Status: Currently Official on 14-Feb-2025
Official Date: Official Prior to 2013
Document Type: USP Monographs
DocId: GUID-1888FC9A-F354-4D07-BCBA-A07A63610616_1_en-US
DOI: https://doi.org/10.31003/USPNF_M9796_01_01
DOI Ref: j3sjy

Bisoprolol Fumarate and Hydrochlorothiazide Tablets

» Bisoprolol Fumarate and Hydrochlorothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of bisoprolol fumarate $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩—

USP Bisoprolol Fumarate RS
USP Chlorothiazide RS
USP Hydrochlorothiazide RS

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Finely powder 1 Tablet, and transfer the powder to a 5-mL volumetric flask. Dilute with methanol to volume, sonicate for 5 minutes, centrifuge, and use the supernatant.

Standard solution 1—Dissolve a suitable quantity of USP Bisoprolol Fumarate RS in methanol to obtain a solution containing 1 mg per mL.

Standard solution 2—Dissolve a suitable quantity of USP Hydrochlorothiazide RS in methanol to obtain a solution containing 1 mg per mL.

Application volume: 25 µL.

Developing solvent system: a mixture of methylene chloride, methanol, and 14.5 M ammonium hydroxide solution (43:20:8).

Procedure—Locate the spots on the plate under short-wavelength UV light and by exposure to iodine vapors: the R_F values of the principal spots in the chromatogram obtained from the *Test solution* correspond to those of the principal spots in the chromatograms obtained from *Standard solution 1* and *Standard solution 2*.

B: The retention times of the major peaks in the chromatograms of the *Bisoprolol fumarate assay preparation* and the *Hydrochlorothiazide assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 75 rpm.

Times: 20 minutes for bisoprolol fumarate; 30 minutes for hydrochlorothiazide.

Triethylamine solution—Mix 2 mL of triethylamine with 1000 mL of water, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Triethylamine solution* (1:4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution 1—Quantitatively dissolve an accurately weighed quantity of USP Bisoprolol Fumarate RS in *Medium* to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard stock solution 2—Transfer about 30 mg of USP Hydrochlorothiazide RS, accurately weighed, to a 50-mL volumetric flask, dissolve in 5 mL of methanol, dilute with *Medium* to volume, and mix.

Standard solution—Dilute accurately measured volumes of *Standard stock solution 1* and *Standard stock solution 2* with *Medium* to obtain a solution having known concentrations of bisoprolol fumarate and hydrochlorothiazide corresponding to those of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a UV detector capable of measuring peak responses at 227 nm and 272 nm, simultaneously, and a 3.9-mm × 15-cm column that contains packing L11. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the filtered portions of the solution under test into the chromatograph, record the chromatograms, and measure the peak areas for bisoprolol at 227 nm and for hydrochlorothiazide at 272 nm. Calculate the quantities, in mg, of bisoprolol fumarate $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ is dissolved in 20 minutes and not less than 80% *(Q)* of the labeled amount of $C_7H_8ClN_3O_4S_2$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** Meet the requirements with respect to bisoprolol fumarate and to hydrochlorothiazide.

Chromatographic purity—

Diluent, Solution A, Solution B, Mobile phase, and *System suitability solution*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Hydrochlorothiazide RS in *Diluent*, and quantitatively dilute with *Diluent,* if necessary, to obtain a solution having a known concentration of about 2 µg per mL.

Test stock solution—Proceed as directed for *Assay stock preparation* in the *Assay.*

Test solution—Quantitatively dilute an accurately measured volume of the *Test stock solution* with *Diluent* to obtain a solution having a concentration of about 100 µg of bisoprolol fumarate per mL.

Chromatographic system (see *Chromatography ⟨621⟩*)—Prepare as directed in the *Assay,* but use a 260-nm detector. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between chlorothiazide and hydrochlorothiazide is not less than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.3; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$(100/F)(W_B/W_H)(C_S/C_B)(r_i/r_S)$$

in which F is the response factor, equal to 1.2 for the peak with a relative retention time of 0.69 and 1.4 for the peak with a relative retention time of 1.2, both retention times relative to that of the hydrochlorothiazide peak; W_B and W_H are the labeled quantities, in mg, of bisoprolol fumarate and hydrochlorothiazide, respectively, in each Tablet; C_S is the concentration, in mg per mL, of USP Hydrochlorothiazide RS in the *Standard solution;* C_B is the concentration, in mg per mL, of bisoprolol fumarate in the *Test solution;* r_i is the peak response of each of the two impurities obtained from the *Test solution;* and r_S is the response for the hydrochlorothiazide peak obtained from the *Standard solution:* not more than 1.0% for the impurity with a relative retention time of 0.69 is found; and not more than 2.0% for the impurity with a relative retention time of 1.2 is found.

Assay—

Diluent—Mix 10 mL of 1 M dibutylammonium phosphate with 1000 mL of a mixture of water and acetronitrile (1:1).

Solution A—Mix 10 mL of 1 M dibutylammonium phosphate with 1000 mL of water.

Solution B—Prepare a mixture of acetonitrile and water (3:2). Add 10 mL of 1 M dibutylammonium phosphate per liter, stir vigorously for 2 minutes, filter, and degas.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

System suitability solution—Prepare a solution of USP Chlorothiazide RS and USP Hydrochlorothiazide RS in *Diluent* containing 40 µg of each per mL.

Standard preparation—Dissolve suitable quantities of USP Bisoprolol Fumarate RS and USP Hydrochlorothiazide RS in *Diluent* to obtain a solution having known concentrations of about 100 µg of each per mL. Stir by mechanical means for 1 hour.

Assay stock preparation—Weigh 10 Tablets, and transfer to a 100-mL volumetric flask. Add about 50 mL of *Diluent*, sonicate for 10 minutes, and cool. Dilute with *Diluent* to volume, stir by mechanical means for 1 hour, and centrifuge.

Bisoprolol fumarate assay preparation—Quantitatively transfer a portion of the *Assay stock preparation* to a 50-mL volumetric flask, and dilute with *Diluent* to volume to obtain a solution having a concentration of about 100 µg of bisoprolol fumarate per mL.

Hydrochlorothiazide assay preparation—Quantitatively transfer a portion of the *Assay stock preparation* to a 50-mL volumetric flask, and dilute with *Diluent* to volume to obtain a solution having a concentration of about 62.5 µg of hydrochlorothiazide per mL.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with 225-nm detector and an 8-mm × 10-cm column that contains packing L11. The flow rate is about 3 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–9.0	100→40	0→60	linear gradient
9.0–9.1	40→100	60→0	linear gradient
9.1–12.0	100	0	re-equilibration

Chromatograph the *System suitability solution,* and record the peak areas as directed for *Procedure:* the resolution, *R,* between chlorothiazide and hydrochlorothiazide is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the tailing factor for the hydrochlorothiazide peak is not more than 1.3; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation, Bisoprolol fumarate assay preparation,* and *Hydrochlorothiazide assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantities, in mg, of bisoprolol fumarate $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken by the formula:

$$5000(C/V)(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Bisoprolol Fumarate RS or USP Hydrochlorothiazide RS in the *Standard preparation,* as appropriate; *V* is the volume of the *Assay stock preparation* used to prepare the *Bisoprolol fumarate assay preparation* or the *Hydrochlorothiazide assay preparation;* r_U is the peak area obtained from the *Bisoprolol fumarate assay preparation* or the *Hydrochlorothiazide assay preparation,* as appropriate; and r_S is the corresponding peak area obtained from the *Standard preparation.*

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
BISOPROLOL FUMARATE AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 45(2)

Current DocID: GUID-1888FC9A-F354-4D07-BCBA-A07A63610616_1_en-US

DOI: https://doi.org/10.31003/USPNF_M9796_01_01

DOI ref: j3sjy