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Phenytoin Sodium Injection

DEFINITION

Phenytoin Sodium Injection is a sterile solution of Phenytoin Sodium with Propylene Glycol and Alcohol in Water for Injection. It contains NLT 95.0% and NMT 105.0% of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$).

IDENTIFICATION

Change to read:

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

Sample: Transfer an equivalent of 250 mg of phenytoin sodium from a volume of Injection to a separator containing 25 mL of water. Extract first with 50 mL of ethyl acetate and then with two additional 30-mL portions of ethyl acetate. Wash each extract with two 20-mL portions of sodium acetate solution (10 mg/mL). Evaporate the combined ethyl acetate extracts, and dry the residue of phenytoin at 105° to constant weight.

Acceptance criteria: Residue obtained from the *Sample* 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**

Mobile phase: Methanol and water (55:45)

Standard solution: 0.23 mg/mL of USP Phenytoin RS in *Mobile phase*

Sample solution: Nominally 0.25 mg/mL of phenytoin sodium from a volume of Injection equivalent to 250 mg of phenytoin sodium in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 25-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

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*

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

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

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 sodium 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%

OTHER COMPONENTS

• **Alcohol and Propylene Glycol Content**

Internal standard solution: 0.02 mL/mL of methanol and 0.04 mL/mL of ethylene glycol in water

Standard stock solution: 0.01 mL/mL of alcohol from USP Alcohol Determination–Alcohol RS and 0.04 mL/mL of USP Propylene Glycol RS in water

Standard solution: 0.005 mL/mL of alcohol and 0.02 mL/mL of propylene glycol prepared as follows. Pipet 5 mL each of *Standard stock solution* and *Internal standard solution* into a 10-mL volumetric flask.

Sample solution: 0.05 mL/mL of Injection in water prepared as follows. Pipet 5 mL of Injection and 50 mL of the *Internal standard solution* into a 100-mL volumetric flask, and dilute with water to volume.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 30-m × 0.53-mm (ID) capillary column with a 1-µm coating of G16 phase

Temperatures

Injection port: 240°

Detector: 250°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	4
50	15	230	5

Carrier gas: Hydrogen or helium

Flow rate: 5 mL/min

Injection volume: 0.2 µL

Injection type: Split ratio, 10:1

System suitability

Sample: *Standard solution*

[Note—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 5.0 between methanol and alcohol; NLT 5.0 between propylene glycol and ethylene glycol

Relative standard deviation: NMT 2.0% for each of the response ratios of alcohol to methanol and propylene glycol to ethylene glycol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the alcohol content, as a percentage, in the portion of Injection taken:

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

R_U = peak response ratio of alcohol to methanol from the *Sample solution*

R_S = peak response ratio of alcohol to methanol from the *Standard solution*

C_S = concentration of alcohol in the *Standard solution* (mL/mL)

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

Calculate the propylene glycol content, as a percentage, in the portion of Injection taken:

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

R_U = peak response ratio of propylene glycol to ethylene glycol from the *Sample solution*

R_S = peak response ratio of propylene glycol to ethylene glycol from the *Standard solution*

C_S = concentration of propylene glycol in the *Standard solution* (mL/mL)

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Methanol[a]	0.27	—
Alcohol	0.32	9.0–11.0
Propylene glycol	0.98	37.0–43.0
Ethylene glycol[a]	1.0	—

[a] Internal standard included for peak identification purposes only.

SPECIFIC TESTS

- **Bacterial Endotoxins Test ⟨85⟩:** It contains NMT 0.3 USP Endotoxin Unit/mg of phenytoin sodium.
- **pH ⟨791⟩:** 10.0–12.3
- **Particulate Matter in Injections ⟨788⟩:** It meets the requirements under small-volume injections.
- **Other Requirements:** It meets the requirements under *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass, at controlled room temperature.
- **Labeling:** The label states the following: “Do not use the Injection if it is hazy or contains a precipitate.”
- **USP Reference Standards ⟨11⟩**
  USP Alcohol Determination–Alcohol RS
  USP Phenytoin RS
  USP Propylene Glycol RS

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

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

Chromatographic Database Information: Chromatographic Database

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