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 ($C_8H_6N_4O_5$).

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 ($C_8H_6N_4O_5$) in the portion of the powder included in the sample aliquot:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

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

Time (h)	Amount Dissolved
1	20%–60%
3	NLT 45%
8	NLT 60%

The percentage of the labeled amount of nitrofurantoin ($C_8H_6N_4O_5$) 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*)

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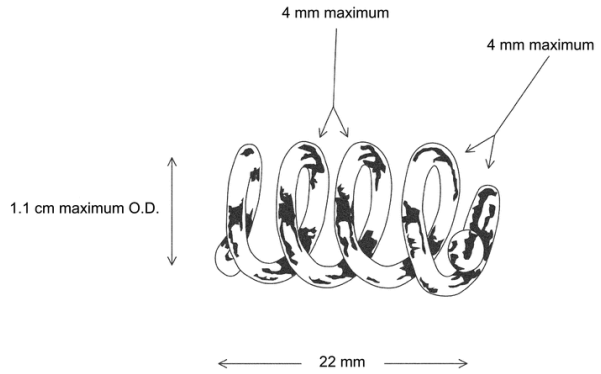

Figure 1. Sinker.

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_i) of nitrofurantoin ($C_8H_6N_4O_5$) 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 2

Time (h)	Amount Dissolved (Individual)	Amount Dissolved (Mean)
1	2%–16%	5%–13%
3	27%–69%	39%–56%
7	NLT 68%	NLT 81%

The percentages of the labeled amount of nitrofurantoin ($C_8H_6N_4O_5$) dissolved at the specified times conform to *Table 3*.

Table 3

Level	Number Tested	Criteria
L_1	12	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.
L_2	12	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.

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 4

Time (h)	Amount Dissolved (Individual)	Amount Dissolved (Mean)
1	2%–16%	5%–13%
3	50%–80%	55%–75%
7	NLT 85%	NLT 90%

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 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 ($C_8H_6N_4O_5$) 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.

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Tolerances: See *Table 5*.

Table 5

Time (h)	Amount Dissolved
1	NMT 25%
3	25%–50%
10	NLT 80%

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 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 ($C_8H_6N_4O_5$) 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*):

$$\text{Result}_1 = C_1 \times V_1 \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V_2) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V_3) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

Time Point (*i*)	Time (h)	Amount Dissolved (Individual)	Amount Dissolved (Mean)
1	1	NMT 12%	NMT 12%
2	3	NLT 80%	80%–100%
3	7	NLT 85%	NLT 90%

The percentages of the labeled amount of nitrofurantoin ($C_8H_6N_4O_5$) dissolved at the specified times conform to *Table 7*.

Table 7

Level	Number Tested	Criteria
L_1	12	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.
L_2	12	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.

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

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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 ($C_8H_6N_4O_5$) 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 8

Time (h)	Amount Dissolved (Individual)	Amount Dissolved (Mean)
1	2%–16%	3%–11%
3	15%–45%	22%–37%
4	45%–95%	65%–85%
7	NLT 80%	NLT 85%

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 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 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 requirements

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):

$$\text{Result}_1 = C_1 \times V_1 \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V_2) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V_3) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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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, 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 9

Time point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 23
2	3	55–80
3	7	NLT 85

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

Time (h)	Amount Dissolved (individual, %)	Amount Dissolved (mean, %)
1	NMT 17	NMT 17
3	27–69	35–59
7	NLT 68	NLT 80

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

Table 11

Level	Number Tested	Criteria
L_1	12	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.
L_2	12	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.

▲**Test 9** (where it is labeled as containing nitrofurantoin macrocrystals)**:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 9*.
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 12

Time (h)	Amount Dissolved (%)
0.5	15–35
1	35–55
6	NLT 80

See *Table 13* for 50-mg strength.

Table 13

Time (h)	Amount Dissolved (%)
1	29–49
3	55–75
8	NLT 80

See *Table 14* for 100-mg strength.

Table 14

Time (h)	Amount Dissolved (%)
1	27–47
3	48–68
12	NLT 80

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*.▲ (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

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