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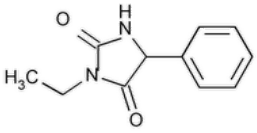
Ethotoin



$C_{11}H_{12}N_2O_2$ 204.23

2,4-Imidazolidinedione, 3-ethyl-5-phenyl-, (±)-.

(±)-3-Ethyl-5-phenylhydantoin CAS RN®: 86-35-1; UNII: 46QG38NC4U.

» Ethotoin contains not less than 97.5 percent and not more than 102.0 percent of $C_{11}H_{12}N_2O_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—

USP Ethotoin RS

USP 5-Phenylhydantoin RS

Identification—

Change to read:

A: ▲*Spectroscopic Identification Tests* ⟨197⟩*, Ultraviolet-Visible Spectroscopy: 197U*▲ (CN 1-May-2020) —

Solution: 1 mg per mL.

Medium: alcohol.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Chloride—Transfer 1.0 g of Ethotoin to a suitable separator, and dissolve in 50 mL of ether. Extract with three 15-mL portions of water, collect the combined extracts in a beaker, heat on a steam bath to expel any traces of ether, and allow to cool to room temperature. Transfer the solution to a 50-mL color-comparison tube, add 2 N nitric acid until the solution is acidic, add 1 mL of 2 N nitric acid in excess, mix, add 1 mL of silver nitrate TS, dilute with water to 50 mL, and allow to stand for 5 minutes, protected from direct sunlight. The turbidity produced does not exceed that of a solution prepared by mixing 2 mL of freshly prepared 0.002 N hydrochloric acid, 1 mL of 2 N nitric acid, 1 mL of silver nitrate TS, and 46 mL of water (0.014%).

Related compounds—

Buffer solution—Dissolve about 1 g of monobasic sodium phosphate in 1 L of water. Adjust the solution with 1.5 M phosphoric acid to a pH of 3.5 ± 0.1.

Diluent—Prepare a mixture of *Buffer solution* and methanol (65:35).

Solution A—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80:20).

Solution B—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (60:40).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Ethotoin RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 2.5 µg of ethotoin per mL.

Test solution—Transfer about 50 mg of Ethotoin, accurately weighed, to a 200-mL volumetric flask, dissolve in about 100 mL of *Diluent* with sonication, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 0.8 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	100	0	isocratic
10–30	100→0	0→100	linear gradient
30–40	0	100	isocratic
40–42	0→100	100→0	linear gradient
42–55	100	0	re-equilibration

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0 for ethotoin; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. [NOTE—Discard any peak due to the *Diluent*.] Calculate the percentage of any impurity in the portion of Ethotoin taken by the formula:

$$(20{,}000/F)(C/W)(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Ethotoin RS in the *Standard solution; F* is the response factor for the impurity as shown in the table below; W is the weight, in mg, of the portion of Ethotoin taken; r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for ethotoin in the *Standard solution*. The impurities meet the requirements given in the table below.

Compound name	RRT[1]	RRF[2]	Limit (%)
5-Phenylhydantoin	about 0.4	1.0	1.5
3-Methyl-5-phenylhydantoin	about 0.6	1.0	0.9
Ethotoin	1.0	—	—
Ethotoin/5-Phenylhydantoin dimer	about 1.9	1.0	0.3
Ethotoin dimer	about 2.5	0.58	0.4
Unknown impurities	—	1.0	0.1 Individual
			1.0 Total Unknown
Total	—	—	2.0

[1] RRT—Relative retention time.

[2] RRF—Relative response factor.

Assay—

Mobile phase—Dissolve 0.65 g of monobasic potassium phosphate in 600 mL of water, adjust with phosphoric acid solution (1 in 10) to a pH of 3.5 ± 0.1, and dilute with water to 650 mL. Add 350 mL of methanol, mix, filter through a membrane filter of 0.5 µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

5-Phenylhydantoin stock solution—Dissolve, with the aid of sonication if necessary, an accurately weighed quantity of USP 5-Phenylhydantoin RS in *Mobile phase* to obtain a solution having a known concentration of about 0.37 mg per mL.

Standard preparation—Dissolve, with the aid of sonication if necessary, an accurately weighed quantity of USP Ethotoin in *Mobile phase* to obtain a solution having a known concentration of about 0.25 mg of ethotoin per mL.

System suitability solution—Transfer 25 mg of USP Ethotoin RS, accurately weighed, to a 100-mL volumetric flask, add about 1.0 mL of *5-Phenylhydantoin stock solution*, add *Mobile phase* to volume, and sonicate to dissolve.

Assay preparation—Transfer about 50 mg of Ethotoin, accurately weighed, to a 200-mL volumetric flask, dissolve in *Mobile phase*, dilute with *Mobile phase* to volume, and sonicate to dissolve.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between the 5-phenylhydantoin and ethotoin peaks is not less than 6.0. The relative retention times are about 0.4 for 5-phenylhydantoin and 1.0 for ethotoin. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Separately inject equal volumes (about 20 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 $C_{11}H_{12}N_2O_2$ in the portion of Ethotoin taken by the formula:

$$200C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Ethotoin 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.

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

Topic/Question	Contact	Expert Committee
ETHOTOIN	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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