

Extended Phenytoin Sodium Capsules

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Extended Phenytoin Sodium Capsules monograph. The purpose for the revision is to add *Dissolution Test 6* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). The revision also necessitates a change in the table number in the test for *Organic Impurities*.

- *Dissolution Test 6* was validated using the Inertsil ODS-3V brand of L1 column. The typical retention time for phenytoin is about 2.3 min.

The Extended Phenytoin Sodium Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Claire Chisolm, Scientific Liaison (301-230-3215 or cnc@usp.org).

Extended Phenytoin Sodium Capsules

DEFINITION

Extended Phenytoin Sodium Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$).

IDENTIFICATION

• **A. SPECTROSCOPIC IDENTIFICATION TESTS (197), Infrared Spectroscopy**

Sample: 300 mg of phenytoin sodium from the contents of Capsules in 50 mL of [water](#) in a separator. Add 10 mL of [3 N hydrochloric acid](#), and extract with three successive portions, measuring 100, 60, and 30 mL, respectively, of [ether](#) and [chloroform](#) (1:2). Evaporate the combined extracts, and dry the residue of phenytoin at 105° for 4 h.

Acceptance criteria: The spectrum of the *Sample* corresponds to that of a similarly prepared [USP Phenytoin RS](#).

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

• **PROCEDURE**

Buffer: 0.05 M [monobasic potassium phosphate](#). Adjust with [phosphoric acid](#) to a pH of 3.5.

Mobile phase: [Methanol](#) and *Buffer* (55:45)

Standard solution: 0.6 mg/mL of [USP Phenytoin RS](#) in *Mobile phase*. [NOTE—Dissolve the required quantity of phenytoin in a small amount of [methanol](#) before diluting with *Mobile phase*.]

Sample stock solution: Transfer the contents of 10 Capsules to a 250-mL volumetric flask. Add 150 mL of [methanol](#), and sonicate for 20 min. Cool to room temperature, and dilute with [methanol](#) to volume.

Sample solution: Nominally 0.6 mg/mL of phenytoin from the *Sample stock solution* in *Mobile phase*

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 229 nm

Column: 4.6-mm × 25-cm; packing [L1](#)

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 3000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of phenytoin from the *Sample solution*

r_S = peak response of phenytoin from the *Standard solution*

C_S = concentration of [USP Phenytoin RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of phenytoin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of phenytoin sodium, 274.25

M_{r2} = molecular weight of phenytoin, 252.27

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** (711)

Test 1

Medium: [Water](#); 900 mL

Apparatus 1: 50 rpm

Times: 30, 60, and 120 min

Mobile phase: [Methanol](#) and [water](#) (70:30)

Standard solution: Dissolve [USP Phenytoin RS](#) in [methanol](#), and dilute with [water](#) to obtain a concentration similar to that of the *Sample solution*.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 229 nm

Column: 4.6-mm × 25-cm; packing [L1](#)

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 3200 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times V \times (100/L)$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of [USP Phenytoin RS](#) in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of phenytoin sodium, 274.25

M_{r2} = molecular weight of phenytoin, 252.27

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances (for products labeled as 30-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 40% (Q) in 30 min, 56% (Q') in 60 min, and NLT 65% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to [Table 1](#).

Table 1

Stage	Number Tested	Acceptance Criteria
S ₁	6	Each unit is within the range between $Q - 15\%$ and $Q - 5\%$, is within the range $Q' \pm 10\%$, and is NLT $Q'' + 5\%$ at the stated <i>Times</i> .
S ₂	6	Average of 12 units ($S_1 + S_2$) is within the range between $Q - 10\%$ and Q , is within the range $Q' \pm 8\%$, and is NLT Q'' ; no unit is outside the range between $Q - 20\%$ and $Q + 10\%$, no unit is outside the range $Q' \pm 18\%$, and no unit is less than $Q'' - 10\%$ at the stated <i>Times</i> .
S ₃	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between $Q - 10\%$ and Q , is within the range $Q' \pm 8\%$, and is NLT Q'' ; NMT 2 units are outside the range between $Q - 20\%$ and $Q + 10\%$, and no unit is outside the range $Q - 30\%$ and $Q + 20\%$; NMT 2 units are outside the range $Q' \pm 18\%$, and no unit is outside the range $Q' \pm 25\%$; NMT 2 units are less than $Q'' - 10\%$, and no unit is less than $Q'' - 20\%$ at the stated <i>Times</i> .

Tolerances (for products labeled as 100-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 45% (Q) in 30 min, 60% (Q') in 60 min, and NLT 70% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to [Table 2](#).

Table 2

Stage	Number Tested	Acceptance Criteria
S ₁	6	Each unit is within the range between $Q - 25\%$ and $Q - 5\%$, is equal to $Q' \pm 20\%$, and is NLT $Q'' + 5\%$ at the stated <i>Times</i> .
S ₂	6	Average of 12 units ($S_1 + S_2$) is within the range between $Q - 20\%$ and Q , is within the range $Q' \pm 15\%$, and is NLT Q'' ; no unit is outside the range between $Q - 30\%$ and $Q + 10\%$, no unit is outside the range $Q' \pm 25\%$, and no unit is less than $Q'' - 10\%$ at the stated <i>Times</i> .
S ₃	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between $Q - 20\%$ and Q , is within the range $Q' \pm 15\%$, and is NLT Q'' ; NMT 2 units are outside the range between $Q - 30\%$ and $Q + 10\%$, and no unit is outside the range between $Q - 40\%$ and $Q + 20\%$; NMT 2 units are outside the range $Q' \pm 25\%$, and no unit is outside the range $Q' \pm 35\%$; NMT 2 units are less than $Q'' - 10\%$, and no unit is less than $Q'' - 20\%$ at the stated <i>Times</i> .

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. Proceed as directed in *Test 1*, except use *Apparatus 1* at 75 rpm and the following *Tolerances*.

Tolerances (for products labeled as 100-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 45% (Q) in 30 min, 65% (Q') in 60 min, and NLT 70% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to [Table 3](#).

Table 3

Stage	Number Tested	Acceptance Criteria
S ₁	6	Each unit is within the range between $Q - 25\%$ and $Q - 5\%$, is equal to $Q' \pm 20\%$, and is NLT $Q'' + 5\%$ at the stated <i>Times</i> .
S ₂	6	Average of 12 units ($S_1 + S_2$) is within the range between $Q - 25\%$ and $Q - 5\%$, is within the range of $Q' - 20\%$ and $Q' + 10\%$, and is NLT Q'' ; no unit is outside the range between $Q - 30\%$ and $Q + 5\%$, no unit is outside the range $Q' - 25\%$ and $Q' + 20\%$, and no unit is less than $Q'' - 10\%$ at the stated <i>Times</i> .
S ₃	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between $Q - 25\%$ and $Q - 5\%$, is within the range of $Q' - 20\%$ and $Q' + 10\%$, and is NLT Q'' ; NMT 2 units are outside the range between $Q - 30\%$ and $Q + 5\%$; and no unit is outside the range of $Q - 40\%$ and $Q + 15\%$; NMT 2 units are outside the range $Q' - 25\%$ and $Q' + 20\%$, and no unit is outside the range $Q' - 35\%$ and $Q' + 25\%$; NMT 2 units are less than $Q'' - 10\%$; and no unit is less than $Q'' - 20\%$ at the stated <i>Times</i> .

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: [Water](#); 900 mL

Apparatus 1: 75 rpm

Times: 30, 60, and 120 min

Determine the amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved by using the method described in *Test 1*.

Tolerances (for products labeled as 200- and 300-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 30% (Q) in 30 min, 50% (Q') in 60 min, and NLT 60% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to [Table 4](#).

Table 4

Stage	Number Tested	Acceptance Criteria
S ₁	6	Each unit is within the range between $Q - 20\%$ and $Q + 5\%$, is equal to $Q' - 20\%$ and $Q' + 25\%$, and is NLT $Q'' + 5\%$ at the stated <i>Times</i> .
S ₂	6	Average of 12 units ($S_1 + S_2$) is within the range between $Q - 20\%$ and Q , is within the range of $Q' \pm 20\%$, and is NLT Q'' ; no unit is outside the range between $Q - 25\%$ and $Q + 10\%$, no unit is outside the range $Q' \pm 25\%$, and no unit is less than $Q'' - 10\%$ at the stated <i>Times</i> .

Stage	Number Tested	Acceptance Criteria
S ₃	12	Average of 24 units (S ₁ + S ₂ + S ₃) is within the range between Q – 20% and Q, is within the range of Q' ± 20%, and is NLT Q"; NMT 2 units are outside the range between Q – 25% and Q + 10%, and no unit is outside the range Q – 25% and Q + 15%; NMT 2 units are outside the range Q' ± 25%; and no unit is outside the range Q' ± 30%; NMT 2 units are less than Q" – 10%; and no unit is less than Q" – 20% at the stated <i>Times</i> .

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium, Apparatus 1, Times, and Analysis: Proceed as directed for *Test 1*.

Tolerances (for products labeled as 30-mg Capsules): The percentage of the labeled amount of phenytoin sodium (C₁₅H₁₁N₂NaO₂) dissolved is NMT 40% (Q) in 30 min, 56% (Q') in 60 min, and NLT 65% (Q") in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to [Table 5](#).

Table 5

Stage	Number Tested	Acceptance Criteria
S ₁	6	Each unit is within the range between Q – 10% and Q, is within the range Q' – 9% and Q' + 7%, and is NLT Q" + 5% at the stated <i>Times</i> .
S ₂	6	Average of 12 units (S ₁ + S ₂) is within the range between Q – 8% and Q + 2%, is within the range Q' – 9% and Q' + 7%, and is NLT Q"; no unit is outside the range between Q – 20% and Q + 10%, no unit is outside the range Q' – 19% and Q' + 17%, and no unit is less than Q" – 10% at the stated <i>Times</i> .
S ₃	12	Average of 24 units (S ₁ + S ₂ + S ₃) is within the range between Q – 8% and Q + 2%, is within the range Q' – 9% and Q' + 7%, and is NLT Q"; NMT 2 units are outside the range between Q – 20% and Q + 10%, and no unit is outside the range Q – 30% and Q + 20%; NMT 2 units are outside the range Q' – 19% and Q' + 17%, and no unit is outside the range Q' – 26% and Q' + 24%; NMT 2 units are less than Q" – 10%, and no unit is less than Q" – 20% at the stated <i>Times</i> .

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium, Apparatus 1, Times, and Analysis: Proceed as directed for *Test 1*.

Tolerances (for products labeled as 100-mg Capsules): The percentage of the labeled amount of phenytoin sodium (C₁₅H₁₁N₂NaO₂) dissolved is NMT 45% (Q) in 30 min, 65% (Q') in 60 min, and NLT 80% (Q") in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to [Table 6](#).

Table 6

Stage	Number Tested	Acceptance Criteria
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Stage	Number Tested	Acceptance Criteria
S ₁	6	Each unit is within the range between $Q - 25\%$ and $Q - 5\%$, is between $Q' + 20\%$ and $Q' - 15\%$, and is NLT $Q'' + 5\%$ at the stated <i>Times</i> .
S ₂	6	Average of 12 units (S ₁ + S ₂) is within the range between $Q - 25\%$ and $Q - 5\%$, is within the range $Q' \pm 15\%$, and is NLT Q'' ; no unit is outside the range between $Q - 30\%$ and $Q + 10\%$, no unit is outside the range $Q' + 25\%$ and $Q' - 20\%$, and no unit is less than $Q'' - 10\%$ at the stated <i>Times</i> .
S ₃	12	Average of 24 units (S ₁ + S ₂ + S ₃) is within the range between $Q - 25\%$ and $Q - 5\%$, is within the range $Q' \pm 15\%$, and is NLT Q'' ; NMT 2 units are outside the range between $Q - 30\%$ and $Q + 10\%$, and no unit is outside the range $Q - 35\%$ and $Q + 20\%$; NMT 2 units are outside the range between $Q' + 25\%$ and $Q' - 20\%$, and no unit is outside the range $Q' + 30\%$ and $Q' - 25\%$; NMT 2 units are less than $Q'' - 10\%$, and no unit is less than $Q'' - 20\%$ at the stated <i>Times</i> .

▲ **Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: [Water](#); 900 mL, deaerated

Apparatus 1: 50 rpm

Times: 30, 60, and 180 min

Buffer: 2.72 g/L of [monobasic potassium phosphate](#) in [water](#). Adjust with [phosphoric acid](#) to a pH of 3.5.

Mobile phase: [Acetonitrile](#) and *Buffer* (50:50)

Standard stock solution: 2.0 mg/mL of [USP Phenytoin RS](#) in [methanol](#). Sonicate if necessary.

Standard solution: 0.1 mg/mL of [USP Phenytoin RS](#) from *Standard stock solution*, in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size, and discard the first 2 mL of filtrate. Replace the portion of solution removed from the vessel with an equivalent volume of *Medium* equilibrated to $37 \pm 0.5^\circ$.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 229 nm

Column: 4.6-mm \times 15-cm; 5 μ m packing [L1](#)

Column temperature: 35 $^\circ$

Flow rate: 1.5 mL/min

Injection volume: 10 μ L

Run time: NLT 1.7 times the retention time of phenytoin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the concentration (C_i) of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response of phenytoin from the *Sample solution*

r_S = peak response of phenytoin from the *Standard solution*

C_S = concentration of [USP Phenytoin RS](#) in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of phenytoin sodium, 274.25

M_{r2} = molecular weight of phenytoin, 252.27

Calculate the percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

C_i = concentration of phenytoin sodium in the portion of sample withdrawn at each time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* at each time point (mL)

Tolerances (for products labeled as 100-mg Capsules): See [Table 7](#).

Table 7

Time Point (<i>i</i>)	Time (min)	Amount Dissolved (%)
1	30	NMT 52 (<i>Q</i>)
2	60	65 (<i>Q'</i>)
3	180	NLT 80 (<i>Q''</i>)

The requirements are met if the percentages of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved from the Capsules at the times specified conform to [Table 8](#).

Table 8

Stage	Number Tested	Acceptance Criteria
L_2	12	Average of 12 units is within the range between $Q - 20\%$ and Q , is within the range $Q' \pm 10\%$, and is NLT Q'' ; no unit is outside the range between $Q - 30\%$ and $Q + 10\%$, no unit is outside the range $Q' \pm 20\%$, and no unit is less than $Q'' - 10\%$ at the stated <i>Times</i> .

Stage	Number Tested	Acceptance Criteria
L ₃	12	Average of 24 units (L ₂ + L ₃) is within the range between Q – 20% and Q, is within the range Q' ± 10%, and is NLT Q"; NMT 2 units are outside the range between Q – 30% and Q + 10%, and no unit is outside the range Q – 40% and Q + 20%; NMT 2 units are outside the range Q' ± 20%, and no unit is outside the range Q' ± 30%; NMT 2 units are less than Q" – 10%, and no unit is less than Q" – 20% at the stated <i>Times</i> . ▲ (RB 1-Mar-2021)

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Buffer, Mobile phase, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

Standard solution: 600 µg/mL of [USP Phenytoin RS](#), 3 µg/mL of [USP Phenytoin Related Compound A RS](#), and 3 µg/mL of [USP Phenytoin Related Compound B RS](#) in [methanol](#)

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for phenytoin related compound A, phenytoin related compound B, and phenytoin are 0.38, 0.45, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 8 between phenytoin related compound B and phenytoin; NLT 1.5 between phenytoin related compound A and phenytoin related compound B

Tailing factor: NMT 2.0 for the phenytoin peak

Relative standard deviation: NMT 2.0% for phenytoin; NMT 5.0% for phenytoin related compound A or phenytoin related compound B

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each phenytoin related compound in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of phenytoin related compound A or phenytoin related compound B from the *Sample solution*

r_S = peak response of phenytoin related compound A or phenytoin related compound B from the *Standard solution*

C_S = concentration of the corresponding analyte in the *Standard solution* (µg/mL)

C_U = nominal concentration of phenytoin in the *Sample solution* (µg/mL)

Calculate the percentage of any individual unspecified degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each unspecified degradation product from the *Sample solution*

r_S = peak response of phenytoin from the *Standard solution*

C_S = concentration of [USP Phenytoin RS](#) in the *Standard solution* (µg/mL)

C_U = nominal concentration of phenytoin in the *Sample solution* (µg/mL)

Acceptance criteria: See [▲Table 9](#).

Table 9▲ (RB 1-Mar-2021)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Phenytoin related compound A	0.38	0.5
Phenytoin related compound B	0.45	1.0
Phenytoin	1.0	—
Any individual, unspecified degradation product	—	0.2

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Protect from moisture. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** (11)

[USP Phenytoin RS](#)

[USP Phenytoin Related Compound A RS](#)

Diphenylglycine.

$C_{14}H_{13}NO_2$ 227.26

[USP Phenytoin Related Compound B RS](#)

Diphenylhydantoic acid.

$C_{15}H_{14}N_2O_3$ 270.29

Page Information:

Not Applicable

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