Bendroflumethiazide Tablets

General Notices

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 1
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Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Content** limits revised **Identification** TLC test replaced **Dissolution** new test added **Related substances** TLC procedure replaced with LC method **Assay** UV procedure replaced with LC method

Action and use

Thiazide diuretic.

DEFINITION

Bendroflumethiazide Tablets contain Bendroflumethiazide.

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

Content of bendroflumethiazide, $C_{15}H_{14}F_3N_3O_4S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210-400 nm:

the UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the 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 1, rotating the basket at 50 revolutions per minute.
(b) Use 900 mL of 0.005M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 45 minutes withdraw a sample of the medium and filter (a polyethylene filter is suitable), diluted with the dissolution medium, if necessary, to produce a solution containing of 0.00028% w/v of Bendroflumethiazide.
(2) 0.028% w/v of *bendroflumethiazide BPCRS* in *methanol*. Dilute 1 volume to 100 volumes with the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters SunFire C18 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 273 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes of *acetonitrile* and 60 volumes of *water*, adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of bendroflumethiazide is about 8 minutes.

DETERMINATION OF CONTENT

Calculate the total content of bendroflumethiazide, $C_{15}H_{14}F_3N_3O_4S_2$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{14}F_3N_3O_4S_2$ in *bendroflumethiazide BPCRS*.

LIMITS

The amount of bendroflumethiazide 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 mobile phase A. *Protect the solutions from light.*

(1) Shake a quantity of powdered tablets containing 12.5 mg of Bendroflumethiazide with 15 mL of *methanol*, dilute to 25 mL with mobile phase A and filter through a 0.45-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with mobile phase A.

(3) 0.5% w/v of *bendroflumethiazide BPCRS* and 0.005% w/v of *bendroflumethiazide impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with mobile phase A.

(4) Dilute 1 volume of solution (2) to 5 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters SunFire 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 273 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *acetonitrile* and 80 volumes of *water*; adjusted to pH 2.0 with *orthophosphoric acid*.

Mobile phase B 40 volumes of *water* and 60 volumes of *acetonitrile*; adjusted to pH 2.0 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100	0	isocratic
10-14	100→0	0→100	linear gradient
14-18	0	100	isocratic
18-22	0→100	100→0	linear gradient
22-28	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention time of bendroflumethiazide is about 16 minutes and the relative retention of impurity A is about 0.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity A and bendroflumethiazide is at least 40.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any*secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions. *Protect the solutions from light.*

(1) Shake a quantity of powdered tablets containing 12.5 mg of Bendroflumethiazide with 30 mL of *methanol* and dilute to 50 mL with the mobile phase . Dilute 1 volume to 50 volumes with the mobile phase and filter through a 0.45-µm nylon filter.
(2) 0.005% w/v of *bendroflumethiazide BPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.
(3) 0.005% w/v of *bendroflumethiazide BPCRS* and 0.0005% w/v of *bendroflumethiazide impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters SunFire C18 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 20°.
(e) Use a detection wavelength of 273 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes of *water* and 60 volumes of *acetonitrile*, adjusted to pH 2.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity A and bendroflumethiazide is at least 15.

DETERMINATION OF CONTENT

Calculate the content of bendroflumethiazide, $C_{15}H_{14}F_3N_3O_4S_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{14}F_3N_3O_4S_2$, in *bendroflumethaizide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Bendroflumethiazide.