Ethacrynic Acid Tablets

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Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Ethacrynic Acid Tablets monograph. The purpose of the revision is to add *Dissolution Test 3* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

Existing references to reagents have been updated for consistency with the reagent entry. For additional information about reagent cross references, please see the related Compendial Notice.

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: April 1, 2021

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

Change to read:

- **A. Ultraviolet Absorption**

Diluent: A mixture of hydrochloric acid and ▲ (RB 1-Apr-2021) 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

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 1 N sodium hydroxide or 1 M 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.

▲**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: Citrate buffer, pH 3.0 (dissolve 17.4 g of citric acid, anhydrous and 2.7 g of sodium citrate dihydrate in 800 mL of water, adjust with 5 N sodium hydroxide TS to a pH of 3.0, and dilute with water to 1000 mL); 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Diluent: Phosphate buffer, pH 8.0, prepared as follows. Dissolve 13.6 g of potassium phosphate, monobasic in 800 mL of water, add 92 mL of 1 N sodium hydroxide VS, and dilute with water to 1000 mL. Adjust with 1 N sodium hydroxide VS to a pH of 8.0.

Standard stock solution: 0.3 mg/mL of USP Ethacrynic Acid RS, prepared as follows. Transfer a portion of USP Ethacrynic Acid RS to a suitable volumetric flask,add *Diluent* to 60% of the flask volume, and sonicate to dissolve. Dilute with *Diluent* to volume.

Standard solution: (L/900) mg/mL of USP Ethacrynic Acid RS from the *Standard stock solution* in *Medium*, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size,discard a few milliliters, and collect the filtrate.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 277 nm

Blank: *Medium*

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:

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

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

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-Apr-2021)

- **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.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩
  USP Ethacrynic Acid RS

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