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Bendroflumethiazide Oral Suspension

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Thiazide diuretic.

DEFINITION

Bendroflumethiazide Oral Suspension is a suspension of Bendroflumethiazide in a suitable flavoured aqueous vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

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

92.5 to 105.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Mix a quantity of the oral suspension with sufficient *acetone* to produce a solution containing 0.025% w/v of Bendroflumethiazide; shake for 10 minutes and filter.
(2) 0.1% w/v of *bendroflumethiazide BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 20 µL of solution (1) and 5 µL of solution (2).
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry it in air, examine under *ultraviolet light (254 nm)* and then reveal the spots by *Method I*.

MOBILE PHASE

Ethyl acetate.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds in position and colour 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

Acidity

pH, 2.6 to 3.0, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions. Store and inject the solutions at 4°, using a cooled autosampler.

(1) Add 30 mL of *methanol* to a quantity of the oral suspension containing 2.5 mg of Bendroflumethiazide and shake vigorously. Add about 10 mL of a 5% w/v solution of *sodium chloride*, allow to cool and add sufficient of the 5% w/v *sodium chloride* to produce 50 mL. Filter the resulting solution through a 0.45-µm nylon filter, discarding the first 5 mL of filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.
(3) Dilute 1 volume of solution (2) to 10 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) fitted with a stainless steel guard column (4 mm × 3 mm) packed with the same material.
(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.

When the chromatograms are recorded under the prescribed conditions the retention time of bendroflumethiazide is about 16.5 minutes and the relative retention of impurity A [4-amino-6-(trifluoromethyl)benzene-1,3-disulfonamide] is about 0.33.

MOBILE PHASE

Mobile phase A

4 volumes of *acetonitrile* and 16 volumes of *water*; adjust the pH of the mixture to 2.0 using *orthophosphoric acid*.

Mobile phase B

4 volumes of *water* and 6 volumes of *acetonitrile*; adjust the pH of the mixture to 2.0 using *orthophosphoric acid*.

Equilibrate the column with mobile phase A for at least 1 hour before starting the elution programme.

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

SYSTEM SUITABILITY

The following test applies only if a peak due to impurity A and a peak with a retention relative to that of bendroflumethiazide of about 0.24 are present.

The test is not valid unless, in the chromatogram obtained with solution (1), the *resolution* between the peak due to impurity A and the peak with a retention relative to bendroflumethiazide of about 0.24 is at least 1.5. If co-elution of these peaks occurs, re-equilibrate the column for at least 1 hour and repeat using freshly prepared mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

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

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks*, excluding the peak due to impurity A, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions. Store and inject the solutions at 4°, using a cooled autosampler.

(1) Add 30 mL of *methanol* to a weighed quantity of the oral suspension containing 2.5 mg of Bendroflumethiazide and shake vigorously. Add about 10 mL of a 5% w/v solution of *sodium chloride*, allow to cool and add sufficient of the 5% w/v *sodium chloride* to produce 50 mL. Filter the resulting solution through a 0.45-µm nylon filter, discarding the first 5 mL of filtrate.
(2) Dilute 1 volume of a 0.025% w/v solution of *bendroflumethiazide BPCRS* in *methanol* to 5 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak corresponding to bendroflumethiazide is between 0.9 and 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{14}F_3N_3O_4S_2$, weight in volume, using the declared content of $C_{15}H_{14}F_3N_3O_4S_2$ in *bendroflumethiazide BPCRS*.

STORAGE

Bendroflumethiazide Oral Suspension should be stored at a temperature of 2° to 8°.

IMPURITIES

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