Amlodipine Besylate

C_{20}H_{25}ClN_2O_5 \cdot C_6H_5O_3S \quad 567.05
3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.

Monohydrate \quad 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_5O_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—
Adsortent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Transfer 140 mg of Amlodipine Besylate to a 2-mL volumetric flahs, 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:

\[ 100 \times \frac{(F(C_6 / C_7))}{(F(C_i / C_j))} \]

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_i and C_j 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_j 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 C20H25ClN2O5 to C20H25N2O5 in the portion of Amlodipine Besylate taken by the formula: 100(Cs/C0)(r0 / rs) in which Cs and C0 are the concentrations, in mg per mL, of amlodipine besylate in the Standard preparation and the Assay preparation, respectively; and r0 and rs 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 (C20H25ClN2O5).

IDENTIFICATION
• A. ULTRAVIOLET ABSORPTION (1971)
  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.]
  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 (C20H25ClN2O5) in the portion of Tablets taken: Result = (r1/r0) × (C0/Cs) × 100

  r0 = peak response from the Sample solution
  r1 = peak response from the Standard solution
  C0 = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
  Cs = concentration of USP Amlodipine Related Compound A

Acceptance criteria: 90%–110% of the labeled amount of amlodipine (C20H25ClN2O5)

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 (C20H25ClN2O5) 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 (C20H25ClN2O5) dissolved: Result = (A0/A1) × (Cs/L) × D × (M1/M0) × V × 100

  A0 = absorbance of the Sample solution
  A1 = absorbance of the Standard solution
  Cs = concentration of the Standard solution (mg/mL)
  L = label claim (mg/Tablet)
  D = dilution factor of the Sample solution
  M1 = molecular weight of amlodipine, 408.88
  M0 = molecular weight of amlodipine besylate, 567.06
  V = volume of Medium, 500 mL

  Tolerances: NLT 75% (Q) of the labeled amount of amlodipine (C20H25ClN2O5) is dissolved.

• UNIFORMITY OF DOSAGE UNITS (905): Meet the requirements