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 yec@usp.org).

Bumetanide Tablets

DEFINITION

Bumetanide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bumetanide ($C_{17}H_{20}N_2O_5S$).

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_F 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*

Standard solution: 125 µg/mL from *Standard stock solution* in water

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 × 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 ($C_{17}H_{20}N_2O_5S$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

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_S = 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**▲ (RB 1-May-2018)
Medium: Water; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Solution A: 7.505 g/L of glycine 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 ($C_{17}H_{20}N_2O_5S$) dissolved.
Tolerances: NLT 85% (*Q*) of the labeled amount of bumetanide ($C_{17}H_{20}N_2O_5S$) 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°
Flow rate: 1.5 mL/min
Injection volume: 100 µL
Run time: NLT 1.7 times retention time of bumetanide
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 bumetanide ($C_{17}H_{20}N_2O_5S$) dissolved:

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

r_U = peak response of bumetanide from the *Sample solution*

r_S = peak response of bumetanide from the *Standard solution*
C_S = concentration of USP Bumetanide 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 bumetanide ($C_{17}H_{20}N_2O_5S$) is dissolved.▲ (RB 1-May-2018)

• **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: 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.▲ (RB 1-May-2018)

• **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