Nitrofurantoin Capsules

Type of Posting                  Revision Bulletin
Posting Date                    25–May–2018
Official Date                   01–Jun–2018
Expert Committee                Chemical Medicines Monographs 1
Reason for Revision             Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Nitrofurantoin Capsules monograph. The purpose for the revision is to add *Dissolution Test 7* to accommodate FDA-approved drug products.

The Nitrofurantoin Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Shankari Shivaprasad, Ph.D., Senior Scientific Liaison (301-230-7426 or sns@usp.org).
Nitrofurantoin Capsules

DEFINITION
Nitrofurantoin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of nitrofurantoin (C₉H₇N₃O₃).

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. 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 acetanilide 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 acetanilide 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 (C₉H₇N₃O₃) in the portion of the powder included in the sample aliquot:

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

\(R_u\) = 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)
\(C_p\) = 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 microcrystals)
  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 (C₉H₇N₃O₃) 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 microcrystalline 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)
Nitrofurantoin

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Official June 1, 2018

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 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 68%</td>
<td>NLT 81%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of nitrofurantoin (C₆H₆N₃O₅) 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, deaerated

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 (C₆H₆N₃O₅) 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.
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 stock solution in a 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 \( (\text{C}_3\text{H}_4\text{N}_2\text{O}_5) \) in the sample withdrawn from the vessel at each time point \((i)\):

\[
\text{Result}_i = (A_i / A_j) \times C_j
\]

\( A_i \) = absorbance of the Sample solution

\( A_j \) = absorbance of the Standard solution

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

The mean percentage of dissolved label claim of all 24 Capsules 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.

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 sinks 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

The percentages of the labeled amount of nitrofurantoin \( (\text{C}_3\text{H}_4\text{N}_2\text{O}_5) \) dissolved at the specified times conform to Table 7.
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 the 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 the 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 (C₈H₉N₂O₄) dissolved at each time point (i) of nitrofurantoin (C₈H₉N₂O₄) 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 (C₈H₉N₂O₄) 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 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
Times: 1, 3, and 7 h

Standard stock solution: 2.5 mg/mL of USP Nitrofurantoin RS in Buffer stage blank.

Acid stage standard solution: 0.025 mg/mL of USP Nitrofurantoin RS in Buffer stage blank.

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) of nitrofurantoin (C₈H₉N₂O₄) in the sample withdrawn from the vessel at each time point (i):

Result₁ = (Aᵢ/Aₛ) × Cₛ

Aᵢ = absorbance of the Sample solution
Aₛ = absorbance of the Standard solution
Cₛ = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of nitrofurantoin (C₈H₉N₂O₄) dissolved at each time point (i):

Result₂ = (Cᵢ × Vᵢ × (1/L) × 100
Result₃ = [(Cᵢ × Vᵢ) + (Cᵢ × Vᵢ)] × (1/L) × 100
Result₄ = [(Cᵢ × Vᵢ) + (Cᵢ × Vᵢ)] × (1/L) × 100

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= concentration of nitrofurantoin in the portion of sample withdrawn at the specified time point (mg/mL)

\[ V_j \]

= volume of medium, 900 mL

\[ L \]

= label claim (mg/Capsule)

\[ V_k \]

= volume of medium, 945 mL

\[ V_i \]

= volume of the Sample solution withdrawn at each time point, 5 mL

\[ V_j \]

= volume of medium, 940 mL

Tolerances: See Table 9.

<table>
<thead>
<tr>
<th>Time point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 23</td>
</tr>
<tr>
<td>2</td>
<td>55–80</td>
</tr>
<tr>
<td>3</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

Table 9

The percentages of the labeled amount of nitrofurantoin \((C_8H_7N_3O_2)\) dissolved at the specified times conform to Dissolution (711), Acceptance Table 2.▲ (08.1-Jun-2018)

**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 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

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

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