Niacin Extended-Release Tablets

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Expert Committee	Non-Botanical Dietary Supplements
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Non-Botanical Dietary Supplement Expert Committee has revised the Niacin Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test* 5 for drug product approved by the FDA.

The Niacin Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Natalia Davydova (301–816-8328 or nd@usp.org)

Niacin Extended-Release Tablets

DEFINITION

Niacin Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of niacin ($C_6H_5NO_2$).

IDENTIFICATION

• **A.** 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**

Diluent: Methanol and water (82:18)

Mobile phase: Methanol and water (82:18), adjusted with glacial acetic acid to a pH of 3.15 ± 0.05

Standard solution: 250 µg/mL of USP Niacin RS, 50 µg/mL of USP 6-Hydroxynicotinic Acid RS, and 97.8 µg/mL of pyridine in *Diluent*

Sample solution: Transfer a quantity of powder, equivalent to 50 mg of niacin from NLT 20 finely powdered Tablets, to a suitable flask, add *Diluent*, and stir for 2 h. Dilute with *Diluent* to a final concentration of 250 µg/mL of niacin.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 260 nm
Column: 4.6-mm × 15-cm; 5-µm packing L8
Flow rate: 1.0 mL/min
Injection volume: 25 µL

System suitability
Sample: *Standard solution*
[NOTE—See *Table 4* for relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between pyridine and 6-hydroxynicotinic acid, and NLT 1.5 between 6-hydroxynicotinic acid and niacin
Relative standard deviation: NMT 3.0% for each of the peaks

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of niacin ($C_6H_5NO_2$) in the portion of Tablets taken:

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

r_U = peak area of niacin from the *Sample solution*
r_S = peak area of niacin from the *Standard solution*
C_S = concentration of USP Niacin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of niacin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨**711**⟩

Test 1
Medium: Water; 900 mL
Apparatus 1: 100 rpm
Times: 1, 3, 6, 9, 12, and 20 h; without *Medium* replacement. [NOTE—Withdraw the same volume at each time point.]

Solution A: Solution of sodium heptanesulfonate in acetic acid, methanol, and water (4:44:33:19), w/w[1]
Mobile phase: Mixture of methanol, water, and *Solution A* (560:440:25)
Standard solution: USP Niacin RS at a known concentration in water in the range of 75–750 µg/mL
Sample solution: Filtered portion of the solution under test suitably diluted with *Medium* if necessary

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 3.9-mm × 15-cm; 10-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 15 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Determine, in mg/mL, the content of niacin ($C_6H_5NO_2$) in the *Medium* at each time point:

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

r_U = peak area of niacin from the *Sample solution*
r_S = peak area of niacin from the *Standard solution*
C_S = concentration of USP Niacin RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*

Calculate the percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at each time point:

At 1 h:

$$\text{Result}_1 = (C_1 \times V/L) \times 100$$

At 3 h:

$$\text{Result}_2 = [C_2 \times (V - V_S) + C_1 \times V_S] \times 100/L$$

At 6 h:

$$\text{Result}_3 = [C_3 \times (V - 2 \times V_S) + (C_1 + C_2) \times V_S] \times 100/L$$

At 9 h:

$$\text{Result}_4 = [C_4 \times (V - 3 \times V_S) + (C_1 + C_2 + C_3) \times V_S] \times 100/L$$

At 12 h:

$$\text{Result}_5 = [C_5 \times (V - 4 \times V_S) + (C_1 + C_2 + C_3 + C_4) \times V_S] \times 100/L$$

At 20 h:

$$\text{Result}_6 = [C_6 \times (V - 5 \times V_S) + (C_1 + C_2 + C_3 + C_4 + C_5) \times V_S] \times 100/L$$

C = as C_1, C_2, …, C_6, the content of niacin in the *Medium* at each time point (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of sample withdrawn at each time point (mL)
L = label claim (mg/Tablet)

Tolerances: The percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at the times specified in *Table 1*, *Table 2*, and *Table 3* conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

[1] Commercially available from Waters Corporation as PIC B7 Reagent (Part #85103).

Table 1. For Tablets Labeled to Contain 500 mg or Less/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 15
3	17–32
6	33–48
9	43–63
12	52–77
20	NLT 75

Table 2. For Tablets Labeled to Contain 750 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 15
3	16–31
6	31–46
9	42–62
12	51–76
20	NLT 75

Table 3. For Tablets Labeled to Contain 1000 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 15
3	15–30
6	30–45
9	40–60
12	50–75
20	NLT 75

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Acid stage medium: 0.1 N hydrochloric acid; 900 mL
Buffer stage medium: 6.8 g of monobasic potassium phosphate and 0.89 g of sodium hydroxide pellets in 1000 mL of water. Adjust with diluted sodium hydroxide or phosphoric acid to a pH of 6.8; 900 mL.
Apparatus 1: 100 rpm
Times: 1, 4, 12, and 24 h: 1 and 4 h in the *Acid stage medium*; 12 and 24 h in the *Buffer stage medium*. Replace the volume withdrawn with the equal volume of medium preheated to 37 ± 0.5°.
Procedure: After 4 h replace the *Acid stage medium* with the *Buffer stage medium*, and run the test for the times specified (additional 20 h for a total of 24 h).
[NOTE—Withdraw the same volume at each time point. Pass a portion of the solution through a suitable filter.]
Standard stock solution: 0.2 mg/mL of USP Niacin RS in water
Standard solution 1: Dilute *Standard stock solution* with *Acid stage medium* to a final concentration of 0.01 mg/mL of USP Niacin RS.
Standard solution 2: Dilute *Standard stock solution* with *Buffer stage medium* to a final concentration of 0.01 mg/mL of USP Niacin RS.
Sample solution
For Tablets labeled to contain 500 mg: Dilute a filtered portion of the solution under test with appropriate dissolution medium 25-fold.
For Tablets labeled to contain 750 mg: Dilute a filtered portion of the solution under test with appropriate dissolution medium 33-fold.
For Tablets labeled to contain 1000 mg: Dilute a filtered portion of the solution under test with appropriate dissolution medium 50-fold.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelength: 262 nm
Path length: 1 cm
Blank: *Acid stage medium* or *Buffer stage medium*
Analysis
Samples: *Standard solution 1* or *Standard solution 2* and *Sample solution*
Determine the concentration, in mg/mL, of niacin ($C_6H_5NO_2$) in the sample withdrawn from the vessel at each time point:

$$\text{Result} = [(A_U - A_B)/A_S] \times C_S \times D$$

A_U = absorbance of the *Sample solution*
A_B = absorbance of the *Blank*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Niacin RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*
Calculate the percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at each time point:
At 1 h:

$$\text{Result}_1 = (C_1 \times V) \times 100/L$$

At 4 h:

$$\text{Result}_2 = (C_2 \times V + C_1 \times V_S) \times 100/L$$

At 12 h:

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

At 24 h:

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

C = as C_1, …, C_4, the content of niacin in the related dissolution medium at each time point (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of sample withdrawn at each time point (mL)
L = label claim (mg/Tablet)
Tolerances: The percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at the times specified in *Table 4* and *Table 5* conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Table 4. For Tablets Labeled to Contain 500 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 25
4	30–50
12	65–85
24	NLT 80

Table 5. For Tablets Labeled to Contain 750 and 1000 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 25
4	30–50

Table 5. For Tablets Labeled to Contain 750 and 1000 mg/Tablet *(Continued)*

Time (h)	Amount Dissolved (%)
12	55–75
24	NLT 80

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: Water; 900 mL
Apparatus 1: 100 rpm
Times: 1, 3, 6, 9, 12, and 20 h; without *Medium* replacement
[NOTE—Withdraw the same volume at each time point. Pass a portion of the solution through a stainless steel filter.]
Solution A: 1 mg/mL of sodium 1-hexanesulfonate monohydrate in water
Mobile phase: Mixture of *Solution A*, methanol, and glacial acetic acid (840:150:10)
Standard solution: (*L*/900) mg/mL of USP Niacin RS in *Medium*, where *L* is the label claim in mg/Tablet
[NOTE—Use sonication for complete dissolution, if necessary.]
Sample solution: Filtered portion of the solution under test
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Sample cooler: 10°
Detector: UV 262 nm
Column: 3.9-mm × 15-cm; 10-µm packing L1
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 2 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Theoretical plates: NLT 1000
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the concentration, in mg/mL, of niacin ($C_6H_5NO_2$) in the *Medium* at each time point:

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

r_U = peak area of niacin from the *Sample solution*
r_S = peak area of niacin from the *Standard solution*
C_S = concentration of USP Niacin RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at each time point:
At 1 h:

$$\text{Result}_1 = (C_1 \times V/L) \times 100$$

At 3 h:

$$\text{Result}_2 = [C_2 \times (V - V_S) + C_1 \times V_S] \times 100/L$$

At 6 h:

$$\text{Result}_3 = [C_3 \times (V - 2 \times V_S) + (C_1 + C_2) \times V_S] \times 100/L$$

At 9 h:

$$\text{Result}_4 = [C_4 \times (V - 3 \times V_S) + (C_1 + C_2 + C_3) \times V_S] \times 100/L$$

At 12 h:

$$\text{Result}_5 = [C_5 \times (V - 4 \times V_S) + (C_1 + C_2 + C_3 + C_4) \times V_S] \times 100/L$$

At 20 h:

$$\text{Result}_6 = [C_6 \times (V - 5 \times V_S) + (C_1 + C_2 + C_3 + C_4 + C_5) \times V_S] \times 100/L$$

C = as C_1, C_2, …, C_6, the content of niacin in the *Medium* at each time point (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of sample withdrawn at each time point (mL)
L = label claim (mg/Tablet)

Tolerances: The percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at the times specified in *Table 6* and *Table 7* conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Table 6. For Tablets Labeled to Contain 500 and 1000 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 20
3	15–35
6	30–50
9	40–65
12	50–80
20	NLT 70

Table 7. For Tablets Labeled to Contain 750 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 16
3	15–35
6	30–50
9	40–65
12	50–75
20	NLT 75

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: Water; 900 mL
Apparatus 1: 100 rpm
Times: 1, 3, 6, 9, 12, and 24 h for Tablets labeled to contain 500 and 1000 mg/Tablet, and 1, 6, 12, and 24 h for Tablets labeled to contain 750 mg/Tablet; without *Medium* replacement
[NOTE—Withdraw the same volume at each time point. Pass a portion of the solution through a 0.45-µm PVDF membrane filter, discarding the first 2 mL of the filtrate.]
Standard stock solution: 0.5 mg/mL of USP Niacin RS in water
Standard solution: Dilute *Standard stock solution* with *Medium* to a final concentration of 0.02 mg/mL of USP Niacin RS.
Sample solution
For Tablets labeled to contain 500 mg: Dilute a filtered portion of the solution under test with *Medium* 25-fold.
For Tablets labeled to contain 750 mg: Dilute a filtered portion of the solution under test with *Medium* 40-fold.

For Tablets labeled to contain 1000 mg: Dilute a filtered portion of the solution under test with *Medium* 50-fold.

Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelength: 262 nm
Path length: 1 cm
Blank: *Medium*

Analysis
Samples: *Standard solution* and *Sample solution*
Determine the concentration, in mg/mL, of niacin ($C_6H_5NO_2$) in the sample withdrawn from the vessel at each time point:

$$\text{Result} = [(A_U - A_B)/A_S] \times C_S \times D$$

A_U = absorbance of the *Sample solution*
A_B = absorbance of the *Blank*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Niacin RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*

For Tablets labeled to contain 500 and 1000 mg: Calculate the percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at each time point:
At 1 h:

$$\text{Result}_1 = (C_1 \times V/L) \times 100$$

At 3 h:

$$\text{Result}_2 = [C_2 \times (V - V_S) + C_1 \times V_S] \times 100/L$$

At 6 h:

$$\text{Result}_3 = [C_3 \times (V - 2 \times V_S) + (C_1 + C_2) \times V_S] \times 100/L$$

At 9 h:

$$\text{Result}_4 = [C_4 \times (V - 3 \times V_S) + (C_1 + C_2 + C_3) \times V_S] \times 100/L$$

At 12 h:

$$\text{Result}_5 = [C_5 \times (V - 4 \times V_S) + (C_1 + C_2 + C_3 + C_4) \times V_S] \times 100/L$$

At 24 h:

$$\text{Result}_6 = [C_6 \times (V - 5 \times V_S) + (C_1 + C_2 + C_3 + C_4 + C_5) \times V_S] \times 100/L$$

For Tablets labeled to contain 750 mg: Calculate the percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at each time point:
At 1 h:

$$\text{Result}_1 = (C_1 \times V/L) \times 100$$

At 6 h:

$$\text{Result}_2 = [C_2 \times (V - V_S) + C_1 \times V_S] \times 100/L$$

At 12 h:

$$\text{Result}_3 = [C_3 \times (V - 2 \times V_S) + (C_1 + C_2) \times V_S] \times 100/L$$

At 24 h:

$$\text{Result}_4 = [C_4 \times (V - 3 \times V_S) + (C_1 + C_2 + C_3) \times V_S] \times 100/L$$

C = as C_1, C_2, …, C_6, the content of niacin in the *Medium* at each time point (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of sample withdrawn at each time point (mL)
L = label claim (mg/Tablet)

Tolerances: The percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at the times specified in *Table 8*, *Table 9*, and *Table 10* conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Table 8. For Tablets Labeled to Contain 500 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 15
3	17–32
6	33–48
9	48–68
12	60–80
24	NLT 80

Table 9. For Tablets Labeled to Contain 750 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 15
6	20–40
12	48–68
24	NLT 80

Table 10. For Tablets Labeled to Contain 1000 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 15
3	12–27
6	25–45
9	35–55
12	50–70
24	NLT 80

•**Test 5:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.
Medium: Water; 900 mL
Apparatus 1: 100 rpm
Times: 1, 6, 12, and 24 h; without *Medium* replacement
[NOTE—Withdraw the same volume at each time point. Pass a portion of the solution through a 0.45-µm nylon membrane filter, discarding the first 2 mL of the filtrate.]
Solution A: 1.1 mg/mL of sodium 1-heptanesulfonate in water
Mobile phase: Mixture of *Solution A* and methanol (70:30)
Standard solution: 0.84 mg/mL of USP Niacin RS in water
[NOTE—Use sonication for complete dissolution, if necessary.]
Sample solution: Filtered portion of the solution under test
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC
Detector: UV 262 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1.0 mL/min
Injection volume: 5 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the concentration, in mg/mL, of niacin ($C_6H_5NO_2$) in the *Medium* at each time point:

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

r_U = peak area of niacin from the *Sample solution*
r_S = peak area of niacin from the *Standard solution*
C_S = concentration of USP Niacin RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at each time point:
At 1 h:

$$\text{Result}_1 = (C_1 \times V/L) \times 100$$

At 6 h:

$$\text{Result}_2 = [C_2 \times (V - V_S) + C_1 \times V_S] \times 100/L$$

At 12 h:

$$\text{Result}_3 = [C_3 \times (V - 2 \times V_S) + (C_1 + C_2) \times V_S] \times 100/L$$

At 24 h:

$$\text{Result}_4 = [C_4 \times (V - 3 \times V_S) + (C_1 + C_2 + C_3) \times V_S] \times 100/L$$

C = as C_1, …, C_4, the content of niacin in the *Medium* at each time point (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of sample withdrawn at each time point (mL)

Tolerances: The percentage of the labeled amount of niacin ($C_6H_5NO_2$) dissolved at the times specified in *Table 11* and *Table 12* conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Table 11. For Tablets Labeled to Contain 500 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 20
6	30–50
12	50–75
24	NLT 80

Table 12. For Tablets Labeled to Contain 1000 mg/Tablet

Time (h)	Amount Dissolved (%)
1	NMT 20
6	20–40
12	45–65
24	NLT 80

● (RB 1-Jan-2018)
• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**
Diluent, Mobile phase, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of 6-hydroxynicotinic acid or pyridine in the portion of Tablets taken:

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

r_U = peak area of 6-hydroxynicotinic acid or pyridine from the *Sample solution*
r_S = peak area of 6-hydroxynicotinic acid or pyridine from the *Standard solution*
C_S = concentration of USP 6-Hydroxynicotinic Acid RS or pyridine in the *Standard solution* (µg/mL)
C_U = nominal concentration of niacin in the *Sample solution* (µg/mL)

Calculate the percentage of any unspecified impurity in the portion of Tablets taken:

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

r_U = peak area of each impurity from the *Sample solution*
r_S = peak area of niacin from the *Standard solution*
C_S = concentration of USP Niacin RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of niacin in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 13*.

Table 13

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Pyridine	0.14	0.2
6-Hydroxynicotinic acid	0.64	0.2
Niacin	1.0	—
Any unspecified impurity	—	0.1
Total impurities	—	1.0

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.
• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
• **USP REFERENCE STANDARDS ⟨11⟩**
USP 6-Hydroxynicotinic Acid RS
USP Niacin RS