Extended Phenytoin Sodium Capsules

» Extended Phenytoin Sodium Capsules contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$).

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. USP Phenytoin Related Compound B RS.*

Identification—

A: The contents of Capsules meet the requirements of *Identification* test *A* under *Phenytoin Sodium*.

B: The contents of Capsules meet the requirements of the flame test for *Sodium* ⟨191⟩.

Change to read:

Dissolution ⟨711⟩**—**

TEST 1—

Medium: water; 900 mL.

Apparatus 1: 50 rpm.

Times: 30, 60, and 120 minutes.

Determine the amount of $C_{15}H_{11}N_2NaO_2$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (7 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a solution of USP Phenytoin RS in methanol, and dilute with water to obtain a solution having a concentration similar to that of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 229-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3200 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved by the formula:

$$(274.25/252.27)900C(r_U / r_S)$$

in which 274.25 and 252.27 are the molecular weights of phenytoin sodium and phenytoin, respectively; C is the concentration, in mg per mL, of USP Phenytoin RS in the *Standard solution;* and r_U and r_S are the peak responses obtained from the solution under test and the *Standard solution*, respectively.

Tolerances (for products labeled as 30-mg Capsules)—The percentage of the labeled amount of $C_{15}H_{11}N_2NaO_2$ dissolved is not more than 40% *(Q)* in 30 minutes, is 56% (Q') in 60 minutes, and is not less than 65% (Q'') in 120 minutes. The requirements are met if the quantities dissolved from the Capsules tested conform to the accompanying *Acceptance Table*.

Acceptance Table

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 not less than 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 not less than 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 not less than Q''; not more than 2 units are outside the range between Q − 20% and Q + 10%, and no unit is outside the range Q − 30% and Q + 20%; not more than 2 units are outside the range Q' ± 18%, and no unit is outside the range Q' ± 25%; not more than 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 $C_{15}H_{11}N_2NaO_2$ dissolved is not more than 45% *(Q)* in 30 minutes, is 60% (Q') in 60 minutes, and is not less than 70% (Q'') in 120 minutes. The requirements are met if the quantities dissolved from the Capsules tested conform to the accompanying *Acceptance Table.*

Acceptance Table

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 not less than 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 not less than 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 not less than Q''; not more than 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%; not more than 2 units are outside the range Q' ± 25%, and no unit is outside the range Q' ± 35%; not more than 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 for using *Apparatus 1* at 75 rpm and the following *Tolerances.*

Tolerances (for products labeled as 100-mg Capsules)—The percentage of the labeled amount of $C_{15}H_{11}N_2NaO_2$ dissolved is not more than 45% *(Q)* in 30 minutes, is 65% (Q') in 60 minutes, and is not less than 70% (Q'') in 120 minutes. The requirements are met if the quantities dissolved from the Capsules tested conform to the accompanying *Acceptance Table*.

Acceptance Table

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 not less than 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 not less than 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 not less than Q''; not more than 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%; not more than 2 units are outside the range Q' − 25% and Q' + 20%, and no unit is outside the range Q' − 35% and Q' + 25%; not more than 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 minutes.

Determine the amount of $C_{15}H_{11}N_2NaO_2$ dissolved by employing the method described under *Test 1*.

Tolerances (for products labeled as 200-mg and 300-mg Capsules)—The percentage of the labeled amount of $C_{15}H_{11}N_2NaO_2$ dissolved is not more than 30% *(Q)* in 30 minutes, is 50% (Q') in 60 minutes, and is not less than 60% (Q'') in 120 minutes. The requirements are met if the quantities dissolved from the Capsules tested conform to the accompanying *Acceptance Table*.

Acceptance Table

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 not less than 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 not less than 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 not less than Q''; not more than 2 units are outside the range between Q − 25% and Q + 10%, and no unit is outside the range Q − 25% and Q + 15%; not more than 2 units are outside the range Q' ± 25%; and no unit is outside the range Q' ± 30%; not more than 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 *Procedure*—Proceed as directed for *Test 1*.

Tolerances (for products labeled as 30-mg Capsules)—The percentage of the labeled amount of $C_{15}H_{11}N_2NaO_2$ dissolved is not more than 40% *(Q)* in 30 minutes, is 56% (Q') in 60 minutes, and is not less than 65% (Q'') in 120 minutes. The requirements are met if the quantities dissolved from the Capsules tested conform to the accompanying *Acceptance Table*.

Acceptance Table

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% to Q' + 7%, and is not less than 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% to Q' + 7%, and is not less than Q''*;* no unit is outside the range between Q − 20% and Q + 10%, no unit is outside the range Q' − 19% to 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% to Q' + 7%, and is not less than Q''; not more than 2 units are outside the range between Q − 20% and Q + 10%, and no unit is outside the range Q − 30% and Q + 20%; not more than 2 units are outside the range Q' − 19% to Q' + 17%, and no unit is outside the range Q' − 26% to Q' + 24%; not more than 2 units are less than Q'' − 10%, and no unit is less than Q'' − 20% at the stated *Times.*

• (RB 1-Apr-2010)

Uniformity of dosage units ⟨905⟩: meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Phosphate buffer and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Phenytoin RS in methanol, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Test solution—Place one intact Capsule or one opened capsule with its contents in a suitable container, add approximately 15 mL of methanol, and place in a shaking water bath at 37° for 30 minutes. Sonicate for 60 minutes with occasional shaking. Dilute with methanol to volume, and mix. Dilute with *Mobile phase*, if necessary, to obtain a final concentration of about 0.5 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay*, except to chromatograph the *Standard solution* instead of the *Standard preparation.*

Procedure—Proceed as directed in the *Assay*, except to inject the *Standard solution* and the *Test solution* instead of the *Standard preparation* and the *Assay preparation*.

Related compounds—

Phosphate buffer and *Mobile phase*—Proceed as directed in the *Assay*.

Standard solution—Dissolve accurately weighed quantities of USP Phenytoin RS, USP Phenytoin Related Compound A RS, and USP Phenytoin Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having known concentrations of about 600, 3, and 3 µg per mL, respectively.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay*. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.38 for phenytoin related compound A, 0.45 for phenytoin related compound B, and 1.0 for phenytoin; the resolution, R, between phenytoin related compound B and phenytoin is not less than 8, and the resolution, R, between phenytoin related compound A and phenytoin related compound B is not less than 1.5; the tailing factor for the phenytoin peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0% determined from phenytoin, and not more than 5.0% determined from phenytoin related compound A or phenytoin related compound B.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of each phenytoin related compound in the portion of Capsules taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of the appropriate USP Reference Standard in the *Standard solution;* and r_U and r_S are the peak responses for the corresponding phenytoin related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% of phenytoin related compound A is found; and not more than 1.0% of phenytoin related compound B is found.

Assay—

Phosphate buffer—Prepare a solution of 0.05 M monobasic potassium phosphate in water, adjust with phosphoric acid to a pH of 3.5, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Phosphate buffer* (11 : 9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Phenytoin RS in methanol, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.6 mg per mL.

Assay preparation—Transfer the contents of 10 Capsules to a 250-mL volumetric flask. Add about 150 mL of methanol, and sonicate for 20 minutes. Cool to room temperature, dilute with methanol to volume, mix, and filter. Transfer an accurately measured portion of the filtered solution, equivalent to about 60 mg of phenytoin, to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 229-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) in the portion of Capsules taken by the formula:

$$(274.25/252.27)100C(r_U / r_S)$$

in which 274.25 and 252.27 are the molecular weights of phenytoin sodium and phenytoin, respectively; C is the concentration, in mg per mL, of USP Phenytoin RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.