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Extended Phenytoin Sodium Capsules

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-ext-phenytoin-na-caps-20210226.

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

Change to read:

- **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 ▲sodium▲ (ERR 1-Jan-2022) 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 ▲sodium▲ (ERR 1-Jan-2022) 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

• **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*' ± 10%, and is NLT *Q*" + 5% at the stated *Times*.
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*' ± 8%, and is NLT *Q*"; no unit is outside the range between *Q* − 20% and *Q* + 10%, no unit is outside the range *Q*' ± 18%, and no unit is less than *Q*" − 10% at the stated *Times*.
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*' ± 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*' ± 18%, and no unit is outside the range *Q*' ± 25%; NMT 2 units are less than *Q*" − 10%, and no unit is less than *Q*" − 20% at the stated *Times*.

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*' ± 20%, and is NLT *Q*" + 5% at the stated *Times*.
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*' ± 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 no unit is less than *Q*" − 10% at the stated *Times*.
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*' ± 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*' ± 25%, and no unit is outside the

Stage	Number Tested	Acceptance Criteria
		range Q' ± 35%; NMT 2 units are less than Q'' − 10%, and no unit is less than Q'' − 20% at the stated *Times*.

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' ± 20%, and is NLT Q'' + 5% at the stated *Times*.
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 *Times*.
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 *Times*.

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 *Times*.
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*' ± 20%, and is NLT *Q*"; no unit is outside the range between *Q* − 25% and *Q* + 10%, no unit is outside the range *Q*' ± 25%, and no unit is less than *Q*" − 10% at the stated *Times*.
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 *Times*.

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 ($C_{15}H_{11}N_2NaO_2$) 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 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 *Times*.
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 *Times*.
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

Stage	Number Tested	Acceptance Criteria
		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 *Times*.

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 ($C_{15}H_{11}N_2NaO_2$) 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
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 *Times*.
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*' ± 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 *Times*.
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*' ± 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 *Times*.

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-µm 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 ± 0.5°.

Chromatographic system

(See *Chromatography (621), System Suitability*.)

Mode: LC

Detector: UV 229 nm

Column: 4.6-mm × 15-cm; 5 µm packing L1

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

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*)	Time (min)	Amount Dissolved (%)
1	30	NMT 52 (*Q*)
2	60	65 (*Q*′)

Time Point (*i*)	Time (min)	Amount Dissolved (%)
3	180	NLT 80 (*Q*")

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*' ± 10%, and is NLT *Q*"; no unit is outside the range between *Q* − 30% and *Q* + 10%, no unit is outside the range *Q*' ± 20%, and no unit is less than *Q*" − 10% at the stated *Times*.
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 *Times*.

• **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 ▲sodium▲ (ERR 1-Jan-2022) 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 ▲sodium▲ (ERR 1-Jan-2022) in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 9*.

Table 9

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

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
EXTENDED PHENYTOIN SODIUM CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

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