Amlodipine and Olmesartan Medoxomil Tablets

Type of Posting  Notice of Intent to Revise
Posting Date  28-Jul-2023
Targeted Official Date  To Be Determined, Revision Bulletin
Expert Committee  Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 2 Expert Committee intends to revise the Amlodipine and Olmesartan Medoxomil Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Amlodipine and Olmesartan Medoxomil Tablets monograph to add Dissolution Test 5.

- Dissolution Test 5 was validated using the Venusil XBP C18(L) brand of column with L1 packing. The typical retention times for amlodipine and olmesartan medoxomil are 3 and 4 min, respectively.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact V. Durga Prasad, Senior Scientist II (+91-40-4448-8723 or durgaprasad.v@usp.org).

¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Amlodipine and Olmesartan Medoxomil Tablets

DEFINITION
Amlodipine and Olmesartan Medoxomil 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_{2}O_{6}) and NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{6}).

IDENTIFICATION
- A. The UV spectra of the amlodipine and olmesartan medoxomil peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.
- B. The retention times of the amlodipine and olmesartan medoxomil peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.

ASSAY
- Procedure
  Solution A: 6.9 g/L of sodium phosphate, monobasic. Adjust with phosphoric acid to a pH of 2.5.
  Solution B: Acetonitrile
  Mobile phase: See Table 1.

Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>21</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>23</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>25</td>
<td>68</td>
<td>32</td>
</tr>
</tbody>
</table>

Diluent: Acetonitrile and water (50:50)
Standard stock solution: 0.28 mg/mL of USP Amlodipine Besylate RS and 0.8 mg/mL of USP Olmesartan Medoxomil RS in Diluent
Standard solution: 0.056 mg/mL of USP Amlodipine Besylate RS and 0.16 mg/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution
Sample stock solution: Nominal concentrations given in Table 2 are prepared as follows.
For Tablet strength 5/20, transfer NLT 5 Tablets equivalent to 25 mg of amlodipine and 100 mg of olmesartan medoxomil into a suitable volumetric flask. Add water to 20% of the total volume and
sonicate for 5 min. Add acetonitrile to 20% of the total volume and sonicate for 5 min. Add Diluent to 30% of the total volume and sonicate for 15 min. Dilute with Diluent to volume. Centrifuge a portion of the solution for 10 min and pass through a filter of 0.45-µm pore size.

For Tablet strength 5/40, 10/20, or 10/40, transfer NLT 5 Tablets equivalent to 25 mg of amlodipine and 200 mg of olmesartan medoxomil, 50 mg of amlodipine and 100 mg of olmesartan medoxomil, or 50 mg of amlodipine and 200 mg of olmesartan medoxomil into a suitable volumetric flask. Add water to 10% of the total volume and sonicate for 5 min. Add acetonitrile to 10% of the total volume and sonicate for 5 min. Add Diluent to 30% of the total volume and sonicate for 15 min. Dilute with Diluent to volume. Centrifuge a portion of the solution for 10 min and pass through a filter of 0.45-µm pore size.

**Table 2**

<table>
<thead>
<tr>
<th>Tablet Strength Amlodipine/Olmesartan Medoxomil (mg/mg)</th>
<th>Nominal Concentration of Amlodipine (mg/mL)</th>
<th>Nominal Concentration of Olmesartan Medoxomil (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20, 10/40</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>5/40</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>10/20</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

**Sample solution**: Nominal concentrations in Diluent from Sample stock solution are given in **Table 3**.

**Table 3**

<table>
<thead>
<tr>
<th>Tablet Strength Amlodipine/Olmesartan Medoxomil (mg/mg)</th>
<th>Nominal Concentration of Amlodipine (mg/mL)</th>
<th>Nominal Concentration of Amlodipine/Olmesartan Medoxomil (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20, 10/40</td>
<td>0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>5/40</td>
<td>0.02</td>
<td>0.16</td>
</tr>
<tr>
<td>10/20</td>
<td>0.04</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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

**Mode**: LC

**Detector**: UV 254 nm. For Identification A, use a diode array detector in the range of 200–400 nm.

**Column**: 4.6-mm × 25-cm; 5-µm packing L11

**Temperatures**

**Autosampler**: 5°

**Column**: 60°

**Flow rate**: 2 mL/min
Injection volume: 10 µL

System suitability
Sample: Standard solution

Suitability requirements
Tailing factor: NMT 2.0 for amlodipine and olmesartan medoxomil peaks
Relative standard deviation: NMT 2.0% for amlodipine and olmesartan medoxomil peaks

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of amlodipine (C_{20}H_{25}ClN_{5}O_{5}) in the portion of Tablets taken:

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

\(r_U\) = peak response of amlodipine from the Sample solution
\(r_S\) = peak response of amlodipine from the Standard solution
\(C_S\) = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
\(C_U\) = 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 olmesartan medoxomil (C_{29}H_{30}N_{6}O_{6}) in the portion of Tablets taken:

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

\(r_U\) = peak response of olmesartan medoxomil from the Sample solution
\(r_S\) = peak response of olmesartan medoxomil from the Standard solution
\(C_S\) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
\(C_U\) = nominal concentration of olmesartan medoxomil in the Sample solution (mg/mL)

Acceptance criteria

Amlodipine: 90.0%–110.0%
Olmesartan medoxomil: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- Dissolution (711)

Test 1

Medium: 6.8 g/L of potassium phosphate, monobasic. Adjust with 0.2 N sodium hydroxide solution to a pH of 6.8; 900 mL.

Apparatus 2: 50 rpm

Times

Amlodipine: 30 min
Olmesartan medoxomil: 45 min

Buffer: 4.08 g/L of potassium phosphate, monobasic. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and Buffer (40:60)

Standard stock solution A: 0.16 mg/mL of USP Amlodipine Besylate RS in Mobile phase
**Standard stock solution B:** 0.44 mg/mL of USP Olmesartan Medoxomil RS in Mobile phase

**Standard solution:** 0.016 mg/mL of USP Amlodipine Besylate RS and 0.044 mg/mL of USP Olmesartan Medoxomil RS in Medium from Standard stock solution A and Standard stock solution B

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first 2–3 mL of the filtrate.

**Chromatographic system**

(See Chromatography, System Suitability.)

**Mode:** LC

**Detector:** UV 254 nm

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

**Autosampler temperature:** 5°

**Flow rate:** 1.2 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 1.4 times the retention time of olmesartan medoxomil

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- **Tailing factor:** NMT 2.0 for amlodipine and olmesartan medoxomil peaks
- **Relative standard deviation:** NMT 2.0% for amlodipine and olmesartan medoxomil peaks

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of amlodipine (C₂₀H₂₅ClN₂O₅) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{M_{r_1}}{M_{r_2}} \right) \times (1/L) \times 100
\]

- \( r_U \) = peak response of amlodipine from the Sample solution
- \( r_S \) = peak response of amlodipine from the Standard solution
- \( C_S \) = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( M_{r_1} \) = molecular weight of amlodipine, 408.88
- \( M_{r_2} \) = molecular weight of amlodipine besylate, 567.05
- \( L \) = label claim of amlodipine (mg/Tablet)

Calculate the concentration (\( C_1 \) or \( C_2 \)) of olmesartan medoxomil (C₂₉H₃₀N₆O₆) in the sample withdrawn from the vessel at the 30- or 45-min time point:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S
\]

- \( r_U \) = peak response of olmesartan medoxomil from the Sample solution at the 30- or 45-min time point
- \( r_S \) = peak response of olmesartan medoxomil from the Standard solution
- \( C_S \) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of olmesartan medoxomil (C₂₉H₃₀N₆O₆) dissolved:

\[
\text{Result} = \left\{ \left[ C_2 \times \left( V - V_S \right) \right] + \left( C_1 \times V_S \right) \right\} \times (1/L) \times 100
\]
\[ C_2 = \text{concentration of olmesartan medoxomil in the Sample solution at the 45-min time point (mg/mL)} \]

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

\[ V_S = \text{volume of the Sample solution withdrawn at the 30-min time point (mL)} \]

\[ C_1 = \text{concentration of olmesartan medoxomil in the Sample solution at the 30-min time point (mg/mL)} \]

\[ L = \text{label claim of olmesartan medoxomil (mg/Tablet)} \]

**Tolerances:** NLT 80.0% \((Q)\) of the labeled amount of amlodipine \((C_{20}H_{25}ClN_2O_5)\) at 30 min and NLT 70.0% \((Q)\) of the labeled amount of olmesartan medoxomil \((C_{29}H_{30}N_6O_6)\) at 45 min are dissolved.

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

**Medium:** 6.8 g/L of potassium phosphate, monobasic and 0.9 g/L of sodium hydroxide. Adjust with 10% sodium hydroxide solution to a pH of 6.8; 900 mL.

**Apparatus 2:** 50 rpm

**Times**
- **Amlodipine:** 30 min
- **Olmesartan medoxomil:** 30 min

**Buffer:** Add 2 mL of triethylamine in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.5.

**Mobile phase:** Acetonitrile and Buffer (30:70)

**Standard stock solution A:** 0.15 mg/mL of USP Amlodipine Besylate RS in methanol

**Standard stock solution B:** 0.44 mg/mL of USP Olmesartan Medoxomil RS in methanol

**Standard solution:** Known concentrations of USP Amlodipine Besylate RS and USP Olmesartan Medoxomil RS in Medium from Standard stock solution A and Standard stock solution B, prepared per Table 4.

### Table 4

<table>
<thead>
<tr>
<th>Tablet Strength Amlodipine/Olmesartan Medoxomil (mg/mg)</th>
<th>Concentration of USP Amlodipine Besylate RS (mg/mL)</th>
<th>Concentration of USP Olmesartan Medoxomil RS (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20</td>
<td>0.0075</td>
<td>0.022</td>
</tr>
<tr>
<td>5/40</td>
<td>0.0075</td>
<td>0.044</td>
</tr>
<tr>
<td>10/20</td>
<td>0.015</td>
<td>0.022</td>
</tr>
<tr>
<td>10/40</td>
<td>0.015</td>
<td>0.044</td>
</tr>
</tbody>
</table>

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 236 nm

**Column:** 4.6-mm × 5-cm; 5-µm packing L1
Temperatures
   Autosampler: 5°
   Column: 30°
Flow rate: 1.0 mL/min
Injection volume: 10 µL
Run time: NLT 1.5 times the retention time of olmesartan medoxomil

System suitability
   Sample: Standard solution
   [Note—The relative retention times for olmesartan, amlodipine, and olmesartan medoxomil are 0.29, 0.68, and 1.00, respectively.]

Suitability requirements
   Tailing factor: NMT 2.0 for amlodipine and olmesartan medoxomil peaks
   Relative standard deviation: NMT 2.0% for amlodipine and olmesartan medoxomil peaks

Analysis
   Samples: Standard solution and Sample solution
   Calculate the percentage of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{5}) dissolved:
   \[
   \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{M_{r1}}{M_{r2}} \right) \times (1/L) \times 100
   \]
   \[r_U\] = peak response of amlodipine from the Sample solution
   \[r_S\] = peak response of amlodipine from the Standard solution
   \[C_S\] = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
   \[V\] = volume of Medium, 900 mL
   \[M_{r1}\] = molecular weight of amlodipine, 408.88
   \[M_{r2}\] = molecular weight of amlodipine besylate, 567.05
   \[L\] = label claim of amlodipine (mg/Tablet)
   Calculate the percentage of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{6}) dissolved:
   \[
   \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times (1/L) \times 100
   \]
   \[r_U\] = sum of peak responses of olmesartan and olmesartan medoxomil from the Sample solution
   \[r_S\] = sum of peak responses of olmesartan and olmesartan medoxomil from the Standard solution
   \[C_S\] = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
   \[V\] = volume of Medium, 900 mL
   \[L\] = label claim of olmesartan medoxomil (mg/Tablet)

Tolerances: NLT 75.0% (Q) of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{5}) and NLT 70.0% (Q) of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{6}) are dissolved.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.
Medium: pH 6.8 phosphate buffer (3.4 g/L of potassium phosphate, monobasic and 3.55 g/L of sodium phosphate, dibasic, anhydrous in water) and water (50:50); 900 mL
Apparatus 2: 50 rpm
Times
**Amlodipine:** 15 min

**Olmesartan medoxomil:** 45 min

**Solution A:** Dissolve 2.72 g of potassium phosphate, monobasic in 1000 mL of water. Add 5 mL of triethylamine and adjust with phosphoric acid to a pH of 3.0.

**Mobile phase:** Acetonitrile and Solution A (35:65)

**Standard stock solution A:** 0.31 mg/mL of USP Amlodipine Besylate RS in acetonitrile. Sonicate to dissolve if necessary.

**Standard stock solution B:** 0.90 mg/mL of USP Olmesartan Medoxomil RS in acetonitrile. Sonicate to dissolve if necessary.

**Standard solution:** Known concentrations of USP Amlodipine Besylate RS and USP Olmesartan Medoxomil RS in Medium from Standard stock solution A and Standard stock solution B, prepared per Table 5

### Table 5

<table>
<thead>
<tr>
<th>Tablet Strength Amlodipine/Olmesartan Medoxomil (mg/mg)</th>
<th>Concentration of USP Amlodipine Besylate RS (mg/mL)</th>
<th>Concentration of USP Olmesartan Medoxomil RS (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20</td>
<td>0.00775</td>
<td>0.0225</td>
</tr>
<tr>
<td>5/40</td>
<td>0.00775</td>
<td>0.045</td>
</tr>
<tr>
<td>10/20</td>
<td>0.0155</td>
<td>0.0225</td>
</tr>
<tr>
<td>10/40</td>
<td>0.00775</td>
<td>0.0225</td>
</tr>
</tbody>
</table>

**Sample solution:** At the end of the specified time, withdraw 10 mL of the solution under test, pass through a suitable filter and discard the first 5 mL of the filtrate. Replace the aliquot withdrawn with equal volumes of pre-equilibrated Medium. For Tablets with strengths of 5/20, 5/40, and 10/20 mg/mg, use the filtrate. For Tablets with a strength of 10/40 mg/mg, dilute 5 mL of the filtrate with Medium to 10 mL.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 250 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Temperatures**

- **Autosampler:** 5°
- **Column:** 30°

**Flow rate:** 1.2 mL/min

**Injection volume:** 20 µL

**Run time:** NLT 1.5 times the retention time of olmesartan medoxomil

**System suitability**

**Sample:** Standard solution
The relative retention times for olmesartan, amlodipine, and olmesartan medoxomil are 0.32, 0.74, and 1.00, respectively.

### Suitability Requirements

**Resolution:** NLT 3.0 between amlodipine and olmesartan medoxomil

**Tailing Factor:** NMT 2.0 for amlodipine and olmesartan medoxomil

**Relative Standard Deviation:** NMT 2.0% for amlodipine and olmesartan medoxomil

### Analysis

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{5}) dissolved at time point 1:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times D \times \left( \frac{M_{r1}}{M_{r2}} \right) \times \left( \frac{1}{L} \right) \times 100
\]

- \( r_U \) = peak response of amlodipine from the Sample solution withdrawn at time point 1
- \( r_S \) = peak response of amlodipine from the Standard solution
- \( C_S \) = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( D \) = dilution factor for the Sample solution withdrawn at time point 1, if needed
- \( M_{r1} \) = molecular weight of amlodipine, 408.88
- \( M_{r2} \) = molecular weight of amlodipine besylate, 567.05
- \( L \) = label claim of amlodipine (mg/Tablet)

Calculate the concentration \( (C_i) \) of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{6}) in the portion of sample withdrawn from the vessel at each time point \( i \):

\[
\text{Result}_i = \left( \frac{r_i}{r_S} \right) \times C_S \times D
\]

- \( r_i \) = peak response of olmesartan medoxomil from the Sample solution withdrawn at time point \( i \)
- \( r_S \) = peak response of olmesartan medoxomil from the Standard solution
- \( C_S \) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
- \( D \) = dilution factor for the Sample solution withdrawn at time point \( i \), if needed

Calculate the percentage of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{6}) dissolved at time point 2:

\[
\text{Result} = \left[ (C_2 \times V) + (C_1 \times V_S) \right] \times \left( \frac{1}{L} \right) \times 100
\]

- \( C_i \) = concentration of olmesartan medoxomil in the portion of sample withdrawn at time point \( i \) (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( V_S \) = volume of the Sample solution withdrawn at each time point and replaced with Medium, 10 mL
- \( L \) = label claim of olmesartan medoxomil (mg/Tablet)

### Tolerances

NLT 75% \( (Q) \) of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{5}) and NLT 70% \( (Q) \) of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{6}) are dissolved. (See Table 6.)

### Table 6
**Test 5:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 5.

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

**Apparatus 2:** 50 rpm

**Times**
- **Amlodipine:** 20 min
- **Olmesartan medoxomil:** 45 min

**Buffer:** Transfer 7.0 mL of triethylamine in to 1000 mL of water. Add 3.0 mL of phosphoric acid. Adjust with phosphoric acid to a pH of 3.0

**Solution A:** Acetonitrile and methanol (70:30)

**Mobile phase:** Solution A and Buffer (50:50)

**Standard stock solution:** 0.16 mg/mL of USP Amlodipine Besylate RS and 0.44 mg/mL of USP Olmesartan Medoxomil RS in acetonitrile. Sonicate to dissolve.

**Standard solution:** 0.016 mg/mL of USP Amlodipine Besylate RS and 0.044 mg/mL of USP Olmesartan Medoxomil RS from Standard stock solution in Medium

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.22-µm pore size, discarding the first 5 mL of the filtrate.

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

- **Mode:** LC
- **Detector:** UV 237 nm
- **Column:** 4.6-mm × 10-cm; 3-µm packing L1
- **Column temperature:** 30°
- **Flow rate:** 1 mL/min
- **Injection volume:** 5 µL
- **Run time:** NLT 1.3 times the retention time of olmesartan medoxomil

**System suitability**
- **Sample:** Standard solution

  [Note—The relative retention times for olmesartan, amlodipine, and olmesartan medoxomil are 0.41, 0.78, and 1.00, respectively.]

**Suitability requirements**
- **Tailing factor:** NMT 2.0 for amlodipine and olmesartan medoxomil
- **Relative standard deviation**
  - **Amlodipine:** NMT 2.0%
Olmesartan medoxomil: NMT 2.0% for the total peak response of olmesartan medoxomil as determined in the Analysis

**Analysis**

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

Calculate the percentage of the labeled amount of amlodipine \((C_{20}H_{25}ClN_{2}O_{5})\) dissolved at time point 1:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \frac{(M_{r1}/M_{r2}) \times (1/L) \times 100}{1}
\]

- \(r_U\) = peak response of amlodipine from the *Sample solution* withdrawn at time point 1
- \(r_S\) = peak response of amlodipine from the *Standard solution*
- \(C_S\) = concentration of USP Amlodipine Besylate RS in the *Standard solution* (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(M_{r1}\) = molecular weight of amlodipine, 408.88
- \(M_{r2}\) = molecular weight of amlodipine besylate, 567.05
- \(L\) = label claim of amlodipine (mg/Tablet)

Calculate the total peak response \((r_S)\) of olmesartan medoxomil \((C_{29}H_{30}N_6O_6)\) in the *Standard solution*:

\[
r_S = r_{S1} + \left[ r_{S2} \times \frac{(M_{r1}/M_{r2}) \times (1/F)}{1} \right]
\]

- \(r_{S1}\) = peak response of olmesartan medoxomil from the *Standard solution*
- \(r_{S2}\) = peak response of olmesartan from the *Standard solution*
- \(M_{r1}\) = molecular weight of olmesartan medoxomil, 558.60
- \(M_{r2}\) = molecular weight of olmesartan, 446.51
- \(F\) = relative response factor, 1.35

Calculate the total peak response \((r_i)\) of olmesartan medoxomil \((C_{29}H_{30}N_6O_6)\) in the portion of sample withdrawn from the vessel at each time point \((i)\):

\[
r_i = r_{U1} + \left[ r_{U2} \times \frac{(M_{r1}/M_{r2}) \times (1/F)}{1} \right]
\]

- \(r_{U1}\) = peak response of olmesartan medoxomil from the *Sample solution* withdrawn at time point \(i\)
- \(r_{U2}\) = peak response of olmesartan from the *Sample solution* withdrawn at time point \(i\)
- \(M_{r1}\) = molecular weight of olmesartan medoxomil, 558.60
- \(M_{r2}\) = molecular weight of olmesartan, 446.51
- \(F\) = relative response factor, 1.35

Calculate the concentration \((C_i)\) of olmesartan medoxomil \((C_{29}H_{30}N_6O_6)\) in the portion of sample withdrawn from the vessel at each time point \((i)\):

\[
C_i = \left( \frac{r_i}{r_S} \right) \times C_S
\]

- \(r_i\) = total peak response of olmesartan medoxomil from the *Sample solution* withdrawn at time point \(i\)
- \(r_S\) = total peak response of olmesartan medoxomil from the *Standard solution*
- \(C_S\) = concentration of USP Olmesartan Medoxomil RS in the *Standard solution* (mg/mL)
Calculate the percentage of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) dissolved at time point 2:

\[
\text{Result} = \left\{ \left[ C_i \times (V - V_S) \right] + (C_i \times V_S) \right\} \times (1/L) \times 100
\]

- \(C_i\) = concentration of olmesartan medoxomil in the portion of sample withdrawn at time point \(i\) (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(V_S\) = volume of the Sample solution withdrawn at each time point
- \(L\) = label claim of olmesartan medoxomil (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and NLT 80% (Q) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) are dissolved at the times specified.▲

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

**Impurities**

- **Organic Impurities**

  **Solution A, Solution B, Mobile phase, Diluent, Standard stock solution, Sample stock solution,** and **Chromatographic system:** Proceed as directed in the Assay.

  **Standard stock solution A:** 28 µg/mL of USP Amlodipine Besylate RS and 80 µg/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution

  **Standard stock solution B:** 50 µg/mL of USP Amlodipine Related Compound A RS in Diluent

  **Standard solution:** 1.4 µg/mL of USP Amlodipine Besylate RS, 2.5 µg/mL of USP Amlodipine Related Compound A RS, and 4 µg/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution A and Standard stock solution B

  **Sensitivity solution:** 0.28 µg/mL of USP Amlodipine Besylate RS, 0.5 µg/mL of USP Amlodipine Related Compound A RS, and 0.8 µg/mL of USP Olmesartan Medoxomil RS in Diluent from Standard solution

**Sample solution:** Use the Sample stock solution, prepared as directed in the Assay.

**System suitability**

**Samples:** Standard solution and Sensitivity solution

[Note—See Table 7 for relative retention times.]

**Suitability requirements**

- **Tailing factor:** NMT 2.0 for amlodipine related compound A, amlodipine, and olmesartan medoxomil peaks, Standard solution

- **Relative standard deviation:** NMT 5.0% for amlodipine related compound A, amlodipine, and olmesartan medoxomil peaks, Standard solution

- **Signal-to-noise ratio:** NLT 10 for amlodipine related compound A, amlodipine, and olmesartan medoxomil peaks, Sensitivity solution

**Analysis**

**Samples:** Standard solution and Sample solution

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

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

- \(r_U\) = peak response of amlodipine related compound A from the Sample solution
\( r_S \) = peak response of amlodipine related compound A from the *Standard solution*
\( C_S \) = concentration of *USP Amlodipine Related Compound A RS* in the *Standard solution* (mg/mL)
\( C_U \) = nominal concentration of amlodipine in the *Sample solution* (mg/mL)
\( M_{r1} \) = molecular weight of amlodipine related compound A free base, 406.86
\( M_{r2} \) = molecular weight of amlodipine related compound A, 522.94

Calculate the percentage of any unspecified amlodipine related impurity in the portion of Tablets taken:

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

\( r_U \) = peak response of any unspecified amlodipine related impurity from the *Sample solution*
\( r_S \) = peak response of amlodipine from the *Standard solution*
\( C_S \) = concentration of *USP Amlodipine Besylate RS* in the *Standard solution* (mg/mL)
\( C_U \) = 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 olmesartan or any unspecified olmesartan medoxomil related impurity in the portion of Tablets taken:

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

\( r_U \) = peak response of olmesartan or any unspecified olmesartan medoxomil related impurity from the *Sample solution*
\( r_S \) = peak response of olmesartan medoxomil from the *Standard solution*
\( C_S \) = concentration of *USP Olmesartan Medoxomil RS* in the *Standard solution* (mg/mL)
\( C_U \) = nominal concentration of olmesartan medoxomil in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 7*.

**Table 7**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzenesulfonic acid(^a)</td>
<td>0.13</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan(^a)</td>
<td>0.25</td>
<td>2.0</td>
</tr>
<tr>
<td>Amlodipine related compound A(^c)</td>
<td>0.36</td>
<td>0.5</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.47</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan medoxomil related compound A(^d,e)</td>
<td>1.13</td>
<td>—</td>
</tr>
<tr>
<td>Name</td>
<td>Relative Retention Time</td>
<td>Acceptance Criteria, NMT (%)</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Olmesartan olefinic impurity[^a^]</td>
<td>1.50</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan N-alkyl impurity[^a^][^b^]</td>
<td>2.03</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified amlodipine or olmesartan medoxomil related impurity[^b^]</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities[^i^]</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

[^a^] This peak is due to the counterion and is not to be reported or included in the total impurities.

[^b^] 1-{[2′-(1H-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid.

[^c^] 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].

[^d^] 1-{[2′-(1H-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one.

[^e^] 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.

[^f^] (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-((2′-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-4-(prop-1-en-2-yl)-2-propyl-1H-imidazole-5-carboxylate.

[^g^] (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2′-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate.

[^h^] The relative retention times for unspecified amlodipine related impurities are up to 1.0. The relative retention times for unspecified olmesartan medoxomil related impurities are after 1.0 and also at 0.45, 0.60, 0.76, 0.79, and 0.92.

[^i^] Excluding olmesartan.

**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 *Dissolution* test used only if *Test 1* is not used.

**• USP Reference Standards (11)**

- USP Amlodipine Besylate RS
- USP Amlodipine Related Compound A RS
- 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate] fumarate. $C_{20}H_{23}ClN_2O_5 \cdot C_4H_4O_4$ 522.94
- USP Olmesartan Medoxomil RS