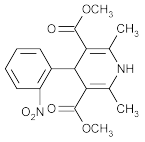
Nifedipine



$C_{17}H_{18}N_2O_6$ 346.33

3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate [21829-25-4].

» Nifedipine contains not less than 98.0 percent and not more than 102.0 percent of $C_{17}H_{18}N_2O_6$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩**—**

USP Nifedipine RS

USP Nifedipine Nitrophenylpyridine Analog RS
Dimethyl 4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate.
$C_{17}H_{16}N_2O_6$ 344.33

USP Nifedipine Nitrosophenylpyridine Analog RS
Dimethyl 4-(2-nitrosophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate.
$C_{17}H_{16}N_2O_5$ 328.33

[NOTE—Nifedipine, when exposed to daylight and certain wavelengths of artificial light, readily converts to a nitrosophenylpyridine derivative. Exposure to UV light leads to the formation of a nitrophenylpyridine derivative. Perform assays and tests in the dark or under golden fluorescent or other low-actinic light. Use low-actinic glassware.]

Identification—

A: *Infrared Absorption* ⟨197K⟩—Do not dry specimens.

B: *Ultraviolet Absorption* ⟨197U⟩—

Spectral range: 450 to 200 nm.

Solution—To a 10-mL volumetric flask containing 14 mg of Nifedipine add 1.0 mL of chloroform, dilute with methanol to volume, and mix. Pipet a 1.0-mL aliquot of the solution into a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Medium: methanol.

C: 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*.

Melting range, *Class Ia* ⟨741⟩: between 171° and 175°.

Loss on drying ⟨731⟩**—**Dry it at 105° to constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%, an ignition temperature of 600° being used.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Perchloric acid titration—Transfer about 4 g of Nifedipine, accurately weighed, to a 250-mL conical flask, and dissolve in 160 mL of glacial acetic acid with the aid of an ultrasonic bath. Add 3 drops of *p*-naphtholbenzein TS, and titrate to a green endpoint with 0.1 N perchloric acid VS: not more than 0.12 mL of 0.1 N perchloric acid is consumed for each g of Nifedipine.

Chloride and Sulfate—To 5.0 g of Nifedipine in a 140-mL beaker add 4.0 mL of 6 N acetic acid and 46 mL of water. Bring carefully to a boil on a hot plate, cool, and filter through paper free of chloride and sulfate. Use this Nifedipine filtrate for the following tests.

Chloride—Pipet 2.5 mL of the Nifedipine filtrate into a 50-mL color-comparison tube, and add 12.5 mL of water. Into a matched color-comparison tube pipet 10 mL of a Standard solution containing 8.2 µg of sodium chloride per mL corresponding to 5 µg of chloride per mL, add 5.0 mL of water, and mix. To each tube add 0.15 mL of 0.3 M nitric acid and 0.3 mL of silver nitrate TS, and mix: the opalescence exhibited by the Nifedipine filtrate does not exceed that of the Standard solution (0.02%).

Sulfate—Pipet into each of two 50-mL matched color-comparison tubes 1.5 mL of sulfate solution consisting of sufficient potassium sulfate dissolved in water to obtain a sulfate concentration of 10 µg per mL. To each tube add, successively and with continuous shaking, 0.75 mL of alcohol, 0.5 mL of a 6.1% aqueous solution of barium chloride, and 0.25 mL of 6 N acetic acid. Shake for an additional 30 seconds. Pipet into one tube, designated the Standard tube, 15 mL of the sulfate solution. Pipet into the other tube, designated the Specimen tube, 3 mL of the Nifedipine filtrate and 12 mL of water: the turbidity exhibited by the Specimen tube does not exceed that of the Standard tube (0.05%).

Related compounds—[NOTE—Protect the *Standard nifedipine solution* and the *Test preparation* from actinic light. Conduct this test promptly after preparation of the *Standard nifedipine solution* and the *Test solution*.]

Mobile phase—Prepare as directed in the *Assay*.

Standard nifedipine solution—Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol (about 1 mg per mL), and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 0.3 mg per mL.

Reference solution 1—Dissolve an accurately weighed quantity of USP Nifedipine Nitrophenylpyridine Analog RS in methanol (about 1 mg per mL), and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 0.6 µg per mL.

Reference solution 2—Dissolve an accurately weighed quantity of USP Nifedipine Nitrosophenylpyridine Analog RS in methanol (about 1 mg per mL), and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 0.6 µg per mL.

Standard solution—Transfer 5.0 mL of each of the two *Reference solutions* to a container, add 5.0 mL of *Mobile phase*, and mix.

Test solution—Prepare as directed for the *Assay preparation* in the *Assay*.

System suitability solution—Mix equal volumes of the *Standard nifedipine solution* and of each of the two *Reference solutions*.

Chromatographic system—Prepare as directed in the *Assay*. Chromatograph the *System suitability preparation*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between the nitrophenylpyridine analog and nitrosophenylpyridine analog peaks is not less than 1.5; the resolution, *R,* between the nitrosophenylpyridine analog and nifedipine peaks is not less than 1.0; and the relative standard deviation of the response for each analog in replicate injections is not more than 10%. The relative retention times are about 0.8 for the nitrophenylpyridine analog, about 0.9 for the nitrosophenylpyridine analog, and 1.0 for nifedipine.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of each related compound in the portion of Nifedipine taken by the formula:

$$250C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of the appropriate USP Nifedipine Analog RS, in the *Standard solution;* and r_U and r_S are the peak responses for the corresponding related compound obtained from the *Test solution* and the *Standard solution*, respectively. Not more than 0.2% of each of dimethyl

4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate and dimethyl- 4-(2-nitrosophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate, corresponding to Nifedipine Nitrophenylpyridine Analog and Nifedipine Nitrosophenylpyridine Analog, respectively, is found.

Assay—[NOTE—Protect the *Standard preparation* and the *Assay preparation* from actinic light. Conduct the *Assay* promptly after preparation of the *Standard preparation* and the *Assay preparation*.]

Mobile phase—Prepare a suitable mixture of water, acetonitrile, and methanol (50:25:25), and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol (about 1 mg per mL), and quantitatively dilute with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Transfer about 25 mg of Nifedipine, accurately weighed, to a 250-mL volumetric flask. Dissolve in 25 mL of methanol, dilute with *Mobile phase* to volume, and mix to obtain a solution having a concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 4.6-mm × 25-cm column that contains 5-µm 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 column efficiency is not less than 4000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 25 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 quantity, in mg, of $C_{17}H_{18}N_2O_6$ in the portion of Nifedipine taken by the formula:

$$250C(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of USP Nifedipine RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Nifedipine Capsules

» Nifedipine Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$).

Packaging and storage—Preserve in tight, light-resistant containers at a temperature between 15° and 25°.

USP Reference standards ⟨11⟩**—**
USP Nifedipine RS
USP Nifedipine Nitrophenylpyridine Analog RS
Dimethyl 4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate.
$C_{17}H_{16}N_2O_6$ 344.33
USP Nifedipine Nitrosophenylpyridine Analog RS
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[NOTE—Nifedipine, when exposed to daylight and certain wavelengths of artificial light, readily converts to a nitrosophenylpyridine derivative. Exposure to UV light leads to the formation of a nitrophenylpyridine derivative. Perform assays and tests in the dark or under golden fluorescent or other low-actinic light. Use low-actinic glassware.]

Identification—

A: *Visualizing solution*—In a 100-mL volumetric flask dissolve 3 g of bismuth subnitrate and 30 g of potassium iodide with 10 mL of 3 N hydrochloric acid. Dilute with water to volume, and mix. Prior to use, transfer 10.0 mL of solution to a 100-mL volumetric flask, add 10 mL of 3 N hydrochloric acid, dilute with water to volume, and mix.

Standard solution—Prepare a *Standard solution* of USP Nifedipine RS in methylene chloride containing about 1.2 mg per mL.

Test solution—Using the technique described under *Procedure for content uniformity* in the test for *Uniformity of dosage units*, transfer the contents of 3 Capsules to a centrifuge tube, rinsing the scissors with about 20 mL of 0.1 N sodium hydroxide. Pipet 25 mL of methylene chloride into the tube, insert a stopper, invert several times, and carefully release the pressure in the tube. Insert the stopper again tightly, and shake gently for 1 hour. Centrifuge the tube for 10 minutes at 2000 to 2500 rpm. Remove the supernatant aqueous phase by aspiration with a syringe, and transfer 5.0 mL of the clarified lower layer to a suitable vial.

Procedure—Mix equal portions of the *Standard solution* and the *Test solution*. Apply separately 500 µL each of the *Standard solution*, the *Test solution*, and their mixture to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.5-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram, protected from light, in a solvent system consisting of a mixture of ethyl acetate and cyclohexane (1:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and air-dry the plate until no odor is detectable. Immediately view the plate under short-wavelength UV light: each solution exhibits a dark blue major band at the same R_F value of about 0.3. Spray the plate with *Visualizing solution:* each solution exhibits a compact light orange band on a yellow background.

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*.

Dissolution ⟨711⟩**—**

Medium: simulated gastric fluid TS (without pepsin); 900 mL.

Apparatus 2: 50 rpm.

Time: 20 minutes.

Standard solution—Dissolve an accurately weighed quantity of USP Nifedipine RS in an amount of methanol not exceeding 2% of the final volume, and dilute quantitatively and stepwise, if necessary, with *Dissolution Medium* to obtain a solution having a known appropriate concentration.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 340 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with the *Standard solution*. [NOTE—Filters must be checked for absorptive loss of nifedipine.]

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{17}H_{18}N_2O_6$ is dissolved in 20 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Procedure for content uniformity—With the point of a pair of sharp scissors, make a small hole at the end of 1 Capsule. Squeeze most of the contents into a 200-mL volumetric flask, cut the capsule in half, and drop it into the flask. Rinse the scissors with about 20 mL of methanol, quantitatively collecting the rinse in the flask. Dilute with methanol to volume, and mix to obtain the test solution. Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol, and dilute quantitatively and stepwise with methanol to obtain a Standard solution having a known concentration of about 50 µg per mL. Concomitantly determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 350 nm, with a suitable spectrophotometer, using methanol as the