

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 Supplements Expert Committee has revised the Niacin Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 3* and *Dissolution Test 4*, for drug products 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 40–NF 35*.

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 $\mu\text{g/mL}$ of USP Niacin RS, 50 $\mu\text{g/mL}$ of USP 6-Hydroxynicotinic Acid RS, and 97.8 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ of niacin.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm \times 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/w¹

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 $\mu\text{g/mL}$

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 \times 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:

$$\text{Result}_2 = [C_2 \times (V - V_3) + C_1 \times V_3] \times 100/L$$

At 6 h:

$$\text{Result}_3 = [C_3 \times (V - 2 \times V_3) + (C_1 + C_2) \times V_3] \times 100/L$$

At 9 h:

$$\text{Result}_4 = [C_4 \times (V - 3 \times V_3) + (C_1 + C_2 + C_3) \times V_3] \times 100/L$$

At 12 h:

$$\text{Result}_5 = [C_5 \times (V - 4 \times V_3) + (C_1 + C_2 + C_3 + C_4) \times V_3] \times 100/L$$

At 20 h:

$$\text{Result}_6 = [C_6 \times (V - 5 \times V_3) + (C_1 + C_2 + C_3 + C_4 + C_5) \times V_3] \times 100/L$$

C = as C_1, C_2, \dots, C_6 , the content of niacin in the *Medium* at each time point (mg/mL)

V = volume of *Medium*, 900 mL

V_3 = 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 *Acceptance Table 2* in *Dissolution* (711).

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

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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 $37 \pm 0.5^\circ$.

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:

$$\text{Result}_2 = (C_2 \times V + C_1 \times V_3) \times 100/L$$

At 12 h:

$$\text{Result}_3 = [(C_3 + C_2) \times V + C_1 \times V_3] \times 100/L$$

At 24 h:

$$\text{Result}_4 = [(C_4 + C_2) \times V + (C_1 + C_3) \times V_3] \times 100/L$$

C = as C_1, \dots, C_4 , the content of niacin in the related dissolution medium at each time point (mg/mL)

V = volume of *Medium*, 900 mL

V_3 = 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 *Acceptance Table 2* in *Dissolution* (711).

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 (C₆H₅NO₂) 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 (C₆H₅NO₂) 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 C₁, C₂, ..., C₆, 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 (C₆H₅NO₂) 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.

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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, \dots, 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 |

• (RB 1-Feb-2017)

• **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* ($\mu\text{g/mL}$)

C_U = nominal concentration of niacin in the *Sample solution* ($\mu\text{g/mL}$)

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 11*.

Table 11

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|-------------------------|-------------------------|------------------------------|
| Pyridine | 0.14 | 0.2 |
| 6-Hydroxynicotinic acid | 0.64 | 0.2 |

Table 11 (Continued)

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|--------------------------|-------------------------|------------------------------|
| 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