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).
Ethacrynic Acid Tablets

**DEFINITION**
Ethacrynic Acid Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ethacrynic acid \((C_{13}H_{12}Cl_{2}O_{4})\).

**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 ($C_{13}H_{12}Cl_{2}O_{4}$) in the portion of Tablets taken:

$$\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100$$

$r_U$ = 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 1A (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 ($C_{13}H_{12}Cl_{2}O_{4}$) dissolved:

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

$A_U$ = 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
\[ L = \text{label claim (mg/Tablet)} \]

**Tolerances:** NLT 75% \((Q)\) of the labeled amount of ethacrynic acid \(\text{C}_{13}\text{H}_{12}\text{Cl}_{2}\text{O}_{4}\) 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 \(L_1\)
- **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 \(\text{C}_{13}\text{H}_{12}\text{Cl}_{2}\text{O}_{4}\) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \(r_U\) = 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 \(\text{C}_{13}\text{H}_{12}\text{Cl}_{2}\text{O}_{4}\) 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

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**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 (C₁₃H₁₂Cl₂O₄) in the Tablet taken:

  \[
  \text{Result} = \left( \frac{A_U}{A_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
  \]

  - \(A_U\) = 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.\(^{\uparrow}\) (RB 1-Oct-2020)
- **USP Reference Standards (11).**
  - **USP Ethacrynic Acid RS**

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Page Information:
Not Applicable

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