Ethacrynic Acid Tablets

Type of Posting	Revision Bulletin
Posting Date	25–Sep–2020
Official Date	01–Oct–2020
Expert Committee	Small Molecules 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2020–2025 Council of Experts, the Small Molecules 2 Expert Committee has revised the Ethacrynic Acid Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test.

- *Dissolution Test 2* was validated using a µBondapak C18 brand of L1 column. The typical retention time for ethacrynic acid is about 4.5 min.

Labeling information also has been incorporated to support the inclusion of *Dissolution Test 2*.

The Ethacrynic Acid Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Tsion Bililign, Scientific Liaison (301-816-8286 or tb@usp.org).

Revision Bulletin
Official: October 1, 2020

Ethacrynic Acid Tablets

DEFINITION

Ethacrynic Acid Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$).

IDENTIFICATION

- **A. Ultraviolet Absorption**

Diluent: A mixture of hydrochloric acid and anhydrous methanol (9 in 1000)

Standard solution: 50 µg/mL of USP Ethacrynic Acid RS in *Diluent*

Sample solution: Nominally 50 µg/mL of ethacrynic acid in *Diluent* prepared as follows. Weigh a portion of finely powdered Tablets, equivalent to 50 mg of ethacrynic acid, and transfer to a separator containing 25 mL of 0.1 N hydrochloric acid. Extract with two 40-mL portions of methylene chloride, filter the extracts into a 100-mL volumetric flask, and dilute with methylene chloride to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, evaporate in a gentle current of air to dryness, and promptly dissolve the residue in a portion of *Diluent*, then dilute with *Diluent* to volume.

Acceptance criteria: The UV absorption spectrum of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the *Standard solution*, concomitantly measured.

- **B.**

Sample solution: Nominally 12.5 mg/mL of ethacrynic acid prepared as follows. Add 2 mL of 1 N sodium hydroxide to a portion of the powdered Tablets equivalent to 25 mg of ethacrynic acid.

Analysis

Sample: *Sample solution*

Heat the *Sample solution* for several minutes in a boiling water bath. Cool the solution, acidify with 0.25 mL of 18 N sulfuric acid, add 0.5 mL of chromotropic acid sodium salt solution (1 in 10), then cautiously add 2 mL of sulfuric acid TS.

Acceptance criteria: A deep violet color is produced.

ASSAY

- **Procedure**

Solution A: Mix 10 mL of triethylamine and about 900 mL of water in a 1-L volumetric flask. Adjust with phosphoric acid to a pH of 6.8 ± 0.1, dilute with water to volume, mix, and filter.

Mobile phase: Acetonitrile and *Solution A* (40:60). Filter and degas.

Diluent: Acetonitrile and water (40:60)

Standard solution: 0.5 mg/mL of USP Ethacrynic Acid RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of ethacrynic acid in *Diluent* prepared as follows. Transfer a portion of the powder from NLT 20 finely powdered Tablets, equivalent to about 50 mg of ethacrynic acid, to a 100-mL volumetric flask, add about 80 mL of *Diluent*, and shake or sonicate to dissolve the ethacrynic acid. Dilute with *Diluent* to volume, and mix.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Capacity factor, *k'*: NLT 0.8

Column efficiency: NLT 1200 theoretical plates

Tailing factor: NMT 2

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$) in the portion of Tablets taken:

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

r_U = peak response of ethacrynic acid from the *Sample solution*

r_S = peak response of ethacrynic acid from the *Standard solution*

C_S = concentration of USP Ethacrynic Acid RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲Test 1▲ (RB 1-Oct-2020)

Medium: 0.1 M phosphate buffer, prepared by mixing 13.6 g of monobasic potassium phosphate and 92.2 mL of 1 N sodium hydroxide with water to obtain 1000 mL of a solution having a pH of 8.0 ± 0.05; 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Standard solution: A known concentration of USP Ethacrynic Acid RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute suitably with *Medium*.

Instrumental conditions

Mode: UV

Analytical wavelength: Maximum absorbance at about 277 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Ethacrynic Acid RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*

L = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Citrate buffer, pH 3.0 (17.2 g/L of citric acid and 5.3 g/L of sodium citrate dihydrate in water, adjusted with 1N sodium hydroxide or 1M acetic acid TS to a pH of 3.0 ±0.05); 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 30 min

Solution A: 1% triethylamine solution in water, prepared as follows. Transfer a suitable aliquot of triethylamine to an appropriate volumetric flask containing 90% of the flask volume of water. Adjust with phosphoric acid to a pH of 6.8 ±0.1. Dilute with water to volume.

Mobile phase: Acetonitrile and *Solution A* (40:60)

Standard stock solution: 0.28 mg/mL of USP Ethacrynic Acid RS, prepared as follows. Transfer a portion of USP Ethacrynic Acid RS to a suitable volumetric flask and add 10% of the flask volume of methanol. Dilute with *Medium* to volume.

Standard solution: 0.028 mg/mL of USP Ethacrynic Acid RS from the *Standard stock solution*, in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 277 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 2.4 times the retention time of ethacrynic acid

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 ethacrynic acid ($C_{13}H_{12}Cl_2O_4$) dissolved:

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

r_U = peak response of ethacrynic acid from the *Sample solution*

r_S = peak response of ethacrynic acid from the *Standard solution*

C_S = concentration of USP Ethacrynic Acid RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$) is dissolved.▲ (RB 1-Oct-2020)

- **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

Procedure for content uniformity (if applicable)

Diluent: A mixture of hydrochloric acid and methanol (9 in 1000)

Standard solution: 50 µg/mL of USP Ethacrynic Acid RS in *Diluent*

Sample stock solution: Add 1 Tablet to a 100-mL volumetric flask containing 10 mL of water, and allow to stand for 15 min, shaking occasionally until the Tablet is disintegrated. Add *Diluent* to volume and mix. Pass a portion of the mixture through a suitable filter.

Sample solution: Nominally 50 µg/mL of ethacrynic acid in *Diluent* from the *Sample stock solution* prepared as follows. Pipet a volume of the *Sample stock solution*, equivalent to 5 mg of ethacrynic acid, into a 100-mL volumetric flask. Dilute with *Diluent* to volume and mix.

Instrumental conditions

Mode: UV

Analytical wavelength: Maximum absorbance at about 269 nm

Cell: 1 cm

Blank: *Diluent*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$) in the Tablet taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

C_U = nominal concentration of ethacrynic acid in the *Sample solution* (µg/mL)

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.

Add the following:

▲- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-Oct-2020)

- **USP Reference Standards** ⟨11⟩

USP Ethacrynic Acid RS

Page Information:

Not Applicable

DocID: