Nifedipine Extended-Release Tablets

DEFINITION

Nifedipine Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$). [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.** The retention time of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. ULTRAVIOLET ABSORPTION ⟨197U⟩**

Standard solution: Dissolve a quantity of USP Nifedipine RS in methanol to 1 mg/mL, and dilute with *Mobile phase* to obtain a solution having a known concentration of 0.02 mg/mL.

Sample solution: Prepare as directed for the *Sample solution* in the *Assay*, except to dilute further with *Mobile phase* to obtain a solution having a concentration of 0.02 mg/mL.

ASSAY

- **PROCEDURE**

[NOTE—Conduct the *Assay* promptly after preparation of the *Standard solution* and the *Sample solution*.]

Mobile phase: Acetonitrile, methanol, and water (25:25:50)

Standard stock solution: 1 mg/mL of USP Nifedipine RS in methanol

Standard solution: 0.1 mg/mL of USP Nifedipine RS from the *Standard stock solution* in *Mobile phase*

Sample stock solution: Dissolve an amount equivalent to 420 mg of nifedipine from powdered Tablets in 130 mL of water in a 250-mL volumetric flask; or transfer the intact Tablets to a 400-mL, high-speed blender cup containing 130 mL of water. Homogenize until a uniform suspension is achieved (about 2 min), and transfer the suspension with the aid of a mixture of acetonitrile and methanol (1:1) to a 250-mL volumetric flask. Dilute with a mixture of acetonitrile and methanol (1:1) to volume, and stir for 30 min. Centrifuge the resulting suspension to obtain a clear supernatant.

Sample solution: Transfer 3.0 mL of the *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume. Filter to obtain a solution having a concentration of 0.1 mg/mL of nifedipine. [NOTE—Reserve a portion of this solution for use as the *Sample solution* in the *Procedure* for *Organic Impurities*.]

Chromatographic system

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

Mode: LC

Detector: UV 265 nm

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

Guard column: 2.1-mm × 3-cm; packing L1

Flow rate: 1 mL/min

Injection size: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 4000 theoretical plates

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{17}H_{18}N_2O_6$ 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 Nifedipine RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

Medium: Water; 50 mL

Apparatus 7 (see *Drug Release* ⟨**724**⟩): 15–30 cycles/min. Do not use the reciprocating disk; use a 25-cm plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue. The solution containers are 25-mm test tubes, 150–200 mm in length, and the water bath is maintained at 37 ± 0.5°. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.

Times: 4, 8, 12, 16, 20, and 24 h

Diluent: A mixture of methanol and water (1:1)

Standard solution: Transfer 50 mg of USP Nifedipine RS to a 100-mL volumetric flask. Dissolve in 50 mL of methanol, and dilute with water to volume. Quantitatively dilute this solution with *Diluent* to obtain solutions having suitable known concentrations.

Sample solution: Use portions of the solution under test, passed through a 0.4-µm filter, suitably diluted with methanol, and stepwise if necessary, with *Diluent* to obtain a final mixture consisting of equal parts of methanol and water.

Spectrometric conditions

(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)

Mode: UV

Analytical wavelength: 338 nm

Cell: 0.5 cm

Analysis: Determine the amount of $C_{17}H_{18}N_2O_6$ released in the *Sample solution* at each 4-h interval from UV absorbances. [NOTE—For the 4-h time period, determine the absorbance at 456 nm, and use this determination to correct for excipient interference.]

Tolerances: The cumulative percentages of the labeled amount of $C_{17}H_{18}N_2O_6$, released at the times specified, conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved[a]
4	5%–17%
8	—
12	43%–80%
16	—
20	—
24	NLT 80%

[a] The amount dissolved is expressed in terms of the labeled Tablet strength rather than in terms of the labeled total contents.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Solution A: Dissolve 330.9 mg of sodium phosphate and 38 g of citric acid in water in a 1-L volumetric flask. Add 10 mL of phosphoric acid, and dilute with water to volume.
Medium: Mix 125.0 mL of *Solution A* and 1 L of 10% sodium lauryl sulfate solution, and dilute to 10 L. Adjust, if necessary, to a pH of 6.8; 900 mL.
Apparatus 2: 50 rpm, with sinkers (see *Figure 1*)

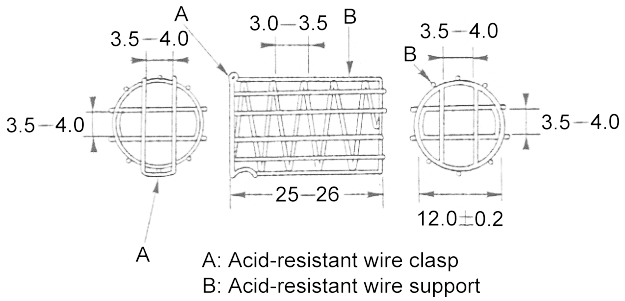

Figure 1

Times: 3, 6, and 12 h
Determine the amount of $C_{17}H_{18}N_2O_6$ dissolved by using the following method.
Mobile phase: Acetonitrile and water (7:3)
Standard stock solution: 1.11 mg/mL of USP Nifedipine RS in methanol
Standard solution: 0.1 mg/mL of USP Nifedipine RS from the *Standard stock solution* in *Medium*
Sample solution: Sample per *Dissolution* ⟨711⟩
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 350 nm
Column: 4.0-mm × 125-mm; 3-µm packing L1
Temperature: 40°
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 2000 theoretical plates
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the amount of $C_{17}H_{18}N_2O_6$ dissolved.
Tolerances: The percentages of the labeled amount of $C_{17}H_{18}N_2O_6$ released in vivo and dissolved at the times specified conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved
3	10%–30%
6	40%–65%
12	NLT 80%

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
For Tablets labeled to contain 30 mg of nifedipine: Phase 1
Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL
Apparatus 2: 100 rpm
Time: 1 h
Standard solution: 0.034 mg/mL of USP Nifedipine RS in *Medium*. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]
Sample solution: Sample per *Dissolution* ⟨711⟩
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 238 nm
Cell: 0.5 cm
Analysis
[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.]
Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1*, using filtered portions of the *Sample solution*, in comparison with the *Standard solution*, using the *Medium* as the blank.
For Tablets labeled to contain 30 mg of nifedipine: Phase 2
Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL
Apparatus 2: 100 rpm
Times: 1, 4, 8, and 12 h
Standard solution: 0.034 mg/mL of USP Nifedipine RS in *Medium*. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]
Sample solution: Sample per *Dissolution* ⟨711⟩
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 238 nm
Analysis: Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2*, using filtered portions of the *Sample solution*, in comparison with the *Standard solution*, using *Medium* as the blank.
Tolerances: The cumulative percentages of the labeled amount of $C_{17}H_{18}N_2O_6$, released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved[a]
1	NMT 30
4	30–55
8	NLT 60
12	NLT 80

[a] For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

For Tablets labeled to contain 60 mg of nifedipine: Phase 1

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL
Sample solution: Sample per *Dissolution* ⟨711⟩
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 238 nm
Analysis
[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.]
Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1*, using filtered portions of the *Sample solution*, in comparison with the *Standard solution*, using the *Medium* as the blank.
Apparatus 2: 100 rpm
Time: 25 min
Standard solution: 0.067 mg/mL of USP Nifedipine RS in *Medium*. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

For Tablets labeled to contain 60 mg of nifedipine: Phase 2
Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL
Apparatus 2: 100 rpm
Times: 1, 4, 8, and 12 h
Standard solution: 0.067 mg/mL of USP Nifedipine RS in *Medium*. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]
Sample solution: Sample per *Dissolution* ⟨711⟩
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 238 nm
Analysis: Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2*, using filtered portions of the *Sample solution*, in comparison with the *Standard solution*, using *Medium* as the blank.
Tolerances: The cumulative percentages of the labeled amount of $C_{17}H_{18}N_2O_6$, released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 4*.
Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL
Apparatus 2: 100 rpm
Times: 1, 4, and 12 h
Standard solution: 0.067 mg/mL of USP Nifedipine RS for Tablets labeled to contain 60 mg, and 0.034 mg/mL of USP Nifedipine RS for Tablets labeled to contain 30 mg, in *Medium*. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]
Sample solution: Sample per *Dissolution* ⟨711⟩
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: UV 238 nm
Cell: 0.5 cm
Analysis: Determine the amount of $C_{17}H_{18}N_2O_6$ released, using filtered portions of the *Sample solution*, in comparison with the *Standard solution*, using the *Medium* as the blank.
Tolerances: The cumulative percentages of the labeled amount of $C_{17}H_{18}N_2O_6$, released at the times specified, conform to *Acceptance Table 2*.

For Tablets Labeled to Contain 30 mg of Nifedipine

Time (h)	Amount Dissolved
1	12%–35%
4	44%–67%
12	NLT 80%

For Tablets Labeled to Contain 60 mg of Nifedipine

Time (h)	Amount Dissolved
1	10%–30%
4	40%–63%
12	NLT 80%

Test 5: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 5*.
Medium: Water; 50 mL
Apparatus 7
(See *Drug Release* ⟨724⟩.)
Use a 25-cm plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue; 30 dips/min. The solution containers are 25-mm test tubes, 150–200 mm in length, and the water bath is maintained at 37 ± 0.5°.
Times: 4, 12, and 24 h
Diluent A: Methanol and acetonitrile (1:1)
Diluent B: *Diluent A* and water (1:1)
Standard stock solution: 50 mg of USP Nifedipine RS in *Diluent A* and water (50:50)
Standard solution: 0.01, 0.05, and 0.20 mg/mL from *Standard stock solution* in *Diluent B* that are used at 4-, 12-, and 24-h sampling
Sample solution: Sample per *Dissolution* ⟨711⟩
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 238 nm
Cell: 0.5 cm
Analysis
[NOTE—For the 4-h time period, filter the solution under test, and determine the absorbance at 456 nm. Use this absorbance value to correct for excipient interference at the other time points.]
Determine the amount of nifedipine released at each interval on portions of the *Sample solution* passed through a suitable 0.45-µm filter, suitably diluted, if necessary, with *Diluent A* and water to obtain a final mixture of water, methanol, and acetonitrile (2:1:1), in comparison with the appropriate *Standard solution*, using *Diluent B* as the blank.
Tolerances: The cumulative percentages of the labeled amount of nifedipine, released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved
4	NMT 14%
12	39%–75%
24	NLT 75%

Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.
Medium: Simulated gastric fluid without enzyme containing 0.5% of sodium lauryl sulfate, pH 1.2; 900 mL, deaerated
Apparatus 1: 100 rpm
Times: 1, 4, and 12 h
Standard stock solution: 0.33 mg/mL of USP Nifedipine RS in methanol

Standard solution: Quantitatively dilute the *Standard stock solution* with *Medium* to obtain a solution having a concentration of about 0.033 mg/mL.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Detector: UV 329 nm
Path length: 0.5 cm
Blank: *Medium*
Tolerances: The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved
1	NMT 15%
4	20%–40%
12	NLT 80%

•**Test 7:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.
Medium: pH 1.2 simulated gastric fluid without enzyme containing 0.5% sodium lauryl sulfate; 900 mL
Apparatus 2: 100 rpm, with three-prong sinker
Times: 1, 4, and 12 h
Standard solution: L/900 (mg/mL) of USP Nifedipine RS in *Medium*, where L is the label claim, in mg, of nifedipine. A small amount of methanol, not exceeding 5% of the final volume of the first dilution, can be used to solubilize nifedipine.
Sample solution: Pass a portion of the solution under test through a suitable filter.
Detector: UV 238 nm
Path length: 1 mm, flow cell
Blank: *Medium*
Tolerances: The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved
1	NMT 15%
4	25%–50%
12	NLT 80%

• (RB 1-Aug-2010)
• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Organic Impurities

• **PROCEDURE**
[NOTE—Conduct this test promptly after preparation of the *Standard solution* and the *Sample solution*.]
Mobile phase: Acetonitrile, methanol, and water (25:25:50)
System suitability solution: *Standard stock solution*, *Quantitative limit solution A*, and *Quantitative limit solution B* (1:1:1)
Standard stock solution: 1 mg/mL of USP Nifedipine RS in methanol
Standard solution: 0.3 mg/mL of USP Nifedipine RS from *Standard stock solution* in *Mobile phase*
Quantitative limit stock solution A: 1 mg/mL of USP Nifedipine Nitrophenylpyridine Analog RS in methanol
Quantitative limit solution A: 6 µg/mL of USP Nifedipine Nitrophenylpyridine Analog RS from *Quantitative limit stock solution A* in *Mobile phase*
Quantitative limit stock solution B: 1 mg/mL of USP Nifedipine Nitrosophenylpyridine Analog RS in methanol
Quantitative limit solution B: 1.5 µg/mL of USP Nifedipine Nitrosophenylpyridine Analog RS from *Quantitative limit stock solution B* in *Mobile phase*
Standard solution: *Quantitative limit solution A*, *Quantitative limit solution B*, and *Mobile phase* (1:1:1)
[NOTE—Each mL of this solution contains about 2 µg of USP Nifedipine Nitrophenylpyridine Analog RS and 0.5 µg of USP Nifedipine Nitrosophenylpyridine Analog RS.]
Sample solution: Use a portion of the *Sample solution* prepared as directed in the *Assay*.
Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 265 nm
Column: 4.6-mm × 25-cm; packing L1
Guard column: 2.1-mm × 3-cm; packing L1
Flow rate: 1 mL/min
Injection size: 25 µL
System suitability
Samples: *System suitability solution*
Suitability requirements
Resolution: NLT 1.5 between the nitrophenylpyridine analog and nitrosophenylpyridine analog peaks; NLT 1.0 between the nitrosophenylpyridine analog and nifedipine peaks
Relative standard deviation: NMT 10% for each analog
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each related compound in the portion of Tablets taken:

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

r_U = peak response of the corresponding related compound from the *Sample solution*
r_S = peak response of the corresponding related compound from the *Standard solution*
C_S = concentration of the appropriate analog USP Reference Standard in the *Standard solution* (µg/mL)
C_U = nominal concentration of nifedipine in the *Sample solution* (µg/mL)
Acceptance criteria: NMT 2.0% of nifedipine nitrophenylpyridine analog and NMT 0.5% of nifedipine nitrosophenylpyridine analog, both relative to the nifedipine content

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
• **LABELING:** The labeling indicates the *Dissolution Test* with which the product complies.
• **USP REFERENCE STANDARDS ⟨11⟩**
USP Nifedipine RS
USP Nifedipine Nitrophenylpyridine Analog RS
USP Nifedipine Nitrosophenylpyridine Analog RS