Benzonatate Capsules

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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 [$C_{30}H_{53}NO_{11}$ (av.)].

IDENTIFICATION

• **A. Infrared Absorption ⟨197F⟩**

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 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, 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 [$C_{30}H_{53}NO_{11}$ (av.)] in the Capsules 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 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**▲ (RB 1-Jul-2018)

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 × 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 [$C_{30}H_{53}NO_{11}$ (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 [$C_{30}H_{53}NO_{11}$ (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 [$C_{30}H_{53}NO_{11}$ (av.)] 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 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 [$C_{30}H_{53}NO_{11}$ (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 [$C_{30}H_{53}NO_{11}$ (av.)] dissolved:

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

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
D = dilution factor for the *Sample solution*
L = label claim (mg/Capsule)

Tolerances: NLT 75% (*Q*) of the labeled amount of benzonatate [$C_{30}H_{53}NO_{11}$ (av.)] is dissolved. ▲ (RB 1-Jul-2018)

- **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. ▲ (RB 1-Jul-2018)

- **USP Reference Standards ⟨11⟩**
USP Benzonatate RS