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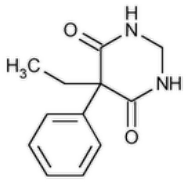
Primidone



$C_{12}H_{14}N_2O_2$ 218.25

4,6(1*H*,5*H*)-Pyrimidinedione, 5-ethyldihydro-5-phenyl-;

5-Ethyldihydro-5-phenyl-4,6(1*H*,5*H*)-pyrimidinedione CAS RN®: 125-33-7; UNII: 13AFD7670Q.

DEFINITION

Primidone contains NLT 98.0% and NMT 102.0% of $C_{12}H_{14}N_2O_2$, calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020) **:** If a difference appears, dissolve portions of both the sample and the Reference Standard in alcohol, evaporate the solutions to dryness, and repeat the tests.

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

ASSAY

• **Procedure**

Solution A: 6.8 g/L of monobasic potassium phosphate

Mobile phase: Methanol, tetrahydrofuran, and *Solution A* (35:0.5:65)

Diluent: Methanol and water (35:65)

Standard stock solution: 0.5 mg/mL of USP Primidone RS in methanol

Standard solution: 0.05 mg/mL of USP Primidone RS in *Diluent*, prepared from the *Standard stock solution*

Sample stock solution: 0.5 mg/mL of Primidone in methanol

Sample solution: 0.05 mg/mL of Primidone from the *Sample stock solution* diluted with *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 35°

Flow rate: 1.3 mL/min

Injection size: 20 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 $C_{12}H_{14}N_2O_2$ in the portion of Primidone 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 Primidone RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

Inorganic Impurities

- **Residue on Ignition ⟨281⟩:** NMT 0.2%

Organic Impurities

- **Procedure**

Solution A: 1.36 g/L of monobasic potassium phosphate

Solution B: Methanol

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	75	25
1.0	75	25
6.0	40	60
8.0	40	60
8.5	75	25
10.0	75	25

Standard stock solution: 1000 µg/mL of USP Primidone RS in methanol

Standard solution: 1 µg/mL of USP Primidone RS in methanol, prepared from the *Standard stock solution* in methanol

System suitability solution: 1000 µg/mL of USP Primidone RS and 10 µg/mL each of USP Phenobarbital RS and USP Primidone Related Compound C RS. Prepare by diluting weighed quantities of USP Phenobarbital RS and USP Primidone Related Compound C RS with the *Standard stock solution*.

Sample solution: 1000 µg/mL of Primidone in methanol

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 10-cm; monolithic packing L1

Flow rate: 3.2 mL/min

Injection size: 10 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

Suitability requirements

Resolution: NLT 2.5 between phenobarbital and primidone related compound C, *System suitability solution*

Tailing factor: NMT 2.0 for primidone, *Standard solution*

Relative standard deviation: NMT 5.0% for primidone, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Identify the impurities using the relative retention times listed in *Impurity Table 1*. Calculate the percentage of each impurity in the portion of sample taken:

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

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

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

C_S = concentration of USP Primidone RS in the *Standard solution* (µg/mL)

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

F = relative response factor (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.5%

[NOTE—Disregard impurity peaks below 0.05%.]

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Primidone related compound A[a]	0.5	0.67	0.1
Phenobarbital	1.4	1.0	0.1
Primidone related compound C[b]	1.6	0.67	0.1
2-Cyano-2-phenylbutyramide	1.8	0.71	0.1
2-Phenylbutyric acid	2.0	0.77	0.1
Phenylpropylprimidone[c]	2.8	1.0	0.3
Any unspecified impurity	—	1.0	0.1

[a] 2-Ethyl-2-phenylmalonamide (2-ethyl-2-phenylpropanediamide).

[b] 2-Phenylbutyramide.

[c] 5-Ethyl-5-phenyl-2-(1-phenylpropyl)dihydropyrimidine-4,6(1*H*,5*H*)-dione.

SPECIFIC TESTS

• **LOSS ON DRYING ⟨731⟩:** Dry a sample at 105° for 2 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Phenobarbital RS

USP Primidone RS

USP Primidone Related Compound C RS

2-Phenylbutyramide.

$C_{10}H_{13}NO$ 163.22

Topic/Question	Contact	Expert Committee
PRIMIDONE	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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