**Bumetanide Tablets**

Type of Posting: Revision Bulletin  
Posting Date: 27–Apr–2018  
Official Date: 01–May–2018  
Expert Committee: Chemical Medicines Monographs 2  
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Bumetanide Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate a drug product that was approved with different dissolution conditions and acceptance criteria. Labeling information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using a Waters XBridge C18 brand of L1 column. The typical retention time for bumetanide is about 3.5 min.

Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Bumetanide Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Edith Chang, Ph.D., Scientific Liaison (301-816-8392 or vec@usp.org).
Bumetanide Tablets

**DEFINITION**

Bumetanide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bumetanide \((C_{19}H_{20}N_{2}O_{5}S)\).

**IDENTIFICATION**

- A. The relative retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
- B. The principal spot of the Sample solution exhibits an \(R_s\) value corresponding to that of the Identification solution, as obtained in the test for Organic Impurities.

**ASSAY**

- **PROCEDURE**

  **Mobile phase:** Methanol, tetrahydrofuran, glacial acetic acid, and water (50:5:2:45)

  **Internal standard stock solution:** 0.5 mg/mL of 4-ethylbenzaldehyde in methanol

  **Internal standard solution:** Add 10.0 mL of Internal standard stock solution, 10.0 mL of tetrahydrofuran, and 4.0 mL of glacial acetic acid to a 100-mL volumetric flask, and dilute with methanol to volume.

  **Standard stock solution:** 250 µg/mL of USP Bumetanide RS in Internal standard solution

  **Sample solution:** Nominally 0.05 mg/mL of bumetanide prepared as follows. Transfer a nominal equivalent to 0.5 mg of bumetanide, from finely powdered Tablets (NLT 20), to a 10-mL volumetric flask. Add 2.0 mL of Internal standard solution and sonicate for 5 min. Add 2.0 mL of water. Cool and filter, discarding the first 1 mL of the filtrate.

  **Chromatographic system**

  (See Chromatography (621), System Suitability.)

  **Mode:** LC

  **Detector:** UV 254 nm

  **Column:** 3.9-mm x 30-cm; packing L1

  **Flow rate:** 1 mL/min

  **Injection volume:** 20 µL

  **System suitability**

  **Sample:** Standard solution

  [Note—The relative retention times for 4-ethylbenzaldehyde and bumetanide are 0.7 and 1.0, respectively.]

  **Suitability requirements**

  **Resolution:** NLT 1.5 between 4-ethylbenzaldehyde and bumetanide

  **Tailing factor:** NMT 1.4

  **Relative standard deviation:** NMT 2.0%

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Calculate the percentage of bumetanide \((C_{19}H_{20}N_{2}O_{5}S)\) in the portion of Tablets taken:

  \[
  \text{Result} = \left( \frac{R_U}{R_S} \right) \times \left( \frac{C_I}{C_U} \right) \times 100
  \]

  \(R_U\) = peak response ratio of bumetanide to the internal standard from the Sample solution

  \(R_S\) = peak response ratio of bumetanide to the internal standard from the Standard solution

  \(C_I\) = concentration of USP Bumetanide RS in the Standard solution (mg/mL)

  \(C_U\) = nominal concentration of the bumetanide in the Sample solution (mg/mL)

  **Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**

  **Test 1**

  **Medium:** Water; 900 mL

  **Apparatus 2:** 50 rpm

  **Time:** 30 min

  **Solution A:** 7.505 g/L of glycerine and 5.85 g/L of sodium chloride in water

  **Solution B:** Solution A, 0.1 N hydrochloric acid, and water (4:1:45). Adjust, if necessary, with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide to a pH of 2.9.

  **Standard solution:** USP Bumetanide RS at a known concentration in Medium

  **Sample solution:** Dilute with Solution B as needed.

  **Instrumental conditions**

  **Mode:** Fluorescence

  **Detectors**

  **Excitation wavelength:** 350 nm

  **Emission wavelength:** 450 nm

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Determine the percentage of the labeled amount of bumetanide \((C_{19}H_{20}N_{2}O_{5}S)\) dissolved.

  **Tolerances:** NLT 85% (Q) of the labeled amount of bumetanide \((C_{19}H_{20}N_{2}O_{5}S)\) is dissolved.

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

  **Medium, Apparatus 2, and Time:** Proceed as directed in Test 1.

  **Buffer:** 2.72 g/L of potassium phosphate, monobasic in water. Adjust with 1.8 N potassium hydroxide to a pH of 7.0.

  **Mobile phase:** Acetonitrile and Buffer (30:70)

  **Diluent:** Acetonitrile and water (50:50)

  **Standard stock solution:** 55.5 µg/mL of USP Bumetanide RS in Diluent

  **Standard solution:** (L/1000) µg/mL of USP Bumetanide RS in Medium, from Standard stock solution, 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.

  **Chromatographic system**

  (See Chromatography (621), System Suitability.)

  **Mode:** LC

  **Detector:** UV 222 nm

  **Column:** 4.6-mm x 15-cm; 5-µm packing L1

  **Column temperature:** 35°C

  **Flow rate:** 1.5 mL/min

  **Injection volume:** 100 µL

  **Run time:** NLT 1.7 times retention time of bumetanide

  **System suitability**

  **Samples:** Standard solution and Sample solution

  Calculate the percentage of the labeled amount of bumetanide \((C_{19}H_{20}N_{2}O_{5}S)\) dissolved:

  \[
  \text{Result} = \frac{r_U}{r_S} \times C_I \times V \times \frac{1}{L} \times 100
  \]

  \(r_U\) = peak response of bumetanide from the Sample solution

  © 2018 The United States Pharmacopeial Convention All Rights Reserved.
\[ R_s = \text{peak response of bumetanide from the Standard solution} \]
\[ C_s = \text{concentration of USP Bumetanide RS in the Standard solution (mg/mL)} \]
\[ V = \text{volume of Medium, 900 mL} \]
\[ L = \text{label claim (mg/Tablet)} \]

Tolerances: NLT 80% (Q) of the labeled amount of bumetanide \((C_{17}H_{20}N_2O_5S)\) is dissolved.

**Uniformity of Dosage Units (905):** Meet the requirements.

**Impurities**

**Organic Impurities**

Identification solution: 20 mg/mL of USP Bumetanide RS in methanol

Standard solution 1: 160 µg/mL of USP Bumetanide RS from Identification solution in methanol

Standard solution 2: 120 µg/mL of USP Bumetanide RS from Standard solution 1 in methanol

Standard solution 3: 80 µg/mL of USP Bumetanide RS from Standard solution 1 in methanol

Standard solution 4: 40 µg/mL of USP Bumetanide RS from Standard solution 1 in methanol

Standard solution 5: 20 µg/mL of USP Bumetanide RS from Standard solution 1 in methanol

Standard solution 6: 40 µg/mL of USP Bumetanide Related Compound A RS in methanol

Sample solution: Nominally 20 mg/mL of bumetanide prepared as follows. Equivalent to 10 mg of bumetanide from powdered Tablets in a 50-mL centrifuge tube. Add 20 mL of acetone (spectrophotometric or HPLC quality), and shake by mechanical means for 10 min. Centrifuge for 10 min, decant the supernatant into a glass-stoppered, 25-mL conical flask, and evaporate with the aid of a stream of nitrogen to dryness. Dissolve the residue in 0.5 mL of methanol.

**Chromatographic system**

(See Chromatography (621), General Procedures, Thin-Layer Chromatography.)

Mode: TLC
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
Application volume: 25 µL
Visualization: Short-wavelength UV light
Developing solvent system: Methanol, cyclohexane, methanol, glacial acetic acid, and chloroform (2.5: 10: 80)

**Analysis**

Samples: Standard solutions 1–6 and Sample solution

Acceptance criteria

- **Bumetanide related compound A:** Any secondary spot from the Sample solution with an \( R_F \) value corresponding to the \( R_F \) value of the principal spot from Standard solution 6 is not larger or more intense than the principal spot from Standard solution 6; NMT 0.2%.
- **Any individual other impurity:** For all other secondary spots from the Sample solution, compare the intensity of each spot with the principal spots from Standard solutions 1–5; NMT 0.2% of any individual other impurity is found.
- **Sum of all other impurities:** NMT 0.8% of the sum of all other impurities is found (excluding bumetanide related compound A).

**Additional Requirements**

- **Packaging and Storage:** Preserve in tight, light-resistant 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.
- **USP Reference Standards (11)**
  - USP Bumetanide RS
  - USP Bumetanide Related Compound A RS
  - 3-Amino-4-phenoxy-5-sulfamoylbenzoic acid. \( C_{13}H_{12}N_2O_5S \) 308.31

© 2018 The United States Pharmacopeial Convention All Rights Reserved.