Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Oct-2024
Document Type: USP Monographs
DocId: GUID-54821A7B-3598-496E-9DE0-0B3FB91C3483_6_en-US
DOI: https://doi.org/10.31003/USPNF_M3580_06_01
DOI Ref: ow3bg

Amlodipine and Benazepril Hydrochloride Capsules

DEFINITION

Amlodipine and Benazepril Hydrochloride Capsules contain an amount of amlodipine besylate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) and NLT 90.0% and NMT 110.0% of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$).

IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*
- **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**

Buffer 1: 0.7% (v/v) triethylamine in water. Adjust with phosphoric acid to a pH of 3.0, and add 1.2 g/L of ▲tetrabutylammonium▲ (ERR-1-Oct-2024) hydrogen sulfate to this solution.

Buffer 2: 0.7% (v/v) triethylamine in water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile, methanol, and *Buffer 1* (10:30:70)

Diluent: Acetonitrile, methanol, and *Buffer 2* (20:30:50)

Standard solution: Concentrations of USP Amlodipine Besylate RS and USP Benazepril Hydrochloride RS in *Diluent* as directed in *Table 1*.

Table 1

Strength of Capsule Amlodipine/Benazepril Hydrochloride (mg/mg)	Concentration of USP Amlodipine Besylate RS/ USP Benazepril Hydrochloride RS (mg/mL)
2.5/10	0.18/0.5
5/20	0.18/0.5
5/10	0.18/0.25
10/20	0.36/0.5
5/40 and 10/40	0.056/0.16

Sample solution: Transfer the contents of 5 Capsules into a suitable volumetric flask to obtain nominal concentrations as given in *Table 2*. Add *Diluent* to about 70% of the volume of the flask and keep on a rotary shaker for about 45 min, sonicate for about 30 min with occasional shaking, and dilute with *Diluent* to volume. Centrifuge a portion of the solution for about 10 min, and pass through a filter of 0.45-µm pore size.

Table 2

Strength of Capsule Amlodipine/Benazepril Hydrochloride (mg/mg)	Nominal Concentration of Amlodipine/Benazepril Hydrochloride (mg/mL)
2.5/10	0.125/0.5
5/20	0.125/0.5

Strength of Capsule Amlodipine/Benazepril Hydrochloride (mg/mg)	Nominal Concentration of Amlodipine/Benazepril Hydrochloride (mg/mL)
5/10	0.125/0.25
10/20	0.25/0.5
5/40	0.02/0.16
10/40	0.04/0.16

Chromatographic system

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

Mode: LC

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

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

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of amlodipine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for the amlodipine and benazepril peaks

Relative standard deviation: NMT 2.0% for the amlodipine and benazepril peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) in the portion of Capsules 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 benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$), in the portion of Capsules taken:

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

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

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

C_S = concentration of USP Benazepril Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of benazepril hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Time: 30 min

Buffer: 2.72 g/L of potassium phosphate, monobasic in water. Add 0.2% (v/v) triethylamine per liter. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile, methanol, and *Buffer* (15:35:50)

Standard solution: Concentrations of USP Amlodipine Besylate RS and USP Benazepril Hydrochloride RS in *Medium* prepared as directed in *Table 3*.

Table 3

Strength of Capsule Amlodipine/Benazepril Hydrochloride (mg/mg)	Concentration of USP Amlodipine Besylate RS/ USP Benazepril Hydrochloride RS (mg/mL)
2.5/10	0.0077/0.0225
5/10	0.0154/0.0225
5/20	0.0154/0.045
10/20	0.0308/0.045
5/40	0.0136/0.08
10/40	0.028/0.08

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 237 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for the amlodipine and benazepril peaks

Relative standard deviation: NMT 2.0% for the amlodipine and benazepril peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) dissolved:

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

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)

L = label claim (mg/Capsule)

M_{r1} = molecular weight of amlodipine, 408.88

M_{r2} = molecular weight of amlodipine besylate, 567.05

V = volume of *Medium*, 500 mL

Calculate the percentage of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) dissolved:

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

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

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

C_S = concentration of USP Benazepril Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) and benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) is dissolved.

- **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

- **Organic Impurities**

Buffer 1, Buffer 2, and **Diluent:** Prepare as directed in the *Assay*.

Solution A: Acetonitrile and *Buffer 1* (20:80)

Solution B: Methanol and *Buffer 1* (80:20)

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	85	15
100	30	70
101	85	15
110	85	15

Standard solution: 1 µg/mL each of USP Amlodipine Besylate RS and USP Amlodipine Related Compound A RS and 3 µg/mL each of USP Benazepril Hydrochloride RS and USP Benazepril Related Compound C RS in *Diluent*

Sample solution: Nominally 0.25 mg/mL of amlodipine in *Diluent* prepared as follows. Transfer a portion of the finely powdered contents of Capsules (NLT 20), equivalent to 25 mg of amlodipine, to a 100-mL volumetric flask. Add *Diluent*, about 70% of the volume of the flask, sonicate for 30 min with intermittent shaking, and dilute with *Diluent* to volume. Pass through a membrane filter of 0.45-µm pore size. [Note—The benazepril hydrochloride concentration may vary depending on the ratio of amlodipine to benazepril hydrochloride in the Capsule.]

Chromatographic system

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

Mode: LC

Detector: UV 237 nm

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

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 40 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between the amlodipine and benazepril peaks

Tailing factor: NMT 2.0 for the amlodipine and benazepril peaks

Relative standard deviation: NMT 5.0% for the amlodipine, amlodipine related compound A, benazepril, and benazepril related compound C peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amlodipine related compound A (free base) in the portion of Capsules 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), 408.88

M_{r2} = molecular weight of amlodipine related compound A, 522.94

Calculate the percentage of benazepril related compound C in the portion of Capsules taken:

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

r_U = peak response of benazepril related compound C from the *Sample solution*

r_S = peak response of benazepril related compound C from the *Standard solution*

C_S = concentration of USP Benazepril Related Compound C RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of benazepril hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any unspecified degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each unspecified degradation product from the *Sample solution*

r_T = sum of responses of all peaks from the *Sample solution*

Acceptance criteria: See *Table 5*. [NOTE—Disregard the peaks at relative retention times of 0.09 and 0.10.]

Table 5

Impurity Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benazepril related compound C	0.23	3.0
Amlodipine related compound A[a]	0.44	1.0
Amlodipine	1.00	—
Benazepril	1.20	—
Any unspecified degradation product	—	0.2
Total degradation products[b]	—	5.0

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

[b] Sum of all degradation products exclude process related impurities.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **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 Benazepril Hydrochloride RS

USP Benazepril Related Compound C RS

(3*S*)-3-[[(1*S*)-1-Carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benazepine]-1-acetic acid;
Also known as (*S*)-2-{[(*S*)-1-(Carboxymethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl]amino}-4-phenylbutanoic acid.

$C_{22}H_{24}N_2O_5$ 396.44

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
AMLODIPINE AND BENAZEPRIL HYDROCHLORIDE CAPSULES	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 45(3)
Current DocID: GUID-54821A7B-3598-496E-9DE0-0B3FB91C3483_6_en-US
DOI: https://doi.org/10.31003/USPNF_M3580_06_01
DOI ref: ow3bg