**  
27–Nov–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 Amlodipine and Atorvastatin Tablets monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test. A Labeling section has also been added. The revision also necessitates the changes in the table numbering in the test for Organic Impurities.

- **Dissolution Test 2** was validated using a Zorbax Eclipse XDB-C18 brand of L1 column from Agilent. The typical retention times for amlodipine and atorvastatin are about 0.46 and 3.9 min, respectively.

The Amlodipine and Atorvastatin Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Edith Chang, Senior Scientific Liaison–Team Leader (301-816-8392 or yec@usp.org).
Amlodipine and Atorvastatin Tablets

**DEFINITION**
Amlodipine and Atorvastatin Tablets contain an amount of amlodipine besylate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of amlodipine (C_{20}H_{25}ClN_2O_5) and an amount of atorvastatin calcium equivalent to NLT 94.5% and NMT 105.0% of the labeled amount of atorvastatin (C_{33}H_{35}FN_2O_5). It may contain suitable antioxidants.

**IDENTIFICATION**
- **A.** The UV spectrum of the major peaks of the **Sample solution** exhibits maxima and minima at the same wavelengths as that of the **Standard solution**, as obtained in the Assay.
- **B.** The retention times of the major peaks of the **Sample solution** correspond to those of the **Standard solution**, as obtained in the Assay.

**ASSAY**

**PROCEDURE**

**Solution A:** Dissolve 1.54 g of ammonium acetate in 1000 mL of water and add 2 mL of triethylamine. Adjust with acetic acid to a pH of 5.0.

**Mobile phase:** Acetonitrile, methanol, and Solution A (38:15:47)

**Buffer:** Transfer 7 mL of triethylamine to a 1000-mL volumetric flask containing 900 mL of water and mix. Adjust with dilute phosphoric acid (1 in 100) to a pH of 3.0 and dilute with water to volume.

**Diluent:** Acetonitrile, methanol, and Buffer (3:7:10)

**Standard stock solution 1:** 0.35 mg/mL of USP Amlodipine Besylate RS in methanol

**Standard stock solution 2:** 0.44 mg/mL of USP Atorvastatin Calcium RS in methanol

**Standard solution:** Prepare solutions of USP Amlodipine Besylate RS and USP Atorvastatin Calcium RS in Mobile phase at concentrations given in Table 1 from **Standard stock solution 1** and **Standard stock solution 2**.

**Table 1**

<table>
<thead>
<tr>
<th>Strength of Tablet, Amlodipine/Atorvastatin (mg/mg)</th>
<th>Concentration of Amlodipine Besylate (mg/mL)</th>
<th>Concentration of Atorvastatin Calcium (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5/10, 5/20, 10/40</td>
<td>0.028</td>
<td>0.088</td>
</tr>
<tr>
<td>2.5/20, 5/40, 10/80</td>
<td>0.014</td>
<td>0.088</td>
</tr>
<tr>
<td>5/10, 10/20</td>
<td>0.028</td>
<td>0.044</td>
</tr>
<tr>
<td>2.5/40, 5/80</td>
<td>0.014</td>
<td>0.176</td>
</tr>
<tr>
<td>10/10</td>
<td>0.028</td>
<td>0.022</td>
</tr>
</tbody>
</table>

**Sample solution:** Transfer NLT 10 Tablets to a suitable volumetric flask. Add about 20% of the final volume of the volumetric flask size in Diluent and sonicate to disperse the Tablets. Add about 40% of the final volume of the volumetric flask size in Diluent, sonicate for 20 min, and dilute with Diluent to volume. Centrifuge and transfer a suitable quantity of the supernatant to an appropriate suitable volumetric flask. Dilute with Mobile phase to volume to obtain the nominal concentrations of amlodipine and atorvastatin similar to that of the **Standard solution**.

**Chromatographic system**
(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 237 nm. For Identification A, use a diode array detector in the range of 200–400 nm.

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

**Column temperature:** 35°

**Flow rate:** 1 mL/min

**Injection volume:** 20 μL

**Run time:** NLT 3.5 times the retention time of amlodipine

**System suitability**

**Sample:** **Standard solution**

**Suitability requirements**

- **Tailing factor:** NMT 2.0 for both peaks
- **Relative standard deviation:** NMT 2.0% for both peaks

**Analysis**

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

Calculate the percentage of the labeled amount of amlodipine (C_{20}H_{25}ClN_2O_5) in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_U}{C_S} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100 \]

where

- \( r_U \) = peak response of amlodipine from the **Sample solution**
- \( r_S \) = peak response of amlodipine from the **Standard solution**
- \( C_U \) = concentration of USP Amlodipine Besylate RS in the **Standard solution** (mg/mL)
- \( C_S \) = nominal concentration of amlodipine in the **Sample solution** (mg/mL)
- \( M_{r1} \) = molecular weight of amlodipine, 408.88
- \( M_{r2} \) = molecular weight of amlodipine besylate, 567.05

Calculate the percentage of the labeled amount of atorvastatin (C_{33}H_{35}FN_2O_5) in the portion of Tablets taken:

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

where

- \( r_U \) = peak response of atorvastatin from the **Sample solution**
- \( r_S \) = peak response of atorvastatin from the **Standard solution**
- \( C_U \) = concentration of USP Atorvastatin Calcium RS in the **Standard solution** (mg/mL)
- \( C_S \) = 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, 1135.34

**Acceptance criteria**

- **Amlodipine:** 90.0%–110.0%
- **Atorvastatin:** 94.5%–105.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution** (711)
- Test 1A (08/27/2019)

**Solution A,** Mobile phase, **Standard stock solution 1,** **Standard stock solution 2,** Chromatographic system, and **System suitability:** Proceed as directed in the Assay.

**Medium:** 0.1% polysorbate 80 in pH 6.8 phosphate buffer; 900 mL

**Apparatus 2:** 75 rpm

**Time:** 20 min

**Standard solution:** (L_1/900) mg/mL of amlodipine and (L_2/900) mg/mL of atorvastatin in Medium from **Standard stock solution 1** and **Standard stock solution 2,** where L_1 is...
If the product complies with this test, the labeling

0.05 M phosphate buffer prepared as follows.

40 μL

−

Pass a portion of the solution under test

10

15.5/11.5 = peak response of amlodipine from the

= molecular weight of amlodipine, 408.88

200 = label claim of amlodipine (mg/Tablet)

30 min

200

15.5/92

35

15.5/23

Standard solution

Prepare solutions of

30

10

200

Acetonitrile

45

20

200

200

7.75/23

UV 240 nm

NLT 1.8 times the retention time of

10

10

200

NLT 1.5 for amlodipine

5 = volume of

7.75/46

30

15.5/46

75 rpm

7.75/11.5

5

20

2 mL/min

7.75/92

Standard solution

= peak response of amlodipine from the

200

20

10

200

NMT 2.0% for

10

460 μg/mL of

50°

40

4.6-mm × 5-cm; 1.8-μm packing

20

7.75/46

Analysis

Sample solution: Centrifuge the solution under test and use the supernatant.

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

Medium: 0.05 M phosphate buffer prepared as follows.

Dissolve 40.8 g of potassium phosphate, monobasic and 5 g of sodium hydroxide in 6 L of water. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.8; 900 mL.

Apparatus 2: 75 rpm

Time: 30 min

Buffer: Dissolve 4.0 g of sodium phosphate, monobasic in 1200 mL of water and add 6 mL of triethylamine. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and Buffer (40:60)

Diluent: Acetonitrile and water (50:50)

Standard stock solution 1: 155 μg/mL of USP Amlodipine Besylate RS in Diluent

Standard stock solution 2: 460 μg/mL of USP Amlodipine Calcium RS in Diluent

Standard solution: Prepare solutions of USP Amlodipine Besylate RS and USP Atorvastatin Calcium RS at concentrations given in Table 2 from Standard stock solution 1 and Standard stock solution 2.

Table 2

<table>
<thead>
<tr>
<th>Strength of Tablet</th>
<th>Sample solution</th>
<th>Volume of Standard Stock Solution 1 to Be Added (mL)</th>
<th>Volume of Standard Stock Solution 2 to Be Added (mL)</th>
<th>Volume of Diluent to Be Added (mL)</th>
<th>Final Volume with Medium (mL)</th>
<th>Final Concentration of USP Amlodipine Besylate RS/USP Atorvastatin Calcium RS (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/10</td>
<td></td>
<td>10</td>
<td>5</td>
<td>45</td>
<td>200</td>
<td>7.75/11.5</td>
</tr>
<tr>
<td>5/20</td>
<td></td>
<td>10</td>
<td>10</td>
<td>40</td>
<td>200</td>
<td>7.75/23</td>
</tr>
<tr>
<td>5/40</td>
<td></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>200</td>
<td>7.75/46</td>
</tr>
<tr>
<td>5/80</td>
<td></td>
<td>10</td>
<td>40</td>
<td>10</td>
<td>200</td>
<td>7.75/92</td>
</tr>
<tr>
<td>10/10</td>
<td></td>
<td>20</td>
<td>5</td>
<td>35</td>
<td>200</td>
<td>15.5/11.5</td>
</tr>
<tr>
<td>10/20</td>
<td></td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>200</td>
<td>15.5/23</td>
</tr>
<tr>
<td>10/40</td>
<td></td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>200</td>
<td>15.5/46</td>
</tr>
<tr>
<td>10/80</td>
<td></td>
<td>20</td>
<td>40</td>
<td></td>
<td>200</td>
<td>15.5/92</td>
</tr>
</tbody>
</table>

Sample solution: Pass a portion of the solution under test through a suitable filter. Discard the first few milliliters of filtrate.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 5-cm; 1.8-μm packing L1

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 20 μL

Run time: NLT 1.8 times the retention time of atorvastatin

System suitability

Sample: Standard solution

[NOTE—The relative retention times for amlodipine and atorvastatin are 0.12 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 1.5 for amlodipine

Relative standard deviation: NMT 2.0% for amlodipine and atorvastatin

Analysis

Sample: Standard solution and Sample solution

Calculate the percentage of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{5}) dissolved:

Result = \left( \frac{r_{u}}{M_{1}} \right) \times \left( \frac{C_{1} \times V}{M_{1}} \right) \times \left( \frac{1}{L} \right) \times 100

r_{u} = \text{peak response of amlodipine from the Sample solution}

C_{1} = \text{concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)}

V = \text{volume of Medium, 900 mL}

M_{1} = \text{molecular weight of amlodipine, 408.88}

L = \text{label claim of amlodipine (mg/Tablet)}

Calculate the percentage of the labeled amount of atorvastatin (C_{33}H_{35}FN_{2}O_{5}) dissolved:

Result = \left( \frac{r_{u}}{M_{1}} \right) \times \left( \frac{C_{1} \times V}{M_{1}} \right) \times \left( \frac{1}{L} \right) \times 100

r_{u} = \text{peak response of atorvastatin from the Sample solution}

C_{1} = \text{concentration of USP Atorvastatin Calcium RS in the Standard solution (mg/mL)}

V = \text{volume of Medium, 900 mL}

M_{1} = \text{molecular weight of atorvastatin, 558.64}

L = \text{label claim of atorvastatin (mg/Tablet)}

Tolerances: NLT 80% (Q) of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{5}) and atorvastatin (C_{33}H_{35}FN_{2}O_{5}) are dissolved.

*Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
\[ r_0 = \text{peak response of atorvastatin from the Sample solution} \]
\[ r_5 = \text{peak response of atorvastatin from the Standard solution} \]
\[ C_{\text{p}} = \text{concentration of USP Atorvastatin Calcium RS in} \]
\[ \text{the Standard solution (mg/mL)} \]
\[ V = \text{volume of Medium, 900 mL} \]
\[ M = \text{number of moles of atorvastatin per mole of} \]
\[ \text{atorvastatin calcium, 2} \]
\[ M_1 = \text{molecular weight of atorvastatin, 558.64} \]
\[ M_2 = \text{molecular weight of atorvastatin calcium, 1155.34} \]
\[ L = \text{label claim of atorvastatin (mg/Tablet)} \]

Tolerances: NLT 80% (Q) of the labeled amount of atorvastatin (C_{28}H_{39}ClN_{4}O_{7}) and atorvastatin (C_{16}H_{20}FN_{3}O_{2}) are dissolved.\(^{(RB\ 27-Nov-2019)}\)

• UNIFORMITY OF DOSAGE UNITS (905): Meet the requirements

**IMPURITIES**

**Change to read:**

• **ORGANIC IMPURITIES RELATED TO AMLODIPINE**

Buffer 1: Add 7 mL of triethylamine in 1000 mL of water and adjust with phosphoric acid to a pH of 2.5. Add 1.8 g of tetrabutylammonium hydrogen sulfate and mix well.

Solution A: Methanol and Buffer 1 (40:60)

Solution B: Acetonitrile, methanol, and Buffer 1 (40:40:20)

Mobile phase: See Table \(^{3}A\) \(^{(RB\ 27-Nov-2019)}\)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>16</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>18</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>24</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>31</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>36</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>40</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Buffer 2: Add 7 mL of triethylamine in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.

Diluent 1: Methanol and water (50:50)

Diluent 2: Methanol and Buffer 2 (50:50)

Standard stock solution: 0.7 mg/mL of USP Amlodipine Besylate RS in Diluent 2, prepared as follows. Transfer a suitable amount of USP Amlodipine Besylate RS to a suitable volumetric flask and dissolve in a quantity of methanol, about 20% of the volume of the flask. Dilute with Diluent 2 to volume.

Standard solution 1: 5 μg/mL of USP Amlodipine Related Compound A RS in Diluent 1

Standard solution 2: 3.5 μg/mL of USP Amlodipine Besylate RS from Standard stock solution in Diluent 2

Sample solution: Nominaly 0.5 mg/mL of amlodipine in Diluent 2, prepared as follows. Finely powder NLT 25 Tablets and transfer a portion of the powder, equivalent to 50 mg of amlodipine to a 100-mL volumetric flask. Add about 40 mL of methanol, shake to disperse, and sonicate for 15 min. Add about 40 mL of Buffer 2 and sonicate for another 10 min. Dilute with Diluent 2 to volume, centrifuge, and use the supernatant. Pass a portion of the solution through a suitable filter of 0.22-μm pore size. Prepare this solution fresh.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 270 nm for amlodipine related compound A; 360 nm for all other impurities

**Column:** 2.1-mm × 15-cm; 1.8-μm packing L1

**Column temperature:** 40°

**Flow rate:** 0.3 mL/min

**Injection volume:** 5 μL

**System suitability**

Sample: Standard solution 2

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 5.0%

**Analysis**

Samples: Standard solution 1, Standard solution 2, and Sample solution

Calculate the percentage of amlodipine related compound A in the portion of Tablets taken:

\[ \text{Result} = (r_0/r_5) \times (C_{\text{A}}/C_{\text{A}0}) \times (M_{\text{A}}/M_{\text{A}0}) \times 100 \]

Calculate the percentage of atorvastatin–amlodipine adduct or any unspecified degradation product in the portion of Tablets taken:

\[ \text{Result} = (r_0/r_5) \times (C_{\text{A}}/C_{\text{A}0}) \times (M_{\text{A}}/M_{\text{A}0}) \times (1/F) \times 100 \]

Disregard peaks at the relative retention times of 2.18, 2.47 (atorvastatin), and 2.79 min."
4 Amlodipine

Change to read:

- **ORGANIC IMPURITIES RELATED TO ATORVASTATIN**

  **Buffer 1**: Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water and adjust with dilute phosphoric acid (1 in 10) to a pH of 3.4.

  **Buffer 2**: Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water and adjust with triethylamine to a pH of 7.0.

  **Solution A**: Tetrahydrofuran, acetonitrile, and Buffer 1 (5:25:70)

  **Solution B**: Tetrahydrofuran, acetonitrile, and Buffer 2 (5:70:25)

  **Mobile phase**: See Table 4 (RB 27-Nov-2019)

<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>Amlodipine related compound A</td>
<td>0.59</td>
<td>—</td>
<td>0.50</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin-amlodipine adducta</td>
<td>3.49</td>
<td>0.47</td>
<td>0.50</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Total degradation products for amlodipine</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

  a 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[2-(2-(3,5,5,6-tetrahydrofuran-6-yl)methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>30</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>70</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>75</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>85</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>90</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

**Diluent**: Acetonitrile and water (50:50)

**System suitability solution**: Heat a suitable amount of USP Atorvastatin Calcium RS at 60°C for 1 h for degradation; 0.55 mg/mL of degraded USP Atorvastatin Calcium RS, 3 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 H RS in Diluent. Sonication may be necessary for complete dissolution.

**Standard solution**: 2.7 μg/mL of USP Atorvastatin Calcium RS in Diluent

**Sample solution**: Nominally 0.5 mg/mL of atorvastatin in Diluent, prepared as follows. Transfer an amount equivalent to 50 mg of atorvastatin from a portion of NLT 20 finely powdered Tablets to a 100-mL volumetric flask. Add about 10 mL of acetonitrile, shake to disperse, and sonicate for 5 min. Add about 70 mL of Diluent and sonicate for another 20 min. Dilute with Diluent to volume and centrifuge. Prepare this solution fresh.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode**: LC

**Detector**: UV 246 nm

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

**Column temperature**: 45°C

**Flow rate**: 1.2 mL/min

**Injection volume**: 20 μL

**System suitability**

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

**Acceptance criteria**: See Table 6 (RB 27-Nov-2019) Disregard any impurity peaks less than 0.05% and the peaks from amlodipine related impurities.

<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 pyrrolidone analogb</td>
<td>0.86</td>
<td>0.67</td>
<td>0.45</td>
</tr>
<tr>
<td>Atorvastatin related compound Aa</td>
<td>0.91</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound Bb</td>
<td>0.95</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound Cc</td>
<td>1.04</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin epoxy pyrrolooxazin 6-hydroxy analogd</td>
<td>1.35</td>
<td>0.39</td>
<td>0.5</td>
</tr>
<tr>
<td>Atorvastatin epoxy pyrrolooxazin 7-hydroxy analogd</td>
<td>1.40</td>
<td>0.52</td>
<td>0.5</td>
</tr>
<tr>
<td>Name</td>
<td>Relative Retention Time</td>
<td>Relative Response Factor</td>
<td>Acceptance Criteria, NMT (%)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Atorvastatin related compound H</td>
<td>1.78</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Atorvastatin epoxy tetrahydrofuran analog</td>
<td>1.96</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin oxirane</td>
<td>2.23</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin tert-butyl ester</td>
<td>2.55</td>
<td>——</td>
<td></td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>——</td>
<td>——</td>
<td>0.20</td>
</tr>
<tr>
<td>Total degradation products for atorvastatin</td>
<td>——</td>
<td>——</td>
<td>2.0</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>——</td>
<td>——</td>
<td>3.0</td>
</tr>
</tbody>
</table>

a (3R,5R)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-oxo-4-phenyl-3-(phenylcarbamoyl)-2,3-dihydro-1H-pyrrol-1-yl]-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 4-(6-(4-Fluorophenyl)-7,8-epoxy-6-hydroxy-8a-isopropyl-7-phenyl-(phenylcarbamoyl)hexahydro-2H-pyroro[2,1-b][1,3]oxazin-2-yl)-3-hydroxybutanoic acid.

d (3R)-4-(1b-(4-Fluorophenyl)-7-hydroxy-7-isopropyl-1a-phenyl-7a-(phenylcarbamoyl)hexahydro-1aH-oxireno[2,3,5,4]pyroro[2,1-b][1,3]oxazin-3-yl)-3-hydroxybutanoic acid.

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

f 3-(4-Fluorobenzoyl)-2-isobutyryl-N,S-diphenyloxirane-2-carboxamide.

h (3R,5R)-tert-Butyl 7-[(2,4-difluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate.

i Sum of the total degradation products for amlodipine from the test for Organic Impurities Related to Amlodipine and the total degradation products for atorvastatin from the test for Organic Impurities Related to Atorvastatin.

Additional Requirements

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

- **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 Amlodipine Besylate RS
  - USP Amlodipine Related Compound A RS
  - USP Amlodipine Related Compound A RS
  - USP Atorvastatin Calcium RS
  - USP Atorvastatin Related Compound A RS
  - USP Atorvastatin Related Compound B RS
  - USP Atorvastatin Related Compound C RS
  - USP Atorvastatin Related Compound H RS

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