Edition: BP 2025 (Ph. Eur. 11.6 update)

Bisoprolol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Bisoprolol Tablets contain Bisoprolol Fumarate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bisoprolol fumarate, $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Dissolve a quantity of the powdered tablets containing 10 mg of Bisoprolol Fumarate in *methanol*, dilute to 10 mL with the same solvent, mix and filter (a 0.45-µm nylon syringe filter is suitable).
(2) 0.1% w/v of *bisoprolol fumarate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.
(b) Use the mobile phase as described below and allow to equilibrate for 1 hour.
(c) Apply 25 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of *ethyl acetate*. At the bottom of the chromatography tank, place a beaker containing 15 mL of *concentrated ammonia*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Solution A Prepare a solution containing 2.5 volumes of *orthophosphoric acid*, 5 volumes of *triethylamine*, 35 volumes of *water* and 160 volumes of *methanol*.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium, filter and dilute with sufficient of solution A to produce a solution expected to contain 0.0001% w/v of bisoprolol fumarate.
(2) 0.0002% w/v of *bisoprolol fumarate BPCRS* in *water*. Dilute 1 volume of this solution to 2 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (3.3 cm × 4.6 mm) packed with *octasilyl silica gel for chromatography* (3 µm) (Pecosphere 3CR C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 227 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

2 volumes of *triethylamine*, 68 volumes of *methanol* and 100 volumes of *water*, previously adjusted to pH 4.0 using *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of bisoprolol fumarate, $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$, in the medium from the chromatograms obtained and using the declared content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$, in *bisoprolol fumarate BPCRS*.

LIMITS

The amount of bisoprolol fumarate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 2 volumes of *acetonitrile* and 8 volumes of *water*.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 10 mg of Bisoprolol Fumarate. Add sufficient solvent to produce a 0.1% w/v solution of Bisoprolol Fumarate and filter (0.45-µm nylon syringe filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 5 volumes.
(4) Dissolve the contents of a vial of *bisoprolol for peak identification EPCRS* in 1.0 mL.
(5) Dissolve the contents of a vial of *bisoprolol for system suitability EPCRS* in 1.0 mL.
(6) Dilute 1 volume of *bisoprolol impurity standard BPCRS* to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Ace C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 20°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1% w/v solution of *orthophosphoric acid*.

Mobile phase B 1% w/v solution of *orthophosphoric acid* in *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	95	5	isocratic
4-8	95→80	5→20	linear gradient
8-15	80	20	isocratic
15-34	80→20	20→80	linear gradient
34-36	20	80	isocratic
36-37	20→95	80→5	linear gradient
37-46	95	5	re-equilibration

Use the chromatogram supplied with *bisoprolol for peak identification EPCRS* and the chromatogram obtained with solution (4) to identify the peaks due to fumaric acid and impurities A and E; use the chromatogram supplied with *bisoprolol for system suitability EPCRS* and the chromatogram obtained with solution (5) to identify the peak due to impurity G; use the chromatogram supplied with *bisoprolol impurity standard BPCRS* and the chromatogram obtained with solution (6) to identify the peaks due to impurities L, K and 1.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to bisoprolol (retention time about 22 minutes) are: impurity A, about 0.48; impurity L, about 0.55; impurity G, about 1.03; impurity K, about 1.05; impurity E, about 1.1; impurity 1, about 1.2 and impurity 2 (double peak), about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 2.5, where H_p is the height above the baseline of the peak due to impurity G and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bisoprolol.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity K is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity L is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity 1 is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.6%);

the area of any peaks corresponding to impurity 2 or G are not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks*, excluding the peaks due to impurity K and L, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%) and any peak due to fumaric acid.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Bisoprolol Fumarate comply with the requirement stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To one tablet add 20 mL and mix with the aid of ultrasound. Dilute to produce a solution containing 0.005% w/v of Bisoprolol Fumarate and filter (0.45-µm nylon syringe filter is suitable).
(2) 0.005% w/v of *bisoprolol fumarate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (LiChrospher RP-Select B is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volume of *glacial acetic acid* and 1000 volumes of 0.136% *sodium acetate trihydrate* in *methanol (50%)*.

When the chromatograms are recorded under the prescribed conditions, the retention time of bisoprolol is about 5 minutes.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to bisoprolol is between 0.8 and 1.6.

DETERMINATION OF CONTENT

Calculate the content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in each tablet using the declared content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in *bisoprolol fumarate BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Bisoprolol Fumarate

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Bisoprolol Fumarate

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) To a quantity of the powdered tablets containing 25 mg of Bisoprolol Fumarate add 45 mL and mix with the aid of ultrasound. Dilute to produce a solution containing 0.005% w/v of Bisoprolol Fumarate and filter (a 0.45-µm nylon syringe filter is suitable).
(2) 0.005% w/v of *bisoprolol fumarate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

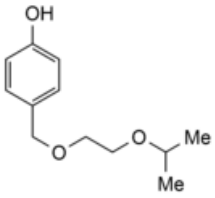
The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

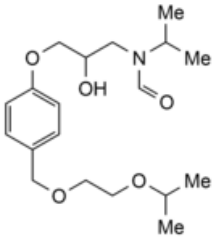
Calculate the content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in the tablets using the declared content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in *bisoprolol fumarate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Bisoprolol Fumarate and:



1. 4-{[2-(propan-2-yloxy)ethoxy]methyl}phenol



2. *rac*-*N*-(propan-2-yl)-*N*-{2-hydroxy-3-[(4-{[2-(propan-2-yloxy)ethoxy]methyl}phenyl)oxy]propyl}formamide (bisoprolol *N*-aldehyde)