Nitrofurantoin Capsules

Type of Posting: Notice of Intent to Revise
Posting Date: 30–Aug–2019
Targeted Official Date: To Be Determined, Revision Bulletin
Expert Committee: Chemical Medicines Monographs 1

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 1 Expert Committee intends to revise the Nitrofurantoin Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add Dissolution Test 9 to accommodate a drug product with different dissolution conditions and/or tolerances than the existing dissolution tests.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Shankari Shivaprasad, Senior Scientific Liaison to the Chemical Medicines Monographs 1 Expert Committee (301-230-7426 or sns@usp.org).

¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Nitrofurantoin Capsules

**DEFINITION**
Nitrofurantoin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of nitrofurantoin (C₅H₄N₂O₃).

**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° 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. ASSAY**
  
  **Sample solution:** Transfer, as completely as possible, the emptied Capsules with another two 25-mL portions of water, dilute with water to 1 L.

  **Standard solution:** Dissolve 50 mg of USP Nitrofurantoin RS in 40.0 mL of dimethylformamide, and add 50.0 mL of Internal standard solution.

**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 acetonilide 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 x 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 acetonilide 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 (C₅H₄N₂O₃) in the portion of the powder included in the sample aliquot:

\[
\text{Result} = \frac{R_s}{R_i} \times \left( \frac{C_i}{C_s} \right) \times 100
\]

\[
R_s = \text{peak response ratio from the Sample solution}
\]

\[
R_i = \text{peak response ratio from the Standard solution}
\]

\[
C_s = \text{concentration of USP Nitrofurantoin RS}
\]

\[
C_i = \text{nominal concentration of the Sample solution}
\]

**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>
<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 (C₅H₄N₂O₃) 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)
2 Nitrofurantoin

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) of nitrofurantoin (C₇H₆N₃O₅) 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>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin (C₇H₆N₃O₅) dissolved at the specified times conform to Table 3.

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>L₁</td>
</tr>
<tr>
<td>L₂</td>
</tr>
</tbody>
</table>

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 Dissolution Test 3.

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

Tolerances: See Table 4.

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin (C₇H₆N₃O₅) dissolved at the specified times conform to Dissolution (711), Acceptance Table 2.

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 Dissolution Test 4.

Acid medium: 0.01 N hydrochloric acid for 1 h; 900 mL, deaeerated
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 9 h.

Apparatus 2: 100 rpm, with helix sinkers
Times: 1, 3, and 10 h

Standard stock solution: Transfer 25 mg of 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.

Acid-stage standard solution: Dilute 2.0 mL of the Standard stock solution with 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 (C₇H₆N₃O₅) 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>
<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 \((C_9H_8N_2O_4)\) dissolved at the specified times conform to \(\text{Dissolution (711), Acceptance Table 2.}\)

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 \(\text{Dissolution Test 5.}\)

**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 \(\text{Buffer concentrate to 890 mL of Acid medium.}\)

**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 \(\text{Acid medium from Standard stock solution.}\) Use an amber volumetric flask.

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

**Buffer-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 \(\text{Acid medium, add 60 mL of pH 7.5 buffer medium.}\) 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.

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

**Buffer-stage blank:** Use \(\text{pH 7.5 buffer medium.}\)

**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 \((C_9H_8N_2O_4)\) in the sample withdrawn from the vessel at each time point \((t)\):

\[
\text{Result}_i = \left(\frac{A_i}{A_0}\right) \times C_i
\]

\(A_0\) = absorbance of the Sample solution

\(A_i\) = absorbance of the Standard solution

\(C_i\) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of nitrofurantoin \((C_9H_8N_2O_4)\) dissolved at each time point \((t)\):

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

\[
\text{Result}_2 = \left[\left(C_i \times V_i\right) + \left(C_i \times V_j\right)\right] \times (1/L) \times 100
\]

\[
\text{Result}_3 = \left[\left(C_i \times V_i\right) + \left(C_i + C_0 \times V_j\right)\right] \times (1/L) \times 100
\]

\(C_i\) = 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)

\(V_j\) = volume of the Sample solution withdrawn at each time point, 10 mL

\(V_j\) = volume of medium, 940 mL

**Tolerances:** See Table 6.

<table>
<thead>
<tr>
<th>Time Point (t)</th>
<th>Time (h)</th>
<th>Amount Dissolved (Individual)</th>
<th>Amount Dissolved (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 \((C_9H_8N_2O_4)\) dissolved at the specified times conform to Table 7.

<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>If the requirements of level (L_1) 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 \(\text{Dissolution Test 6.}\)

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

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

**pH 7.5 buffer medium:** 900 mL of \(\text{Acid medium and 50 mL of pH 7.5 buffer concentrate}\)

**Apparatus 2:** 100 rpm, with sinkers made of Teflon-coated steel wire prepared by forming a coil...
Nitrofurantoin

If the product complies 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.

Tolerances: See Table 8.

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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.

Acid stage blank: Use Acid medium.

Buffer stage blank: Use pH 7.5 buffer medium.

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>

Table 8: Dissolution

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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 2.

Test 7 (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 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.

Tolerances: See Table 8.

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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.

Acid stage blank: Use Acid medium.

Buffer stage blank: Use pH 7.5 buffer medium.

Table 8: Dissolution

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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 2.

Test 7 (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 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.

Tolerances: See Table 8.

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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.

Acid stage blank: Use Acid medium.

Buffer stage blank: Use pH 7.5 buffer medium.

Table 8: Dissolution

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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 2.

Test 7 (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 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.

Tolerances: See Table 8.

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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.

Acid stage blank: Use Acid medium.

Buffer stage blank: Use pH 7.5 buffer medium.

Table 8: Dissolution

The percentages of the labeled amount of nitrofurantoin (C₆H₄N₃O₃) 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 2.

Test 7 (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms):
Nitrofurantoin 5

Medium: pH 7.2 (±0.05) phosphate buffer; 900 mL
Apparatus 1: 100 rpm

Times
For 25-mg strength: 0.5, 1, and 6 h
For 50-mg strength: 1, 3, and 8 h
For 100-mg strength: 1, 3, and 12 h

Standard stock solution: 1.1 mg/mL of USP Nitrofurantoin RS in Medium prepared as follows. Dissolve a suitable amount of USP Nitrofurantoin RS in 5% of the flask volume of dimethylformamide. Dilute with Medium to volume.

Standard solution: (L/900) mg/mL of USP Nitrofurantoin RS in Medium from Standard stock solution

Sample solution: Centrifuge a portion of the solution under test and use the supernatant for analysis. [Note—Centrifuge at 5000 rpm for about 5 min is suitable]. Dilute with Medium, if necessary.

Blank: Medium

Instrumental conditions
Mode: UV
Analytical wavelength: 375 nm
Cell length
For 25-mg strength: 0.2 cm
For 50-and 100-mg strength: 0.1 cm

Tolerances: See Table 12 for 25-mg strength.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>15–35</td>
</tr>
<tr>
<td>1</td>
<td>35–55</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

See Table 13 for 50-mg strength.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29–49</td>
</tr>
<tr>
<td>3</td>
<td>55–75</td>
</tr>
<tr>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

See Table 14 for 100-mg strength.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27–47</td>
</tr>
<tr>
<td>3</td>
<td>48–68</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin (C₈H₇N₂O₃) dissolved at the specified times conform to Dissolution (711), Acceptance Table 2. ▲(TBD)

• **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

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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 × 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