Nifedipine Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	22–Nov–2019
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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Nifedipine Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 13* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 13* was validated using a Chromachemie Puritas Eximius brand of column with L1 packing. The typical retention time for nifedipine is about 5 min.

The Nifedipine Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Yanyin Yang, Associate Scientific Liaison (301-692-3623 or yanyin.yang@usp.org).

Analysis: Use an automatic dissolution system with an appropriate dissolution software. Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved, using portions of the *Sample solution*, in comparison with the *Standard solution*.
Tolerances: See *Table 15*.

Table 15. For Tablets Labeled to Contain 60 mg of Nifedipine

Time (h)	Amount Dissolved (%)
2	NMT 20
6	28–53
8	43–68
16	NLT 80

The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), dissolved at the times specified, conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 13:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 13*.
Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL
Apparatus 2: 100 rpm, with suitable sinkers
Times
For Tablets labeled to contain 30 and 60 mg of nifedipine: 1, 4, 6 and 10 h
For Tablets labeled to contain 90 mg of nifedipine: 1, 4, 6 and 12 h
Mobile phase: Acetonitrile, methanol, water and phosphoric acid (25: 30: 45: 0.1)
Standard stock solution: 1.68 mg/mL of USP Nifedipine RS in methanol
Standard solution: A known concentration of USP Nifedipine RS in *Medium* from *Standard stock solution*, prepared as directed in *Table 16*

Table 16

Tablet Strength (mg)	Concentration (mg/mL)
30	0.0336
60	0.0672
90	0.1008

Sample solution: At each specified time point, withdraw a 10-mL aliquot and replace with the same volume of *Medium*. Pass a portion of the solution under test through a suitable filter and discard the first few milliliters of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 338 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 2.0 mL/min
Injection volume: 20 µL
Run time: NLT 1.6 times the retention time of nifedipine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of nifedipine ($C_{17}H_{18}N_2O_6$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of nifedipine in the *Sample solution* at each time point
r_S = peak response of nifedipine in the *Standard solution*
C_S = concentration of USP Nifedipine RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of nifedipine in the *Sample solution* at the specified time point (*i*) (mg/mL)
V = volume of the *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point (*i*) (mL)

Tolerances: See *Table 17* and *Table 18*.

Table 17. For Tablets Labeled to Contain 30 and 60 mg of Nifedipine

Time (h)	Amount Dissolved (%)
1	3–13
4	29–54
6	52–77
10	NLT 80

Table 18. For Tablets Labeled to Contain 90 mg of Nifedipine

Time (h)	Amount Dissolved (%)
1	3–13
4	27–52
6	45–70
12	NLT 80

The percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-May-2020)

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

• **Organic Impurities**
[Note—Conduct this test promptly after preparation of the *Standard nifedipine solution* and the *Sample solution*.]
Mobile phase: Acetonitrile, methanol, and water (25:25:50)
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 nifedipine stock solution: 1 mg/mL of USP Nifedipine RS in methanol
Standard nifedipine solution: 0.3 mg/mL of USP Nifedipine RS from *Standard nifedipine stock solution* in *Mobile phase*
System suitability solution: *Quantitative limit solution A*, *Quantitative limit solution B*, and *Standard nifedipine solution* (1:1:1)
Standard solution: *Mobile phase*, *Quantitative limit solution A*, and *Quantitative limit solution B* (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
Columns
Guard: 2.1-mm × 3-cm; packing L1
Analytical: 4.6-mm × 25-cm; packing L1
Flow rate: 1 mL/min
Injection volume: 25 µL
System suitability
Sample: *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 analog in the portion of Tablets taken:

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

r_U = peak response of each analog from the *Sample solution*
r_S = peak response of each analog 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
  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