Niacin Extended-Release Tablets

<table>
<thead>
<tr>
<th>Type of Posting</th>
<th>Revision Bulletin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posting Date</td>
<td>27–Jan–2017</td>
</tr>
<tr>
<td>Official Date</td>
<td>01–Feb–2017</td>
</tr>
<tr>
<td>Expert Committee</td>
<td>Non-Botanical Dietary Supplements</td>
</tr>
<tr>
<td>Reason for Revision</td>
<td>Compliance</td>
</tr>
</tbody>
</table>

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 (C₆H₅NO₂).

**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 254 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 (C₆H₅NO₂) in the Medium at each time point:
  \[
  \text{Result} = \frac{r_u}{r_s} \times \left( \frac{C_s}{C_u} \right) \times 100
  \]
  \(r_u\) = 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/v
**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 (C₆H₅NO₂) dissolved at each time point:
  \[
  \text{Result} = \frac{r_u}{r_s} \times C_s \times D
  \]
  \(r_u\) = 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 (C₆H₅NO₂) dissolved at each time point:
  - At 1 h:
    \[
    \text{Result}_1 = \left( \frac{C_1 \times V/L} {V_s} \right) \times 100
    \]
  - At 3 h:
    \[
    \text{Result}_3 = \left( \frac{C_3 \times V/L} {V_s} \right) \times 100
    \]
  - At 6 h:
    \[
    \text{Result}_6 = \left( \frac{C_6 \times V/L} {V_s} \right) \times 100
    \]
  - At 9 h:
    \[
    \text{Result}_9 = \left( \frac{C_9 \times V/L} {V_s} \right) \times 100
    \]
  - At 12 h:
    \[
    \text{Result}_{12} = \left( \frac{C_{12} \times V/L} {V_s} \right) \times 100
    \]
  - At 20 h:
    \[
    \text{Result}_{20} = \left( \frac{C_{20} \times V/L} {V_s} \right) \times 100
    \]
- \(C\) = as \(C_i, C_2, ..., C_9\), 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 1, Table 2, and Table 3 conforms to Acceptance Table 2 in Dissolution (711).

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C181477, C184495-M56534-NBDS2015, Rev. 0 20170127
For Tablets labeled to contain 500 mg or less/Tablet:

<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>3</td>
<td>17–32</td>
</tr>
<tr>
<td>6</td>
<td>33–48</td>
</tr>
<tr>
<td>9</td>
<td>43–63</td>
</tr>
<tr>
<td>12</td>
<td>52–77</td>
</tr>
<tr>
<td>20</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

For Tablets labeled to contain 750 mg/Tablet:

<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>3</td>
<td>16–31</td>
</tr>
<tr>
<td>6</td>
<td>31–46</td>
</tr>
<tr>
<td>9</td>
<td>42–62</td>
</tr>
<tr>
<td>12</td>
<td>51–76</td>
</tr>
<tr>
<td>20</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

For Tablets labeled to contain 1000 mg/Tablet:

<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>3</td>
<td>15–30</td>
</tr>
<tr>
<td>6</td>
<td>30–45</td>
</tr>
<tr>
<td>9</td>
<td>40–60</td>
</tr>
<tr>
<td>12</td>
<td>50–75</td>
</tr>
<tr>
<td>20</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

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 (C₆H₅NO₂) in the sample withdrawn from the vessel at each time point:

\[
\text{Result} = \left(\frac{\text{AU} - \text{AB}}{\text{AS}}\right) \times \text{CS} \times \text{D}
\]

\[
\text{AU} = \text{absorbance of the Sample solution}
\]

\[
\text{AB} = \text{absorbance of the Blank}
\]

\[
\text{AS} = \text{absorbance of the Standard solution}
\]

\[
\text{CS} = \text{concentration of USP Niacin RS in the Standard solution (mg/mL)}
\]

\[
\text{D} = \text{dilution factor for the Sample solution}
\]

At 1 h:

\[
\text{Result}_1 = (\text{C}_1 \times \text{V}) \times 100/\text{L}
\]

At 4 h:

\[
\text{Result}_2 = (\text{C}_2 \times \text{V} + \text{C}_1 \times \text{V}_3) \times 100/\text{L}
\]

At 12 h:

\[
\text{Result}_3 = (\text{C}_3 \times \text{V} + \text{C}_2 \times \text{V}_3) \times 100/\text{L}
\]

At 24 h:

\[
\text{Result}_4 = (\text{C}_4 \times \text{V} + \text{C}_2 \times \text{V}_3) \times 100/\text{L}
\]

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 6.8–9.00 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°C.

**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 750 and 1000 mg/Tablet:

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 25</td>
</tr>
<tr>
<td>4</td>
<td>30–50</td>
</tr>
<tr>
<td>12</td>
<td>65–85</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>
Table 5. For Tablets labeled to contain 750 and 1000 mg/Tablet (Continued)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>35–75</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

**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

**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:

Result ³ = \(\frac{C_1 \times (V - V_3) + (C_1 + C_2 + C_3) \times V_3}{V_3} \times 100\%

At 3 h:

Result ⁴ = \(\frac{C_1 \times (V - 3 \times V_3) + (C_1 + C_2 + C_3) \times V_3}{V_3} \times 100\%

At 6 h:

Result ⁵ = \(\frac{C_1 \times (V - 2 \times V_3) + (C_1 + C_2) \times V_3}{V_3} \times 100\%

At 9 h:

Result ⁶ = \(\frac{C_1 \times (V - V_3) + (C_1 + C_2 + C_3) \times V_3}{V_3} \times 100\%

At 12 h:

Result ⁷ = \(\frac{C_1 \times (V - 4 \times V_3) + (C_1 + C_2 + C_3 + C_4) \times V_3}{V_3} \times 100\%

At 20 h:

Result ⁸ = \(\frac{C_1 \times (V - 5 \times V_3) + (C_1 + C_2 + C_3 + C_4) \times V_3}{V_3} \times 100\%

C = as C₁, C₂, ..., Cₙ, the content of niacin in the Medium at each time point (mg/mL)

V = volume of Medium, 900 mL

Vᵢ = 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

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 20</td>
</tr>
<tr>
<td>3</td>
<td>15–35</td>
</tr>
<tr>
<td>6</td>
<td>30–50</td>
</tr>
<tr>
<td>9</td>
<td>40–65</td>
</tr>
<tr>
<td>12</td>
<td>50–80</td>
</tr>
<tr>
<td>20</td>
<td>NLT 70</td>
</tr>
</tbody>
</table>

Table 7. For Tablets labeled to contain 750 mg/Tablet

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 16</td>
</tr>
<tr>
<td>3</td>
<td>15–35</td>
</tr>
<tr>
<td>6</td>
<td>30–50</td>
</tr>
<tr>
<td>9</td>
<td>40–65</td>
</tr>
<tr>
<td>12</td>
<td>50–75</td>
</tr>
<tr>
<td>20</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

**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 750 mg/Tablet; and 1, 6, 12, and 24 h for Tablets labeled to contain 500 mg/Tablet; and 1, 3, 6, 9, 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.]
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 niacin (C₆H₅NO₂) dissolved at the times specified in Analytical wavelength:

### Analysis

**Path length:** 1 cm

**Blank: Medium**

**Samples:** Standard solution and Sample solution

Determine the concentration, in mg/mL, of niacin (C₆H₅NO₂) in the sample withdrawn from the vessel at each time point:

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

- \(A_U\) = absorbance of the Sample solution
- \(A_B\) = absorbance of the Blank
- \(A_S\) = absorbance of the Standard solution
- \(C_I\) = 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 (C₆H₅NO₂) dissolved at each time point:

At 1 h:

\[
\text{Result}_1 = (C_I \times V/L) \times 100
\]

At 3 h:

\[
\text{Result}_2 = (C_2 \times (V - V_2) + C_I \times V_2) \times 100/L
\]

At 6 h:

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

At 9 h:

\[
\text{Result}_4 = (C_4 \times (V - 3 \times V_4) + (C_I + C_2 + C_4) \times V_4) \times 100/L
\]

At 12 h:

\[
\text{Result}_5 = (C_I \times (V - 4 \times V_5) + (C_I + C_2 + C_4 + C_5) \times V_5) \times 100/L
\]

At 24 h:

\[
\text{Result}_6 = (C_6 \times (V - 5 \times V_6) + (C_I + C_2 + C_4 + C_5 + C_6) \times V_6) \times 100/L
\]

**For Tablets labeled to contain 750 mg:**
Calculate the percentage of the labeled amount of niacin (C₆H₅NO₂) dissolved at each time point:

At 1 h:

\[
\text{Result} = (C_I \times V/L) \times 100
\]

At 6 h:

\[
\text{Result}_2 = (C_2 \times (V - V_2) + C_I \times V_2) \times 100/L
\]

At 12 h:

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

At 24 h:

\[
\text{Result}_4 = (C_4 \times (V - 3 \times V_4) + (C_I + C_2 + C_4) \times V_4) \times 100/L
\]

**IMPURITIES**

- **Organic Impurities:**
  - Digest, 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:

\[
\text{Result} = \left( \frac{r_U}{r_0} \right) \times \left( \frac{C_I}{C_0} \right) \times 100
\]

- \(r_U\) = peak area of 6-hydroxynicotinic acid or pyridine from the Sample solution
- \(r_0\) = peak area of 6-hydroxynicotinic acid or pyridine from the Standard solution
- \(C_I\) = concentration of USP 6-Hydroxynicotinic Acid RS or pyridine in the Standard solution (µg/mL)
- \(C_0\) = nominal concentration of niacin in the Sample solution (µg/mL)

---

**Table 8. For Tablets labeled to contain 500 mg/Tablet**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NLT 15</td>
</tr>
<tr>
<td>3</td>
<td>17–32</td>
</tr>
<tr>
<td>6</td>
<td>33–48</td>
</tr>
<tr>
<td>9</td>
<td>48–68</td>
</tr>
<tr>
<td>12</td>
<td>60–80</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

**Table 9. For Tablets labeled to contain 750 mg/Tablet**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NLT 15</td>
</tr>
<tr>
<td>6</td>
<td>20–40</td>
</tr>
<tr>
<td>12</td>
<td>48–68</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

**Table 10. For Tablets labeled to contain 1000 mg/Tablet**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NLT 15</td>
</tr>
<tr>
<td>3</td>
<td>12–27</td>
</tr>
<tr>
<td>6</td>
<td>25–45</td>
</tr>
<tr>
<td>9</td>
<td>35–55</td>
</tr>
<tr>
<td>12</td>
<td>50–70</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>
Calculate the percentage of any unspecified impurity in the portion of Tablets taken:

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

- \(r_U\) = 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>0.14</td>
<td>0.2</td>
</tr>
<tr>
<td>6-Hydroxynicotinic acid</td>
<td>0.64</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Table 11 (Continued)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified impurity</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**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