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

Indapamide Tablets

General Notices

Action and use

Thiazide-like diuretic.

DEFINITION

Indapamide Tablets contain Indapamide. They are coated.

PRODUCTION

A suitable test is carried out to demonstrate that the content of (2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-amine (impurity C) is not more than 600 ppm.

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

Content of indapamide hemihydrate, $C_{16}H_{16}ClN_3O_3S,½H_2O$

95.0 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) Grind a quantity of the powdered tablets containing 50 mg of Indapamide with 10 mL of *acetone*, mix for 15 minutes, filter through a fine filter paper (Whatman 42 is suitable) and use the filtrate.
(2) 0.5% w/v of *indapamide 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 each solution.
(d) Develop the plate to 12 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*. Spray the plate with a solution prepared by mixing 10 volumes of *potassium iodobismuthate solution* and 20 volumes of *glacial acetic acid* and diluting to 100 volumes with *water* and examine again. Finally, spray the plate with a 5% w/v solution of *sodium nitrite* in a mixture of equal volumes of *water* and *ethanol (96%)* and examine again.

MOBILE PHASE

20 volumes of *acetone* and 80 volumes of *toluene*

CONFIRMATION

By each method of visualisation, the principal spot in the chromatogram obtained with solution (1) is similar in position, colour and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

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

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 60 minutes withdraw a 10-mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maxima at 240 nm and at 275 nm, Appendix II B, using 0.1 M *hydrochloric acid* in the reference cell.
(2) Measure the *absorbance* of a reference solution prepared by diluting 1 volume of a 0.10% w/v solution of *indapamide BPCRS* in *methanol* to 200 volumes with 0.1M *hydrochloric acid* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of indapamide hemihydrate, $C_{16}H_{16}ClN_3O_3S,½H_2O$, in the medium using the differences in absorbance at 240 nm and at 275 nm and using the declared content of $C_{16}H_{16}ClN_3O_3S$ in *indapamide BPCRS*.Each mg of $C_{16}H_{16}ClN_3O_3S$ is equivalent to 1.0246 mg of $C_{16}H_{16}ClN_3O_3S,½H_2O$. The amount of indapamide hemihydrate released is not less than 75% of the stated amount.

Related substances

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

(1) Mix 10 whole tablets with 70 mL of *ethanol (96%)*, mix mechanically until the tablets have disintegrated and continue mixing for 2 hours. Add sufficient *ethanol (96%)* to produce 100 mL, mix and centrifuge. Dilute the supernatant liquid with the mobile phase to produce a solution containing 0.005% w/v of Indapamide.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of this solution to 10 volumes with the mobile phase.
(3) Dilute 1 volume of a 0.00025% w/v solution of *indapamide impurity B BPCRS* in *ethanol (96%)* to 10 volumes with the mobile phase.
(4) Dilute 1 volume of a 0.00025% w/v solution of *4-chloro-3-sulfamoylbenzoic acid* in *ethanol (96%)* to 10 volumes with the mobile phase.
(5) Mix one volume of solution (1), one volume of a 0.00025% w/v solution of *indapamide impurity B BPCRS* in *ethanol (96%)* and 1 volume of a 0.00025% w/v solution of *4-chloro-3-sulfamoylbenzoic acid* in *ethanol (96%)* and add 7 volumes of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

6 volumes of a solution containing 5% w/v of *sodium dodecyl sulfate* and 3% v/v of *glacial acetic acid*, 10 volumes of *triethylamine*, 20 volumes of *butan-2-ol*, 310 volumes of *acetonitrile* and 690 volumes of *water*, the mixture being adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the retention of impurity B relative to indapamide is about 1.7 and the retention of 4-chloro-3-sulfamoylbenzoic acid relative to indapamide is about 0.3.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak corresponding to 4-chloro-3-sulfamoylbenzoic acid is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

The sum of the impurities, excluding impurity B, is not greater than 0.3%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

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

(1) Mix 10 whole tablets with 70 mL of *ethanol (96%)*, mix mechanically until the tablets have disintegrated and continue mixing for 2 hours. Add sufficient *ethanol (96%)* to produce 100 mL, mix and centrifuge. Dilute the supernatant liquid with the mobile phase to produce a solution containing 0.005% w/v of Indapamide.
(2) Dilute 1 volume of a 0.025% w/v solution of *indapamide BPCRS* in *ethanol (96%)* to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

DETERMINATION OF CONTENT

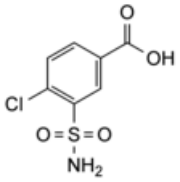
Calculate the content of $C_{16}H_{16}ClN_3O_3S,½H_2O$ in the tablets from the chromatogram obtained using the declared content of $C_{16}H_{16}ClN_3O_3S$ in *indapamide BPCRS*. Each mg of $C_{16}H_{16}ClN_3O_3S$ is equivalent to 1.0246 mg of $C_{16}H_{16}ClN_3O_3S,½H_2O$.

STORAGE

Indapamide Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B and C listed under Indapamide and the following:



1. 4-chloro-3-sulfamoylbenzoic acid