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 ($C_{20}H_{25}ClN_2O_5$) and NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$).

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

Time (min)	Solution A (%)	Solution B (%)
0	68	32
12	68	32
15	30	70
21	30	70
23	68	32
25	68	32

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

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Nominal Concentration of Amlodipine (mg/mL)	Nominal Concentration of Olmesartan Medoxomil (mg/mL)
5/20, 10/40	0.5	2
5/40	0.25	2
10/20	0.5	1

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

Table 3

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Nominal Concentration of Amlodipine (mg/mL)	Nominal Concentration of Amlodipine/ Olmesartan Medoxomil (mg/mL)
5/20, 10/40	0.04	0.16
5/40	0.02	0.16
10/20	0.04	0.08

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 ($C_{20}H_{25}ClN_2O_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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 ($C_{29}H_{30}N_6O_6$) in the portion of Tablets taken:

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

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* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 254 nm

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

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 ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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 concentration (C_1 or C_2) of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) in the sample withdrawn from the vessel at the 30- or 45-min time point:

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

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 ($C_{29}H_{30}N_6O_6$) dissolved:

$$\text{Result} = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

C_2 = concentration of olmesartan medoxomil in the *Sample solution* at the 45-min time point (mg/mL)

V = volume of *Medium*, 900 mL

V_S = volume of the *Sample solution* withdrawn at the 30-min time point (mL)

C_1 = concentration of olmesartan medoxomil in the *Sample solution* at the 30-min time point (mg/mL)

L = 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

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Concentration of USP Amlodipine Besylate RS (mg/mL)	Concentration of USP Olmesartan Medoxomil RS (mg/mL)
5/20	0.0075	0.022
5/40	0.0075	0.044
10/20	0.015	0.022
10/40	0.015	0.044

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 ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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 ($C_{29}H_{30}N_6O_6$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

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 ($C_{20}H_{25}ClN_2O_5$) and NLT 70.0% (Q) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) 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

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Concentration of USP Amlodipine Besylate RS (mg/mL)	Concentration of USP Olmesartan Medoxomil RS (mg/mL)
5/20	0.00775	0.0225
5/40	0.00775	0.045
10/20	0.0155	0.0225
10/40	0.00775	0.0225

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*

[NOTE—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 ($C_{20}H_{25}ClN_2O_5$) dissolved at time point 1:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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 ($C_{29}H_{30}N_6O_6$) in the portion of sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = (r_i/r_S) \times C_S \times D$$

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 ($C_{29}H_{30}N_6O_6$) dissolved at time point 2:

$$\text{Result} = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

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 and replaced with *Medium*, 10 mL

L = label claim of olmesartan medoxomil (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and NLT 70% (Q) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) are dissolved. (See *Table 6*.)

Table 6

Time point (*i*)	Time (min)
1	15
2	45

▲**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 ($C_{20}H_{25}ClN_2O_5$) dissolved at time point 1:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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*:

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

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):

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

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):

$$C_i = (r_i/r_S) \times C_S$$

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:

$$\text{Result} = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

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. ▲(TBD)

- **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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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:

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

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

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benzenesulfonic acid[a]	0.13	—
Olmesartan[b]	0.25	2.0
Amlodipine related compound A[c]	0.36	0.5
Amlodipine	0.47	—
Olmesartan medoxomil	1.0	—
Olmesartan medoxomil related compound A[d,e]	1.13	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Olmesartan olefinic impurity[f,e]	1.50	—
Olmesartan *N*-alkyl impurity[g,e]	2.03	—
Any unspecified amlodipine or olmesartan medoxomil related impurity[h]	—	0.2
Total impurities[i]	—	2.0

[a] This peak is due to the counterion and is not to be reported or included in the total impurities.
[b] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-2-yl)-2-propyl-1*H*-imidazole-5-carboxylic acid.
[c] 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
[d] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1*H*-furo[3,4-*d*]imidazol-6(4*H*)-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′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-4-(prop-1-en-2-yl)-2-propyl-1*H*-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-2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-1*H*-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

Page Information:

Not Applicable

Current DocID: