Nitrofurantoin Capsules

<table>
<thead>
<tr>
<th>Type of Posting</th>
<th>Revision Bulletin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posting Date</td>
<td>30-Oct-2020</td>
</tr>
<tr>
<td>Official Date</td>
<td>1-Nov-2020</td>
</tr>
<tr>
<td>Expert Committee</td>
<td>Small Molecules 1</td>
</tr>
</tbody>
</table>

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 1 Expert Committee has revised the Nitrofurantoin Capsules monograph. The purpose for the revision is to update the acceptance criteria in Table 9 of Dissolution Test 7 to accommodate FDA-approved drug products with different dissolution tolerances.

The Nitrofurantoin Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Shankari Shivaprasad, Senior Scientific Liaison (301-461-7925 or sns@usp.org).
Nitrofurantoin Capsules

DEFINITION
Nitrofurantoin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of nitrofurantoin (C₈H₆N₄O₂).

IDENTIFICATION
• A. INFRARED ABSORPTION
  Sample: Add 10 mL of 6 N acetic acid to a quantity of the contents of Capsules equivalent to 100 mg of nitrofurantoin. Boil the solution for a few min, and filter while hot. Cool to room temperature, collect the precipitate of nitrofurantoin, and dry at 105°C for 1 h.
  Acceptance criteria: The IR absorption spectrum of a mineral oil dispersion of the precipitate so obtained exhibits maxima only at the same wavelength as that of a similar solution of USP Nitrofurantoin RS.
• B. The retention time of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY
• PROCEDURE
  Solution A: Dissolve 6.8 g of monobasic potassium phosphate in 500 mL of water. Add a volume of 1.0 N sodium hydroxide (about 30 mL) sufficient to adjust to a pH of 7.0, and dilute with water to 1 L.
  Mobile phase: Acetonitrile and Solution A (3:22)
  Internal standard solution: 1 mg/mL of acetylilide in water
  Standard solution: Dissolve 50 mg of USP Nitrofurantoin RS in 40.0 mL of dimethylformamide, and add 50.0 mL of Internal standard solution.
  Sample solution: Transfer, as completely as possible, the contents of 20 Capsules to a 500-mL flask. Place the emptied Capsules in a beaker, add 25 mL of dimethylformamide, and agitate for 1 min. Decant into the flask containing the Capsule contents. Rinse the emptied Capsules with another two 25-mL portions of dimethylformamide, and decant into the flask. Add sufficient dimethylformamide to bring the volume to about 250 mL. Insert the stopper in the flask, and shake by mechanical means for 15 min. Dilute with dimethylformamide to volume, and mix. If necessary, the sample may be homogenized using a disperser. Pass through a medium-porosity, sintered-glass filter into a suitable flask. Transfer an aliquot, equivalent to 50 mg of nitrofurantoin, to a flask. Add an accurately measured volume of dimethylformamide to bring the volume in the flask to 40.0 mL. To the flask add 50.0 mL of Internal standard solution, mix, and cool to room temperature. Pass a portion of the solution through a nylon filter of 0.45-μm pore size, discarding the first few mL of the filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)
  Mode: LC
  Detector: UV 254 nm
  Column: 3.9-mm × 30-cm; packing L1
  Injection volume: 5–10 μL

System suitability
  Sample: Standard solution
  [Note—Adjust the operating parameters so that the retention time of the nitrofurantoin peak is about 8 min, and the peak heights are about half full-scale.]

Suitability requirements
  Resolution: NLT 3.0 between acetylilide and nitrofurantoin
  Relative standard deviation: NMT 2.0%, determined from peak response ratios of replicate injections

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of nitrofurantoin (C₈H₆N₄O₅) in the portion of the powder included in the sample aliquot:

$$\text{Result} = \left( \frac{R_U}{R_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100$$

- $R_U$ = peak response ratio from the Sample solution
- $R_S$ = peak response ratio from the Standard solution
- $C_S$ = concentration of USP Nitrofurantoin RS in the Standard solution (mg/mL)
- $C_U$ = nominal concentration of the Sample solution (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution (711)**

Test 1 (where it is labeled as containing nitrofurantoin macrocrystals)

- **Medium**: pH 7.2 (± 0.05) phosphate buffer; 900 mL
- **Apparatus 1**: 100 rpm
- **Times**: 1, 3, and 8 h

**Standard solution**: USP Nitrofurantoin RS in Medium

**Sample solution**: Pass a portion of the solution under test through a suitable filter. Dilute with Medium, if necessary.

**Blank**: Medium

**Instrumental conditions**

- **Mode**: UV
- **Analytical wavelength**: 375 nm

**Tolerances**: See Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20%–60%</td>
</tr>
<tr>
<td>3</td>
<td>NLT 45%</td>
</tr>
<tr>
<td>8</td>
<td>NLT 60%</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of nitrofurantoin (C₈H₆N₄O₅) dissolved at the 1-h point conforms to Dissolution (711), Acceptance Table 2, and the percentages dissolved at the 3- and 8-h points conform to the criteria for the final test time in Dissolution (711), Acceptance Table 2.

Test 2 (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms): If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

**Acid medium**: 0.01 N hydrochloric acid for 1 h; 900 mL

**pH 7.5 buffer medium**: Prepare a pH 7.5 buffer concentrate by dissolving 62.2 g of potassium hydroxide and 129.3 g of monobasic potassium phosphate in water, dilute with water to 1 L, and mix. After 1 h, change the Acid medium to pH 7.5 buffer medium by adding 50 mL of pH 7.5 buffer concentrate, and run for an additional 6 h.
**Apparatus 2:** 100 rpm, with sinkers made of Teflon-coated steel wire prepared by forming a coil approximately 22 mm long from a 13-cm length of 20-gauge wire (see Figure 1).

![Figure 1. Sinker.](image)

**Times:** 1, 3, and 7 h

**Acid-stage standard solution:** 0.025 mg/mL of USP Nitrofurantoin RS in Acid medium

**Buffer-stage standard solution:** 0.075 mg/mL of USP Nitrofurantoin RS in pH 7.5 buffer medium

**Instrumental conditions**
- **Mode:** UV
- **Analytical wavelength:** 375 nm

**Analysis:** Calculate the percentages of the labeled amount \( Q_f \) of nitrofurantoin \( \left( \text{C}_8\text{H}_6\text{N}_4\text{O}_5 \right) \) dissolved from UV absorbances at the isosbestic wavelength at about 375 nm on filtered portions of each solution under test, suitably diluted, if necessary, with Acid medium or pH 7.5 buffer medium when appropriate, in comparison with the appropriate Standard solution.

**Tolerances:** See **Table 2**.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (Individual)</th>
<th>Amount Dissolved (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2%–16%</td>
<td>5%–13%</td>
</tr>
<tr>
<td>3</td>
<td>27%–69%</td>
<td>39%–56%</td>
</tr>
<tr>
<td>7</td>
<td>NLT 68%</td>
<td>NLT 81%</td>
</tr>
</tbody>
</table>
The percentages of the labeled amount of nitrofurantoin \((C_8H_6N_4O_5)\) dissolved at the specified times conform to \textit{Table 3}.

### Table 3

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>(L_1)</td>
<td>12</td>
<td>The mean percentage of dissolved label claim lies within the range for the means at each interval and is NLT the stated amount at the final test time. All individual values lie within the ranges for the individuals at each interval and are NLT the stated amount at the final test time.</td>
</tr>
<tr>
<td>(L_2)</td>
<td>12</td>
<td>The mean percentage of dissolved label claim lies within the range for the means at each interval and is NLT the stated amount at the final test time. NMT 2 of the 24 individual values lie outside the stated ranges for individuals at each interval, and NMT 2 of 24 are less than the stated amount at the final test time.</td>
</tr>
</tbody>
</table>

\textbf{Test 3} (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms): If the product complies with this test, the labeling indicates that it meets USP \textit{Dissolution Test 3}.

\textbf{Acid medium, pH 7.5 buffer medium, Apparatus 2, Times, Acid-stage standard solution, Buffer-stage standard solution}, and \textbf{Analysis}: Proceed as directed in \textit{Test 2}.

\textbf{Tolerances}: See \textit{Table 4}.

### Table 4

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (Individual)</th>
<th>Amount Dissolved (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2%-16%</td>
<td>5%-13%</td>
</tr>
<tr>
<td>3</td>
<td>50%-80%</td>
<td>55%-75%</td>
</tr>
<tr>
<td>7</td>
<td>NLT 85%</td>
<td>NLT 90%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin \((C_8H_6N_4O_5)\) dissolved at the specified times conform to \textit{Dissolution (711)}, \textit{Acceptance Table 2}.

\textbf{Test 4} (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms): If the product complies with this test, the labeling indicates that it meets USP \textit{Dissolution Test 4}.

\textbf{Acid medium}: 0.01 N hydrochloric acid for 1 h; 900 mL, deaerated

\textbf{pH 7.5 buffer medium}: Prepare a pH 7.5 buffer concentrate by dissolving 62.2 g of potassium hydroxide and 129.3 g of monobasic potassium phosphate in water, dilute with water to 1 L, and mix. After 1 h change the \textit{Acid medium} to \textit{pH 7.5 buffer medium} by adding 50 mL of pH 7.5 buffer concentrate, and run for an additional 9 h.

\textbf{Apparatus 2}: 100 rpm, with helix sinkers

\textbf{Times}: 1, 3, and 10 h

\textbf{Standard stock solution}: Transfer 25 mg of \textit{USP Nitrofurantoin RS} to a 10-mL volumetric flask. Add 7.5 mL of dimethylformamide, and sonicate until dissolved. Allow to cool to room temperature, and dilute with dimethylformamide to volume.

\textbf{Acid-stage standard solution}: Dilute 2.0 mL of the \textit{Standard stock solution} with \textit{Acid medium} to 200 mL.
**Buffer-stage standard solution:** Transfer 3.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, and dilute with *pH 7.5 buffer medium* to volume.

**Stock capsule shell blank:** Place 10 empty, clean Capsules into a 900-mL volumetric flask, and add 800 mL of *Acid medium*. Gently heat to 37 ± 0.5°, and stir until all the Capsules are dissolved. Allow to cool to room temperature, and dilute with *Acid medium* to volume.

**Buffer-stage capsule shell blank:** Transfer 100.0 mL of the *Stock capsule shell blank* to a 1000-mL volumetric flask. Add 56 mL of *pH 7.5 buffer medium*, dilute with *Acid medium* to volume, and mix. Filter, using the same filter as for the *Sample solution*.

**Sample solution:** Pass portions of the solution under test through a 1.2-µm glass/0.45-µm polyethersulfone combination filter, discarding the first few mL.

**Instrumental conditions**
- **Mode:** UV
- **Analytical wavelength:** 375 nm

**Analysis:** Calculate the percentages of the labeled amount of nitrofurantoin (C₈H₆N₄O₅) dissolved from portions of the *Sample solution* in comparison with the appropriate *Acid-stage standard solution* or *Buffer-stage standard solution*. Correct for the appropriate capsule shell blank absorbance, using a 0.1-cm cell, and the appropriate medium as the blank.

**Tolerances:** See *Table 5*.

### Table 5

<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>3</td>
<td>25%–50%</td>
</tr>
<tr>
<td>10</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin (C₈H₆N₄O₅) dissolved at the specified times conform to *Dissolution (711), Acceptance Table 2*.

**Test 5** (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms): If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

**Acid medium:** 0.01 N hydrochloric acid for 1 h; 900 mL, deaerated

**Buffer concentrate:** 60 g/L of potassium hydroxide and 129.3 g/L of monobasic potassium phosphate in water

**pH 7.5 buffer medium:** Prepare by adding 60 mL of *Buffer concentrate* to 890 mL of *Acid medium*.

**Apparatus 2:** 100 rpm, with Teflon-coated sinkers and paddles

**Times:** 1, 3, and 7 h

**Standard stock solution:** 2.48 mg/mL of *USP Nitrofurantoin RS* in acetonitrile. Sonicate using 50% of the final volume of acetonitrile to dissolve. Use an amber volumetric flask.

**Acid-stage standard solution:** 24.8 µg/mL of *USP Nitrofurantoin RS* in *Acid medium* from *Standard stock solution*. Use an amber volumetric flask.

**Buffer-stage standard solution:** 74.4 µg/mL of *USP Nitrofurantoin RS* in *pH 7.5 buffer medium* from *Standard stock solution*. Use an amber volumetric flask.

**Acid-stage sample solution:** After 1 h, collect 10 mL of the solution under test, and pass through a 0.45-µm PVDF filter, discarding the first 5 mL of the filtrate.

**Buffer-stage sample solution:** After removing 10 mL of *Acid medium*, add 60 mL of *pH 7.5 buffer medium*. The pH of the resulting medium should be about 7.5. Continue the dissolution for another 2 h and 6 h.
Collect 10 mL at each time point, and pass through a 0.45-μm PVDF filter, discarding the first 5 mL of the filtrate.

**Acid-stage blank:** Use *Acid medium.*

**Buffer-stage blank:** Use *pH 7.5 buffer medium.*

**Instrumental conditions**

- **Mode:** UV
- **Analytical wavelength:** 375 nm
- **Cell:** 0.5 cm for acid-stage and 0.1 cm for buffer-stage

**Analysis**

**Samples:** Acid-stage standard solution, Buffer-stage standard solution, Acid-stage sample solution, Buffer-stage sample solution, Acid-stage blank, and Buffer-stage blank

Calculate the concentration \(C_i\) of nitrofurantoin \((C_6H_6N_4O_3)\) in the sample withdrawn from the vessel at each time point \(i\):

\[
\text{Result}_i = (A_U / A_S) \times C_S
\]

- \(A_U\) = absorbance of the Sample solution
- \(A_S\) = absorbance of the Standard solution
- \(C_S\) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of nitrofurantoin \((C_6H_6N_4O_3)\) dissolved at each time point \(i\):

\[
\text{Result}_1 = C_1 \times V_1 \times (1/L) \times 100
\]

\[
\text{Result}_2 = [(C_2 \times V_2) + (C_1 \times V_S)] \times (1/L) \times 100
\]

\[
\text{Result}_3 = [(C_3 \times V_3) + ((C_2 + C_1) \times V_S)] \times (1/L) \times 100
\]

- \(C_i\) = concentration of nitrofurantoin in the portion of sample withdrawn at the specified time point (mg/mL)
- \(V_1\) = volume of medium, 900 mL
- \(L\) = label claim (mg/Capsule)
- \(V_2\) = volume of medium, 950 mL
- \(V_S\) = volume of the Sample solution withdrawn at each time point, 10 mL
- \(V_3\) = volume of medium, 940 mL

**Tolerances:** See **Table 6.**

**Table 6**

<table>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved (\text{(Individual)})</th>
<th>Amount Dissolved (\text{(Mean)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 12%</td>
<td>NMT 12%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>NLT 80%</td>
<td>80%–100%</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>NLT 85%</td>
<td>NLT 90%</td>
</tr>
</tbody>
</table>
The percentages of the labeled amount of nitrofurantoin (C₉H₆N₄O₅) dissolved at the specified times conform to Table 7.

**Table 7**

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₁</td>
<td>12</td>
<td>The mean percentage of dissolved label claim lies within the range for the means at each interval and is NLT the stated amount at the final test time. All individual values lie within the ranges for the individuals at each interval and are NLT the stated amount at the final test time.</td>
</tr>
<tr>
<td>L₂</td>
<td>12</td>
<td>If the requirements of level L₁ are not met, test another twelve (12) Capsules. The requirements are met if the mean percentage of dissolved label claim of all 24 Capsules tested lies within the range for the means at each interval and is NLT the stated amount at the final test time. NMT 2 of the 24 individual values of Capsules lie outside the stated range for individuals at each interval, and NMT 2 of 24 Capsules are less than the stated amount at the final test time.</td>
</tr>
</tbody>
</table>

**Test 6** (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms): If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 6.

**Acid medium:** 0.01 N hydrochloric acid; 900 mL

**pH 7.5 buffer concentrate:** Prepare a pH 7.5 buffer concentrate by dissolving 62.2 g of potassium hydroxide and 129.3 g of monobasic potassium phosphate in water and dilute with water to 1 L.

**pH 7.5 buffer medium:** 900 mL of Acid medium and 50 mL of pH 7.5 buffer concentrate

**Apparatus 2:** 100 rpm, with sinkers made of Teflon-coated steel wire prepared by forming a coil approximately 22 mm long from a 13-cm length of 20-gauge wire (see Figure 1 in Dissolution Test 2)

**Times**

- **Acid stage:** 1 h
- **Buffer stage:** 3, 4, and 7 h

**Acid-stage standard stock solution:** 0.11 mg/mL of USP Nitrofurantoin RS in Acid medium prepared as follows. Weigh a suitable amount of USP Nitrofurantoin RS in a volumetric flask and add about 2.5% of the flask volume of N,N-dimethylformamide. Sonicate to dissolve completely. Dilute with Acid medium to final volume.

**Acid-stage standard solution:** 4.4 µg/mL of USP Nitrofurantoin RS in Acid medium from Acid-stage standard stock solution

**Buffer-stage standard stock solution:** 0.11 mg/mL of USP Nitrofurantoin RS in pH 7.5 buffer medium prepared as follows. Weigh a suitable amount of USP Nitrofurantoin RS in a volumetric flask and add about 2.5% of the flask volume of N,N-dimethylformamide. Sonicate to dissolve completely. Dilute with pH 7.5 buffer medium to final volume.

**Buffer-stage standard solution:** 4.4 µg/mL of USP Nitrofurantoin RS in pH 7.5 buffer medium from Buffer-stage standard stock solution

**Acid-stage sample solution:** Pass portions of the solution under test through a suitable filter and discard the first few mL. Dilute with Acid medium, if necessary.

**Buffer-stage sample solution:** Pass portions of the solution under test through a suitable filter and discard the first few mL. Dilute with pH 7.5 buffer medium, if necessary.

**Instrumental conditions**

- **Mode:** UV
Analytical wavelength: 375 nm
Dissolution medium: After 1 h in the Acid medium, withdraw 10 mL of the solution under test and add 50 mL of pH 7.5 buffer concentrate.
Analysis: After 1 h in Acid medium, withdraw 10 mL of solution under test. Add 10 mL of Acid medium, previously warmed to 37 ± 0.5°. Add 50 mL of pH 7.5 buffer concentrate, previously warmed to 37 ± 0.5° and continue the test for 6 h more. At specified times, withdraw 10 mL of solution under test and replace with 10 mL of pH 7.5 buffer medium, previously warmed to 37 ± 0.5°. Calculate the percentages of the labeled amount of nitrofurantoin (C₈H₆N₄O₅) dissolved from portions of the Acid-stage sample solution or Buffer-stage sample solution in comparison with the appropriate Acid-stage standard solution or Buffer-stage standard solution. Correct for the appropriate capsule shell blank absorbance and the appropriate medium as the blank.
Tolerances: See Table 8.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (Individual)</th>
<th>Amount Dissolved (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2%–16%</td>
<td>3%–11%</td>
</tr>
<tr>
<td>3</td>
<td>15%–45%</td>
<td>22%–37%</td>
</tr>
<tr>
<td>4</td>
<td>45%–95%</td>
<td>65%–85%</td>
</tr>
<tr>
<td>7</td>
<td>NLT 80%</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin (C₈H₆N₄O₅) dissolved at the specified times conform to Dissolution (711), Acceptance Table 2.

Test 7 (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms): If the product compiles with this test, the labeling indicates that it meets USP Dissolution Test 7.

Acid medium: 0.01 N hydrochloric acid, degassed; 900 mL
Buffer concentrate: 62.2 g/L of potassium hydroxide and 129.3 g/L of monobasic potassium phosphate in water
pH 7.5 buffer medium: Prepare by adding 50 mL of Buffer concentrate to 900 mL of Acid medium. Adjust to pH 7.5 ± 0.05 with 1 N hydrochloric acid or 1 N potassium hydroxide
Apparatus 2: 100 rpm, with Teflon-coated helix sinkers
Times: 1, 3, and 7 h
Standard stock solution: 2.5 mg/mL of USP Nitrofurantoin RS in dimethylformamide. Sonicate to dissolve prior to final dilution.
Acid stage standard solution: 0.025 mg/mL of USP Nitrofurantoin RS in Acid medium from Standard stock solution. Prepare this solution immediately before use by diluting from the Standard stock solution.
Buffer stage standard solution: 0.075 mg/mL of USP Nitrofurantoin RS in pH 7.5 buffer medium from Standard stock solution.
Acid stage sample solution: After 1 h, collect 10 mL of the solution under test, and pass through a suitable filter of 0.45-μm pore size, transferring the first 5 mL of the filtrate back into the dissolution vessel.
Buffer stage sample solution: After removing 10 mL of Acid medium, add 50 mL of pH 7.5 buffer medium. Adjust the pH of the resulting medium to 7.5 ± 0.05 with 1 N hydrochloric acid or 1 N potassium hydroxide, if necessary. Continue collecting 10-mL solution under test at each time point, and pass through a suitable filter of 0.45-μm pore size, transferring the first 5 mL of the filtrate back into the dissolution vessel.
Acid stage blank: Use Acid medium.
Buffer stage blank: Use pH 7.5 buffer medium.
Instrumental conditions
**Mode:** UV  
**Analytical wavelength:** 375 nm  
**Cell:** 0.5 cm for acid stage and 0.1 cm for buffer stage  

### System suitability

**Sample:** Acid stage standard solution  
**Suitability requirement**  
**Relative standard deviation:** NMT 2.0%  

### Analysis

**Samples:** Acid stage standard solution, Buffer stage standard solution, Acid stage sample solution, Buffer stage sample solution, Acid stage blank, and Buffer stage blank  
Calculate the concentration ($C_i$) of nitrofurantoin ($C_8H_6N_4O_5$) in the sample withdrawn from the vessel at each time point $(i)$:

$$\text{Result}_i = (A_U/A_S) \times C_S$$

- $A_U$ = absorbance of the Sample solution  
- $A_S$ = absorbance of the Standard solution  
- $C_S$ = concentration of the Standard solution (mg/mL)  

Calculate the percentage of the labeled amount of nitrofurantoin ($C_8H_6N_4O_5$) dissolved at each time point $(i)$:

$$\text{Result}_1 = C_I \times V_I \times (1/L) \times 100$$

$\text{Result}_2 = [(C_2 \times V_2) + (C_I \times V_S)] \times (1/L) \times 100$

$\text{Result}_3 = [(C_3 \times V_3) + [(C_2 + C_I) \times V_S]] \times (1/L) \times 100$

- $C_I$ = concentration of nitrofurantoin in the portion of sample withdrawn at the specified time point (mg/mL)  
- $V_I$ = volume of medium, 900 mL  
- $L$ = label claim (mg/Capsule)  
- $V_2$ = volume of medium, 945 mL  
- $V_S$ = volume of the Sample solution withdrawn at each time point, 5 mL  
- $V_3$ = volume of medium, 940 mL  

### Tolerances:

See Table 9.

<table>
<thead>
<tr>
<th>Time point $(i)$</th>
<th>Time $(h)$</th>
<th>Amount Dissolved $(%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 23</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>55 – ▲85 $(\text{RB 1-Nov-2020})$</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

Table 9
The percentages of the labeled amount of nitrofurantoin \((C_8H_6N_4O_5)\) dissolved at the specified times conform to Dissolution (711), Acceptance Table 2.

**Test 8** (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms): If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 8.

**Acid medium, pH 7.5 buffer medium, Apparatus 2, Times, Acid-stage standard solution, Buffer-stage standard solution, Instrumental conditions**, and **Analysis**: Proceed as directed in Dissolution Test 2.

**Tolerances**: See Table 10.

### Table 10

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (individual, %)</th>
<th>Amount Dissolved (mean, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 17</td>
<td>NMT 17</td>
</tr>
<tr>
<td>3</td>
<td>27–69</td>
<td>35–59</td>
</tr>
<tr>
<td>7</td>
<td>NLT 68</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin \((C_8H_6N_4O_5)\) dissolved at the specified times conform to Table 11.

### Table 11

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₁</td>
<td>12</td>
<td>The mean percentage of dissolved label claim lies within the range for the means at each interval and is NLT the stated amount at the final test time. All individual values lie within the ranges for the individuals at each interval and are NLT the stated amount at the final test time.</td>
</tr>
<tr>
<td>L₂</td>
<td>12</td>
<td>The mean percentage of dissolved label claim lies within the range for the means at each interval and is NLT the stated amount at the final test time. NMT 2 of the 24 individual values lie outside the stated ranges for individuals at each interval, and NMT 2 of 24 are less than the stated amount at the final test time.</td>
</tr>
</tbody>
</table>

- **Uniformity of Dosage Units (905)**

**Procedure for content uniformity**

**Solution A, Mobile phase, Internal standard solution, Standard solution, Chromatographic system, and Analysis**: Proceed as directed in the Assay.

**Sample solution**: Transfer the contents of 1 Capsule to a suitable flask, and add a volume of dimethylformamide to obtain a solution having a concentration of about 1.2 mg/mL of nitrofurantoin. Shake the flask for 15 min. If necessary, the sample may be homogenized, using a disperser. In the case of a 50- or 100-mg Capsule, transfer 40.0 mL of this solution to a suitable flask, add 50.0 mL of Internal standard solution, mix, and cool to room temperature. Pass a portion of the solution through a nylon filter of 0.45-µm pore size, discarding the first few mL of the filtrate. In the case of a 25-mg Capsule, transfer 20.0 mL of the solution to a suitable flask, and add 25.0 mL of Internal standard solution instead of 50.0 mL.

**Acceptance criteria**: Meet the requirements

**IMPURITIES**
Organic Impurities: Limit of Nitrofurazone

Solution A: Prepare as directed in the Assay.

Mobile phase: Tetrahydrofuran and Solution A (1:9)

System suitability stock solution: 5.0 µg/mL each of nitrofurazone and nitrofurantoin in dimethylformamide

System suitability solution: System suitability stock solution and Mobile phase (1:10)

Standard stock solution: 5.0 µg/mL of USP Nitrofurazone RS in dimethylformamide

Standard solution: Transfer 2.0 mL of the Standard stock solution into a glass-stoppered flask, add 20.0 mL of water, and mix.

Sample solution: Transfer a portion of Capsule contents equivalent to 100 mg of nitrofurantoin into a 25-mL glass-stoppered flask. Add 2.0 mL of dimethylformamide, and shake for 5 min. Add 20.0 mL of water, mix, and allow to stand for 15 min. Pass a portion of the mixture through a nylon filter of 0.45-µm pore size.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 375 nm

Column: 3.9-mm x 30-cm; packing L1

Flow rate: 1.6 mL/min

Injection volume: 60–100 µL

System suitability

Samples: System suitability solution and Standard solution

[Note—Adjust the operating parameters so that the nitrofurazone peak in the chromatogram of the Standard solution has a retention time of about 10.5 min and a height of about 0.1 full-scale.]

Suitability requirements

Resolution: NLT 4.0 between the nitrofurazone and nitrofurantoin peaks, System suitability solution

Relative standard deviation: NMT 2.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution

Acceptance criteria: The height of any peak from the Sample solution at a retention time corresponding to that of the main peak from the Standard solution is NMT the height of the main peak from the Standard solution. NMT 0.01% of nitrofurazone is found.

Additional Requirements

• Packaging and Storage: Preserve in tight containers, and store at controlled room temperature.

• Labeling: Capsules that contain the macrocrystalline form of nitrofurantoin are so labeled. 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 Nitrofurantoin RS
  USP Nitrofurazone RS

Page Information:

Not Applicable

DocID: © 2020 The United States Pharmacopeial Convention All Rights Reserved.