



Bisoprolol Fumarate Tablets

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 6 Expert Committee has revised the Bisoprolol Fumarate Tablets monograph. The purpose of this revision is to add *Dissolution Test 4* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

- *Dissolution Test 4* was validated using the Kromasil C18 brand of column with L1 packing. The typical retention time for bisoprolol is about 3 min.

The Bisoprolol Fumarate Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Jasmine Lawrence, Scientist IV (301-230-6363 or jasmine.lawrence@usp.org).

Bisoprolol Fumarate Tablets

DEFINITION

Bisoprolol Fumarate Tablets contain NLT 90.0% and NMT 105.0% of the labeled amount of bisoprolol fumarate $[(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4]$.

IDENTIFICATION

• [THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST](#) (201)

Sample solution: Equivalent to 40 mg of bisoprolol fumarate, from powdered Tablets (NLT 5), in a 50-mL flask. Add about 20 mL of a mixture of [methylene chloride](#) and [methanol](#) (7:3), shake for 30 min, centrifuge, and use the clear solution.

Application volume: 20 μ L

Developing solvent system: [Methylene chloride](#), [methanol](#), and [stronger ammonia water](#) (70:10:0.8)

Analysis

Sample: *Sample solution*

Proceed as directed in the chapter, except to develop the chromatogram until the solvent front has moved about two-thirds of the length of the plate and to dry the plate in a current of cold air.

ASSAY

• PROCEDURE

Diluent: [Acetonitrile](#) and [water](#) (7:13)

Mobile phase: A 1-L portion of *Diluent*. Add 5 mL of [heptafluorobutyric acid](#), 5 mL of [diethylamine](#), and 2.5 mL of [formic acid](#).

System suitability solution: 0.5 mg/mL of propranolol hydrochloride and 1 mg/mL of bisoprolol fumarate in *Diluent*

Standard solution: 1 mg/mL of [USP Bisoprolol Fumarate RS](#) in *Diluent*

Sample solution: Transfer an equivalent of 25 mg of bisoprolol fumarate, from powdered Tablets (NLT 20), to a 25-mL volumetric flask. Add 10 mL of *Diluent*, and sonicate for 10 min. Cool, dilute with *Diluent* to volume, and mix. Centrifuge for 20 min, and use the clear supernatant.

Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

Mode: LC

Detector: UV 273 nm

Column: 4.6-mm \times 12.5-cm; packing [L7](#)

Flow rate: 1 mL/min

Injection size: 10 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 7.0 between bisoprolol and propranolol, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of [USP Bisoprolol Fumarate RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of bisoprolol fumarate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **[DISSOLUTION](#)** [\(711\)](#).

Test 1

Medium: [Water](#); 900 mL

Apparatus 2: 75 rpm

Time: 20 min

Determine the amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ dissolved by using the following method.

Diluent: [Methanol](#), [triethylamine](#), [phosphoric acid](#), and [water](#) (160:5:2.5:35)

Mobile phase: [Methanol](#), [triethylamine](#), and [water](#) (34:1:50). Adjust with [phosphoric acid](#) to a pH of 4.0 ± 0.1 .

Standard stock solution: [USP Bisoprolol Fumarate RS](#) in [water](#) to obtain a solution having a known concentration of about twice the concentration of bisoprolol fumarate in the *Sample solution*

Standard solution: *Standard stock solution* and *Diluent* (1:1)

Sample solution: Sample per [Dissolution](#) [\(711\)](#). Withdraw a portion of the solution under test, filter, and dilute with an equal volume of *Diluent*.

Chromatographic system

(See [Chromatography](#) [\(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 227 nm

Column: 4.6-mm \times 33-mm; packing [L7](#)

Flow rate: 1 mL/min

Injection size: 50 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Tolerances: NLT 80% (Q) of the labeled amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ is dissolved.

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

Medium: 0.5 M [sodium chloride](#); 900 mL

Apparatus 2: 75 rpm

Time: 20 min

Analysis: Proceed as directed for *Test 1* with the following modifications.

Diluent: Prepare a mixture of [methanol](#), 0.1 N [hydrochloric acid](#), [triethylamine](#), and [phosphoric acid](#) (160:35:5:2.5). The dimensions of the column are 4.6 mm × 25 cm.

Tolerances: NLT 80% (Q) of the labeled amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.1 N [hydrochloric acid](#); 500 mL

Apparatus 1: 100 rpm

Time: 20 min

Buffer: Dissolve 4 g of [monobasic potassium phosphate](#) in 1000 mL of [water](#). Add 2 mL of [triethylamine](#) and adjust with [phosphoric acid](#) to a pH of 4.5.

Mobile phase: [Acetonitrile](#) and *Buffer* (20:80)

Diluent: [Acetonitrile](#) and [water](#) (20:80)

Standard stock solution: 0.1 mg/mL of [USP Bisoprolol Fumarate RS](#) prepared as follows. Transfer a quantity of [USP Bisoprolol Fumarate RS](#) to an appropriate volumetric flask and dissolve in 50% of the flask volume of *Diluent*. Shake by mechanical means for 5 min to dissolve and dilute with *Diluent* to volume.

Standard solution: 0.016 mg/mL of [USP Bisoprolol Fumarate RS](#) from the *Standard stock solution* in *Medium*

Sample solution: Pass the portion of the solution under test through a suitable filter of 0.45- μ m pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

[NOTE—The *Sample solution* may be stable for 5 h at room temperature.]

Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 5-cm; 3.5- μ m packing [L7](#)

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 50 μ L

Run time: NLT 2.2 times the retention time of bisoprolol

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 bisoprolol fumarate $[(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4]$ dissolved:

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

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

r_S = peak response of bisoprolol from the *Standard solution*

C_S = concentration of [USP Bisoprolol Fumarate RS](#) in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of bisoprolol fumarate $[(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4]$ is dissolved.

▲ Test 4: If the product complies with this test, the labeling indicates that it meets *USP Dissolution Test 4*.

Medium: 0.1 N [hydrochloric acid](#); 500 mL, deaerated, if necessary

Apparatus 2: 50 rpm

Time: 30 min

Solution A: 100 mL/L of [phosphoric acid](#) in [water](#)

Buffer: Dissolve 1.36 g of [monobasic potassium phosphate](#) in 1000 mL of [water](#). Add 2.0 mL of [triethylamine](#) and adjust with *Solution A* to a pH of 4.0.

Mobile phase: [Acetonitrile](#) and *Buffer* (25:75)

Standard stock solution: 0.25 mg/mL of [USP Bisoprolol Fumarate RS](#) prepared as follows. Transfer a quantity of [USP Bisoprolol Fumarate RS](#) to an appropriate volumetric flask and dissolve in 10% of the flask volume of [methanol](#). Sonicate to dissolve if necessary. Dilute with [methanol](#) to volume.

Standard solution: (L/500) mg/mL of bisoprolol fumarate from the *Standard stock solution* in *Medium*, where L is the label claim in mg/Tablet

[NOTE—The *Standard solution* may be stable for 15 h at room temperature.]

Sample solution: Pass the portion of the solution under test through a suitable filter of 0.45- μ m pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

[NOTE—The *Sample solution* may be stable for 14 h at room temperature.]

Chromatographic system

(See [Chromatography <621>](#), [System Suitability](#).)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm \times 15-cm; 5- μ m packing [L1](#)

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 100 μ L

Run time: NLT 2 times the retention time of bisoprolol

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 bisoprolol fumarate $[(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4]$ dissolved:

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

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

r_S = peak response of bisoprolol from the *Standard solution*

C_S = concentration of [USP Bisoprolol Fumarate RS](#) in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of bisoprolol fumarate $[(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4]$ is dissolved. ▲ (RB 1-Apr-2026)

- **[UNIFORMITY OF DOSAGE UNITS](#)** (905): Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **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 Bisoprolol Fumarate RS](#)
2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (E)-2-butenedioate (2:1) (salt).
 $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ 766.96

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