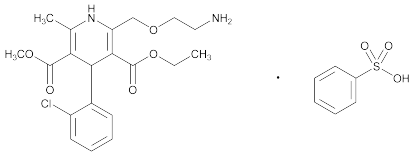
Amlodipine Besylate



$C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ 567.05
3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate.
3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(*o*-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate [111470-99-6].
Monohydrate 585.07

» Amlodipine Besylate is anhydrous or hydrated and contains not less than 97.0 percent and not more than 102.0 percent of $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, protected from light. Store at room temperature.

USP Reference standards ⟨11⟩**—**
USP Amlodipine Besylate RS

Labeling—Where it is the hydrated form, the label so indicates.

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Optical rotation ⟨781A⟩**:** between -0.10° and +0.10°, measured at 20°.

Test solution: 10 mg per mL, in methanol.

Water, *Method I* ⟨921⟩**:** not more than 0.5% for the anhydrous form. If labeled as the hydrated form, the limit is between 3.1% and 5.0%.

Residue on ignition ⟨281⟩**:** not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

TEST 1—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Transfer 140 mg of Amlodipine Besylate to a 2-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

System suitability solution—Transfer about 14 mg of USP Amlodipine Besylate RS to a suitable container, dissolve in 0.2 mL of methanol, and mix.

Standard stock solution—Dissolve an accurately weighed quantity of USP Amlodipine Besylate RS in methanol to obtain a solution containing 7.0 mg per mL.

Standard solution 1—Transfer 3.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Standard solution 2—Transfer 1.0 mL of the *Standard stock solution* to another 100-mL volumetric flask, dilute with methanol to volume, and mix.

Application volume: 10 µL.

Developing solvent system—Use the upper layer of a mixture of methyl isobutyl ketone, water, and glacial acetic acid (50:25:25).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Dry the plate for 15 minutes at 80°. Examine the plate under UV light at 254 nm and 365 nm. The chromatogram from the *System suitability solution* shows two clearly separated minor spots with R_F values of about 0.18 and 0.22. Compare the intensities of any secondary spots observed in the chromatogram of the *Test solution* with those of the principal spots in the chromatograms of the *Standard solutions*. Any spot obtained from the *Test solution,* except for the principal spot, is not greater in size than the spot obtained from *Standard solution 1* (0.3%), and at most two spots are more intense than the spot obtained from *Standard solution 2* (0.1%).

TEST 2—

pH 3.0 Buffer and *Mobile phase*—Prepare as directed in the *Assay.*

System suitability solution—Dissolve about 5 mg of Amlodipine Besylate in 5 mL of hydrogen peroxide, and heat at 70° for 45 minutes.

Standard solution—Dissolve an accurately weighed quantity of USP Amlodipine Besylate RS in *Mobile phase* to obtain a solution having a known concentration of about 0.003 mg per mL.

Test solution—Transfer about 50 mg of Amlodipine Besylate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between amlodipine impurity A and amlodipine is not less than 4.5. [NOTE—For the purpose of identification, the relative retention times are about 0.2 for benzene sulfonate, 0.5 for amlodipine impurity A, and 1.0 for amlodipine. Amlodipine impurity A is 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate.] Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the standard deviation for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for a period of time that is about 3 times the retention time of amlodipine, and measure the peak responses. Calculate the percentage of each impurity in the portion of Amlodipine Besylate taken by the formula:

$$100(1/F)(C_S/C_T)(r_i/r_S)$$

in which F is the relative response factor, which is equal to 0.5 for amlodipine impurity A and to 1.0 for other impurities; C_S and C_T are the concentrations, in mg per mL, of amlodipine besylate in the *Standard solution* and the *Test solution,* respectively; r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for amlodipine besylate obtained from the *Standard solution:* not more than 0.3% of amlodipine impurity A is found, and not more than 0.3% of total other impurities is found. Disregard any peak less than 0.03%, and disregard any peak due to benzene sulfonate.

Assay—

pH 3.0 Buffer—Dissolve 7.0 mL of triethylamine in 800 mL of water. Adjust with phosphoric acid to a pH of 3.0 ± 0.1, and dilute with water to 1 L.

Mobile phase—Prepare a filtered and degassed mixture of *pH 3.0 Buffer,* methanol, and acetonitrile (50:35:15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Amlodipine Besylate RS in *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay preparation—Transfer about 50 mg of Amlodipine Besylate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 237-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ in the portion of Amlodipine Besylate taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of amlodipine besylate in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Amlodipine Besylate Tablets

DEFINITION

Amlodipine Besylate Tablets contain NLT 90% and NMT 110% of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$).

IDENTIFICATION

- **A. Ultraviolet Absorption** ⟨**197U**⟩
  Standard solution and **Sample solution:** Prepare as directed in the test for *Dissolution*.
  Acceptance criteria: Meet the requirements
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**
  Buffer: Add 7.0 mL of triethylamine into a 1000-mL flask containing 900 mL of water. Adjust the solution with phosphoric acid to a pH of 3.0 ± 0.1. Dilute with water to volume, and mix well.
  Mobile phase: Methanol, acetonitrile, and *Buffer* (35:15:50)
  System suitability solution: 0.02 mg/mL of USP Amlodipine Besylate RS and 0.002 mg/mL of USP Amlodipine Related Compound A RS in *Mobile phase*
  Standard solution: 0.02 mg/mL of amlodipine prepared from USP Amlodipine Besylate RS in *Mobile phase*
  Sample stock solution: Place 5 Tablets into a 500-mL volumetric flask. Add 50 mL of *Mobile phase* to the flask, and swirl to disintegrate the Tablets. Add 300 mL of *Mobile phase*, insert the stopper into the flask, and shake on a reciprocating shaker for 30 min. Dilute with *Mobile phase* to volume, and mix well.
  Sample solution: 0.02 mg/mL of amlodipine from the *Sample stock solution* in *Mobile phase*. Pass the sample through a syringe tip filter of 0.45-µm pore size.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 237 nm
  Column: 3.9-mm × 15-cm; 5-µm packing L1
  Flow rate: 1 mL/min
  Injection size: 50 µL
  System suitability
  Sample: *System suitability solution*
  [Note—The run time is about three times the retention of the amlodipine peak.]
  Suitability requirements
  Resolution: NLT 8.5 between amlodipine and amlodipine related compound A
  Tailing factor: NMT 2.0 for both amlodipine and amlodipine related compound A
  Relative standard deviation: NMT 1.0% for amlodipine and NMT 5.0% for amlodipine related compound A
  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 Tablets taken:

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

  r_U = peak response from the *Sample solution*
  r_S = peak response 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)
  Acceptance criteria: 90%–110% of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$)

PERFORMANCE TESTS

- **Dissolution** ⟨**711**⟩
  [Note—Do not expose any of the solutions to stainless steel because of the degradation of amlodipine.]
  Medium: 0.01 N hydrochloric acid; 500 mL
  Apparatus 2: 75 rpm. [Note—Use paddles covered with Teflon or made of any inert material except stainless steel.]
  Time: 30 min
  Standard solution: Make appropriate dilutions of USP Amlodipine Besylate RS in *Medium* to obtain the following concentrations: 0.00695 mg/mL for Tablets labeled to contain 2.5 mg; 0.0139 mg/mL for Tablets labeled to contain 5 mg; 0.0278 mg/mL for Tablets labeled to contain 10 mg. These solutions are stable for one day.
  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
  Analysis: Determine the amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) dissolved by using UV absorption at the wavelength of maximum absorbance at about 239 nm on portions of the *Sample solution* in comparison with the *Standard solution,* using a 1-cm quartz cell and the *Medium* as blank.
  Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times D \times (M_{r1}/M_{r2}) \times V \times 100$$

  A_U = absorbance of the *Sample solution*
  A_S = absorbance of the *Standard solution*
  C_S = concentration of the *Standard solution* (mg/mL)
  L = label claim (mg/Tablet)
  D = dilution factor of the *Sample solution*
  M_{r1} = molecular weight of amlodipine, 408.88
  M_{r2} = molecular weight of amlodipine besylate, 567.06
  V = volume of *Medium*, 500 mL
  Tolerances: NLT 75% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) is dissolved.
- **Uniformity of Dosage Units** ⟨**905**⟩**:** Meet the requirements