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_{2}O_{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.)

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°C. 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. Dilute with 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_{2}O_{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 436 nm, and use this determination to correct for excipient interference.]
  Tolerances: The cumulative percentages of the labeled amount of C_{17}H_{18}N_{2}O_{6} released at the times specified, conform to Acceptance Table 2.

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Nifedipine

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5%–17%</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>43%–80%</td>
</tr>
<tr>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

*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)

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\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{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**

(Note—Determine the amount of C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{6} released in Phase 1, 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\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{6} released in vivo and dissolved at the times specified conform to Acceptance Table 2.

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

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 30</td>
</tr>
<tr>
<td>4</td>
<td>30–55</td>
</tr>
<tr>
<td>8</td>
<td>NLT 60</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

*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.

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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_{2}O_{6} released in vivo and dissolved at the times specified, conform to USP Nifedipine RS for Tablets labeled to contain 30 mg, 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_{2}O_{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_{2}O_{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_{2}O_{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_{2}O_{6} released at the times specified, conform to Acceptance Table 2.

For Tablets Labeled to Contain 30 mg of Nifedipine

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12%–35%</td>
</tr>
<tr>
<td>4</td>
<td>44%–67%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

For Tablets Labeled to Contain 60 mg of Nifedipine

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10%–30%</td>
</tr>
<tr>
<td>4</td>
<td>40%–63%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>NMT 14%</td>
</tr>
<tr>
<td>12</td>
<td>39%–75%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
</tr>
</tbody>
</table>

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

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**Nifedipine**

**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 (C₁₇H₁₈N₂O₆) dissolved at the times specified conform to **Acceptance Table 2**.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 15%</td>
</tr>
<tr>
<td>4</td>
<td>20%–40%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

*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 (C₁₇H₁₈N₂O₆) dissolved at the times specified conform to **Acceptance Table 2**.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 15%</td>
</tr>
<tr>
<td>4</td>
<td>25%–50%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

**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 stock solution B:** 1 mg/mL of USP Nifedipine Nitrophenylpyridine Analog RS in methanol

**Quantitative limit solution B:** 1.5 µg/mL of USP Nifedipine Nitrophenylpyridine Analog RS from Quantitative limit solution *B* in *Mobile phase*.

**Standard solution:** Quantitative limit solution *A*, Quantitative limit solution *B*, and *Mobile phase* (1:1:1)

**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:

\[
\text{Result} = \frac{(r_U/r_S) \times (C_U/C_S)}{100}
\]

\(r_U\) = 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**

- USP Nifedipine RS
- USP Nifedipine Nitrophenylpyridine Analog RS
- USP Nifedipine Nitrosophenylpyridine Analog RS