Benzonatate Capsules

Type of Posting  Revision Bulletin
Posting Date  29–Jun–2018
Official Date  01–Jul–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 Benzonatate Capsules monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate FDA-approved drug products with different dissolution tolerances than the existing dissolution test. A Labeling section has also been added.

- The analytical procedure in Tier 2 of Dissolution Test 2 was validated using a Lichrosorb RP-18 brand of L1 column from Merck KgaA. The typical retention time for benzonatate is about 3.7 min.

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

The Benzonatate Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Wei Yang, Scientific Liaison (301-816-8338 or wiy@usp.org).
**Benzonatate Capsules**

**DEFINITION**
Benzonatate Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of benzonatate \( [C_{17}H_{23}NO_{11} \text{ (av.)}] \).

**IDENTIFICATION**

- **A. INFRARED ABSORPTION (197U)**
  
  **Sample**: The contents of Capsules
  
  **Acceptance criteria**: Meets the requirements. If a difference is observed, or if excipients are present, use an amount of the contents of Capsules equivalent to about 100 mg of benzonatate. Mix with 25 mL of 0.01 N hydrochloric acid, and proceed as directed in Identification —Organic Nitrogenous Bases (181), beginning with “Transfer the liquid to a separator”.

- **B. ULTRAVIOLET ABSORPTION (197U)**
  
  **Sample solution**: Nominally 15 µg/mL of benzonatate from the contents of Capsules
  
  **Acceptance criteria**: Meet the requirements

**ASSAY**

- **PROCEDURE**
  
  **Standard solution**: 500 µg/mL of USP Benzonatate RS
  
  **Sample stock solution**: Nominally 5 mg/mL of benzonatate in chloroform, prepared as follows. Mix a number of Capsules, equivalent to about 500 mg of benzonatate, with 40 mL of chloroform in a suitable high-speed blender, and dilute with chloroform to 100.0 mL.
  
  **Sample solution**: Nominally 500 µg/mL of benzonatate prepared as follows. Transfer 10.0 mL of Sample stock solution into a 100-mL volumetric flask. Evaporate the chloroform on a steam bath with the aid of a current of air. Dissolve the residue in water and dilute with water to volume.

**Instrumental conditions**

- **Mode**: Vis
- **Analytical wavelength**: 500 nm
- **Cell**: 1 cm
- **Blank**: Water

**Analysis**

**Samples**: Standard solution, Sample solution, and Blank

Transfer 4.0 mL of each of the Standard solution, Sample solution, and Blank to separate test tubes. To each tube add in succession 1.0 mL of 1 M hydroxylamine hydrochloride and 1.0 mL of 3.5 N sodium hydroxide, mixing after each addition. Allow to stand for 10 min, accurately timed, then add 1.0 mL of 3.5 N hydrochloric acid, mix, and add 1.0 mL of an 80-mg/mL ferric chloride solution, and mix. Allow to stand for 30 min, accurately timed. Gently swirl the tubes for 1 min to remove any gas bubbles present, then concomitantly determine the absorbances of the solutions.

Calculate the percentage of the labeled amount of benzonatate \( [C_{17}H_{23}NO_{11} \text{ (av.)}] \) in the Capsules taken:

\[
\text{Result} = (A_U/A_L) \times (C_S/C_U) \times 100
\]

- \( A_U \) = absorbance of the Sample solution
- \( A_L \) = absorbance of the Standard solution
- \( C_S \) = concentration of USP Benzonatate RS in the Standard solution (µg/mL)
- \( C_U \) = nominal concentration of benzonatate in the Sample solution (µg/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
  
  **Mobile phase**: Acetonitrile and 0.04 M monobasic potassium phosphate (75:25)
  
  **Standard solution**: 0.1 mg/mL of USP Benzonatate RS.
  
  Sonicate to dissolve, if needed.
  
  **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 310 nm
  
  **Column**: 3.9-mm x 30-cm; packing L1
  
  **Flow rate**: 1.5 mL/min
  
  **Injection volume**: 15 µL

  **System suitability**
  
  **Sample**: Standard solution
  
  **Suitability requirements**
  
  **Relative standard deviation**: NMT 2.0%

  **Analysis**
  
  **Samples**: Standard solution and Sample solution
  
  Calculate the percentage of the labeled amount of benzonatate \( [C_{17}H_{23}NO_{11} \text{ (av.)}] \) dissolved:

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

- \( r_U \) = peak response of benzonatate from the Sample solution
- \( r_S \) = peak response of benzonatate from the Standard solution
- \( C_S \) = concentration of USP Benzonatate RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Capsule)

**Tolerances**: NLT 80% (Q) of the labeled amount of benzonatate \( [C_{17}H_{23}NO_{11} \text{ (av.)}] \) is dissolved.

**Test 2**

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

**Tier 1**

- **Medium**: Water; 900 mL
- **Apparatus 2**: 50 rpm
- **Time**: 45 min

- **Standard solution**: 0.022 mg/mL of USP Benzonatate RS in Medium. Sonicate to dissolve, if needed.

- **Sample solution**: Withdraw a portion of the solution under test, dilute with Medium to a concentration of about 0.022 mg/mL, and pass through a suitable filter of 0.45-µm or finer pore size.

**Instrumental conditions**

(See Ultraviolet-Visible Spectroscopy (857).)

**Mode**: UV

**Analytical wavelength**: 310 nm

**Analysis**

**Samples**: Standard solution and Sample solution

Calculate the percentage of the labeled amount of benzonatate \( [C_{17}H_{23}NO_{11} \text{ (av.)}] \) dissolved:

\[
\text{Result} = (A_U/A_L) \times C_S \times V \times D \times 1/L \times 100
\]

- \( A_U \) = absorbance of the Sample solution
- \( A_L \) = absorbance of the Standard solution

© 2018 The United States Pharmacopeial Convention All Rights Reserved.

C194912-M8260-CHM22015, rev 00 20180629
C benzonatate = concentration of USP Benzonatate RS in the Standard solution (mg/mL)
V = volume of Medium, 900 mL
D = dilution factor for the Sample solution
L = label claim (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amount of benzonatate \([C_{30}H_{53}NO_{11}\text{ (av.)}]\) is dissolved. If this tolerance cannot be met because of the presence of cross-linking in the gelatin Capsules, proceed to Tier 2.

Tier 2: Perform this test only if the Tolerances in Tier 1 cannot be met because of the presence of cross-linking in the gelatin Capsules.

Medium: Simulated gastric fluid; 900 mL

Apparatus 2: 50 rpm
Time: 30 min

Solution A: Dissolve about 5.44 g of monobasic potassium phosphate in 1000 mL of water.
Mobile phase: Acetonitrile and Solution A (75:25)
Standard solution: 0.022 mg/mL of USP Benzonatate RS in Medium. Sonicate to dissolve, if needed.
Sample solution: Withdraw a portion of the solution under test, dilute with Medium to a concentration of about 0.022 mg/mL, and pass through a suitable filter of 0.45-μm or finer pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: UV
Detector: UV 310 nm
Columns
Guard: 4.0-mm × 4.0-mm; 5-μm packing L1
Analytical: 4.0-mm × 25-cm; 7-μm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 20 μL

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 benzonatate \([C_{30}H_{53}NO_{11}\text{ (av.)}]\) dissolved:

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

\(r_U\) = peak response of benzonatate from the Sample solution
\(r_S\) = peak response of benzonatate from the Standard solution
\(C_S\) = concentration of USP Benzonatate RS in the Standard solution (mg/mL)
V = volume of Medium, 900 mL
D = dilution factor for the Sample solution
L = label claim (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amount of benzonatate \([C_{30}H_{53}NO_{11}\text{ (av.)}]\) is dissolved.

• Uniformity of Dosage Units (905): Meet the requirements

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 Benzonatate RS