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Amlodipine, Valsartan, and Hydrochlorothiazide Tablets

DEFINITION

Amlodipine, Valsartan, and Hydrochlorothiazide Tablets contain NLT 92.5% and NMT 107.5% each of the labeled amounts of amlodipine ($C_{20}H_{25}ClN_2O_5$), valsartan ($C_{24}H_{29}N_5O_3$), and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

- **A.** The UV absorption spectra of the amlodipine, valsartan, and hydrochlorothiazide peaks of *Sample solution A*, *Sample solution B*, and *Sample solution C*, and those of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the Assay.
- **B.** The retention times of the amlodipine, valsartan, and hydrochlorothiazide peaks of *Sample solution A*, *Sample solution B*, and *Sample solution C* correspond to those of the *Standard solution*, as obtained in the Assay.

ASSAY

• **PROCEDURE**

Use amber glassware for all solutions containing drug substances.

Solution A: Acetonitrile, water, and phosphoric acid (50:950:1)

Solution B: Acetonitrile, water, and phosphoric acid (950:50:1)

Mobile phase: See [Table 1](#).

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
3	50	50
6	40	60
10	5	95
10.1	95	5
15	95	5

Diluent: Acetonitrile and water (500:500)

0.1% Phosphoric acid: Water and phosphoric acid (1000:1)

Standard solution: 0.14 mg/mL of [USP Amlodipine Besylate RS](#), 0.064 mg/mL of [USP Valsartan RS](#), and 0.025 mg/mL of [USP Hydrochlorothiazide RS](#) in *Diluent*

Sample stock solution: Transfer NLT 10 Tablets into a suitable volumetric flask. Add 0.1% Phosphoric acid to 4% of the total volume to disperse the Tablets. Sonicate for 10 min. Add 4% of the total volume of acetonitrile, swirl to mix, and add 60% of the total volume of *Diluent*. Sonicate for 20 min. Dilute with *Diluent* to volume to obtain solutions of nominal concentrations stated in [Table 2](#). Centrifuge, and use the clear supernatant.

Table 2

Tablet Strength Amlodipine/ Valsartan/ Hydrochlorothiazide (mg/mg/mg)	Nominal Concentration of Amlodipine (mg/mL)	Nominal Concentration of Valsartan (mg/mL)	Nominal Concentration of Hydrochlorothiazide (mg/mL)
5/160/12.5	0.1	3.2	0.25

Tablet Strength Amlodipine/ Valsartan/ Hydrochlorothiazide (mg/mg/mg)	Nominal Concentration of Amlodipine (mg/mL)	Nominal Concentration of Valsartan (mg/mL)	Nominal Concentration of Hydrochlorothiazide (mg/mL)
10/160/12.5	0.2	3.2	0.25
5/160/25	0.1	3.2	0.5
10/160/25	0.2	3.2	0.5
10/320/25	0.1	3.2	0.25

Sample solution A: Nominally equivalent to 0.1 mg/mL of amlodipine in *Diluent* from *Sample stock solution*

Sample solution B: Nominally equivalent to 0.064 mg/mL of valsartan in *Diluent* from *Sample stock solution*

Sample solution C: Nominally equivalent to 0.025 mg/mL of hydrochlorothiazide in *Diluent* from *Sample stock solution*

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 225 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 3-μm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for amlodipine, valsartan, and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for amlodipine, valsartan, and hydrochlorothiazide

Analysis

Samples: *Standard solution*, *Sample solution A*, *Sample solution B*, and *Sample solution C*

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 *Sample solution A*

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 *Sample solution A* (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 valsartan ($C_{24}H_{29}N_5O_3$) in the portion of Tablets taken:

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

r_U = peak response of valsartan from *Sample solution B*

r_S = peak response of valsartan from the *Standard solution*

C_S = concentration of [USP Valsartan RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of valsartan in *Sample solution B* (mg/mL)

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

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

r_U = peak response of hydrochlorothiazide from *Sample solution C*

r_s = peak response of hydrochlorothiazide from the *Standard solution*

C_s = concentration of [USP Hydrochlorothiazide RS](#) in the *Standard solution* (mg/mL)

C_u = nominal concentration of hydrochlorothiazide in *Sample solution C* (mg/mL)

Acceptance criteria: 92.5%–107.5%

PERFORMANCE TESTS

• [DISSOLUTION \(711\)](#)

Test 1

Buffer: Dissolve 6.805 g of monobasic potassium phosphate and 0.896 g of sodium hydroxide in 1000 mL of water. Adjust with 0.2 N sodium hydroxide or 1 M phosphoric acid to a pH of 6.8.

Medium: *Buffer*; 900 mL

Apparatus 2

For 5/160/12.5, 10/160/12.5, 5/160/25, and 10/160/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 50 rpm

For 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 55 rpm

Time: 30 min

Solution A: Acetonitrile, water, and phosphoric acid (50:950:1)

Solution B: Acetonitrile, water, and phosphoric acid (950:50:1)

Mobile phase: See [Table 3](#).

Table 3

Time (min)	Solution A (%)	Solution B (%)
0.00	67	33
2.50	23	77
2.51	67	33
4.00	67	33

Diluent: 1 mg/mL of polysorbate 80 in *Buffer*

Standard stock solution A: 0.07 mg/mL of USP Amlodipine Besylate and 0.124 mg/mL of [USP Hydrochlorothiazide RS](#). Initially dissolve with 4% of the total volume of methanol, and dilute with *Diluent* to volume.

Standard stock solution B: 3.2 mg/mL of [USP Valsartan RS](#) in methanol

Standard solution: 0.014 mg/mL of [USP Amlodipine Besylate RS](#), 0.16 mg/mL of [USP Valsartan RS](#), and 0.0248 mg/mL of [USP Hydrochlorothiazide RS](#) in *Diluent* from *Standard stock solution A* and *Standard stock solution B*, respectively

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size. Discard at least the first 10 mL of the filtrate.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 5-cm; 3-μm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume

For 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 5 μL

For 5/160/12.5, 10/160/12.5, 5/160/25, and 10/160/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 10 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 3.0 between amlodipine and valsartan

Tailing factor: NMT 2.0 for amlodipine, valsartan, and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for amlodipine, valsartan, and hydrochlorothiazide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L_1) \times 100$$

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_1 = label claim of amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_2) \times 100$$

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

r_S = peak response of valsartan from the *Standard solution*

C_S = concentration of [USP Valsartan RS](#) in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L_2 = label claim of valsartan (mg/Tablet)

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_3) \times 100$$

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

r_S = peak response of hydrochlorothiazide from the *Standard solution*

C_S = concentration of [USP Hydrochlorothiazide RS](#) in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L_3 = label claim of hydrochlorothiazide (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) is dissolved, NLT 80% (Q) of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) is dissolved, and NLT 80% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

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

Medium: Proceed as directed under *Dissolution Test 1*; 900 mL.

Apparatus 2

For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 5/80/12.5 (mg/mg/mg): 50 rpm

For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 10/320/25 (mg/mg/mg): 55 rpm

Times

For valsartan and hydrochlorothiazide: 30 min

For amlodipine: 45 min

Buffer: Mix 7.0 mL of [triethylamine](#) with 1000 mL of water. Adjust with [phosphoric acid](#) to a pH of 3.0.

Solution A: [Acetonitrile](#) and *Buffer* (10:90)

Solution B: [Acetonitrile](#) and *Buffer* (90:10)

Mobile phase: See [Table 4](#).

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	90	10