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Phenytoin Oral Suspension

DEFINITION

Phenytoin Oral Suspension is Phenytoin suspended in a suitable medium. It contains NLT 95.0% and NMT 105.0% of the labeled amount of phenytoin ($C_{15}H_{12}N_2O_2$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

Sample: Shake a volume of Oral Suspension equivalent to 100 mg of phenytoin with 50 mL of a mixture of ether and chloroform (1 in 2) in a separator, evaporate the extract to dryness, and dry under vacuum at 105° for 4 h. Weigh 2–4 mg of the residue and 200 mg of potassium bromide in a mortar. Pestle, mix, and grind well, and prepare the potassium bromide pellet.

Acceptance criteria: Meets the requirements

• **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**

Solution A: Prepare a 0.05 M monobasic potassium phosphate solution, and adjust with phosphoric acid to a pH of 2.5.

Solution B: Methanol and acetonitrile (60:40)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
23	60	40
38	42	58
45	30	70
50	30	70
51	60	40
55	60	40

Diluent: *Solution B* and water (1:1)

Standard solution: 0.2 mg/mL of USP Phenytoin RS in *Diluent*. Dissolve with the aid of sonication, if necessary.

Sample solution: Nominally 0.2 mg/mL of phenytoin prepared as follows. Weigh and transfer a suitable volume of Oral Suspension containing the equivalent of 20 mg of phenytoin to a 100-mL volumetric flask. Add 20 mL of methanol, and dissolve. Dilute with *Diluent* to volume. Dissolve with the aid of sonication, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of phenytoin ($C_{15}H_{12}N_2O_2$) in the portion of Oral Suspension taken:

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

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)

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

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Buffer 1: Dissolve 36.3 g of tris(hydroxymethyl)aminomethane and 60 g of sodium lauryl sulfate in 6 L of water, adjust with hydrochloric acid to a pH of 7.5, and degas.

Medium: *Buffer 1*; 900 mL

Apparatus 2: 35 rpm

Time: 60 min

Buffer 2: 2.76 g/L of monobasic sodium phosphate in water

Mobile phase: Methanol, acetonitrile, and *Buffer 2* (27:23:50). Adjust with phosphoric acid to a pH of 3.0.

Standard solution: 0.14 mg/mL of USP Phenytoin RS prepared as follows. Transfer a suitable amount of USP Phenytoin RS to a suitable volumetric flask. Dissolve in 3% of the flask volume of methanol. Dilute with *Medium* to volume.

Sample solution: Shake the sample suspension well (100 shakes). Determine the density, *d* (g/mL), of Oral Suspension using appropriate means. Using a 5-mL syringe, collect approximately 5 mL of Oral Suspension, and record the weight. With the paddles lowered, gently empty the contents of each syringe into the bottom of each vessel containing *Medium*. Start rotating the paddles. Reweigh each syringe, and determine the weight (g) of Oral Suspension delivered into each vessel. At the end of 60 min, remove 4 mL from each vessel, and pass through a nylon filter of 0.45-µm pore size, presaturated with *Medium*. [Note—Dilute with *Medium* if necessary to a concentration that is similar to the *Standard solution*.]

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0% for phenytoin

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of phenytoin ($C_{15}H_{12}N_2O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (d/W) \times (1/L) \times 100$$

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)

V = volume of *Medium*, 900 mL

D = dilution factor (necessary only if the *Sample solution* requires dilution)

d = density of Oral Suspension (g/mL)

W = weight of Oral Suspension delivered (g)

L = label claim of Oral Suspension (mg/mL)

Tolerances: NLT 80% (Q) of the labeled amount of phenytoin ($C_{15}H_{12}N_2O_2$) is dissolved.

- **Uniformity of Dosage Units ⟨905⟩**

For single-unit containers

Acceptance criteria: Meets the requirements

- **Deliverable Volume ⟨698⟩**

For multiple-unit containers

Acceptance criteria: Meets the requirements

IMPURITIES

- **Organic Impurities**

Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 1 µg/mL of USP Phenytoin RS, 9 µg/mL of USP Phenytoin Related Compound A RS, and 9 µg/mL of USP Phenytoin Related Compound B RS in *Diluent*

Sample solution: Nominally 1 mg/mL of phenytoin prepared as follows. Weigh and transfer a suitable volume of Oral Suspension to an appropriate volumetric flask. Add methanol to about 20% of the final flask volume and dissolve. Dilute with *Diluent* to volume. Dissolve with the aid of sonication, if necessary.

System suitability

Sample: *Standard solution*

Suitability requirements

Signal-to-noise ratio: NLT 10

Relative standard deviation: NMT 5.0% for the phenytoin peak

Analysis

Samples: *Standard solution* and *Sample solution*

[Note—The relative retention times are given in *Table 2*.]

Calculate the percentage of phenytoin related compound A and phenytoin related compound B in the portion of Oral Suspension taken:

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

r_U = peak area of each specified impurity from the *Sample solution*

r_S = peak area of each specified impurity from the *Standard solution*

C_S = concentration of each specified impurity in the *Standard solution* (mg/mL)

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

Calculate the percentage of any individual unspecified impurity in the portion of Oral Suspension taken:

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

r_U = peak area for each unspecified impurity

r_S = peak area 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)

Acceptance criteria: See *Table 2*. Disregard any impurity less than 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Phenytoin related compound A	0.14	0.9
Phenytoin related compound B	0.53	0.9
Phenytoin	1.0	—
Any individual unspecified degradation product	—	0.10
Total impurities	—	0.9

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature. Protect from freezing and light.
- **Labeling:** The label bears a statement that the patient must use an accurately calibrated measuring device with multiple-dose containers.
- **USP Reference Standards** ⟨11⟩

USP Phenytoin RS

USP Phenytoin Related Compound A RS

2,2-Diphenylglycine.

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

USP Phenytoin Related Compound B RS

2,2-Diphenyl-2-ureidoacetic acid.

$C_{15}H_{14}N_2O_3$ 270.28

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

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

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