Fluconazole capsules (Fluconazoli capsulae)

2015-01

Category. Antifungal.

Storage. Fluconazole capsules should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential medicines (EML):

50 mg. Strength in the current WHO EML for children: 50 mg.

Requirements

Comply with the monograph for *Capsules*.

Definition. Fluconazole capsules contain Fluconazole. They contain not less than **90.0%** and not more than **110.0%** of the amount of fluconazole ($C_{13}H_{12}F_2N_6O$) stated on the label.

Identity tests

· Either tests A and C or tests B and C may be applied.

A. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 80 volumes of dichloromethane R, 20 volumes of methanol R and 1 volume of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate 10 µL of each of the following three solutions in methanol R. For solution (A) shake a quantity of the contents of the capsules, equivalent to about 100 mg of Fluconazole, with 10 mL of methanol R, filter and use the clear filtrate. For solution (B) use 10 mg of fluconazole RS per mL. For solution (C) use a mixture of 2 mg of fluconazole RS and 1 mg of ketoconazole RS per mL. After removing the plate from the chromatographic chamber allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. Shake a quantity of the contents of the capsules containing the equivalent of about 2 mg of Fluconazole with 10 mL of ethanol R and filter. The absorption spectrum (*1.6*) of the resulting solution, when observed between 230 nm and 300 nm, exhibits maxima at 261 nm and 267 nm and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.

Related substances

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given under "Assay". Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 10 mg of Fluconazole per mL and filter the solution. For solution (2) dilute 5 volumes of solution (1) to 100 volumes then dilute l volume of this solution to 10 volumes. For solution (3) use 0.1 mg of fluconazole impurity C RS per mL. For solution (4) transfer 1.0 mL of solution (3) to a 10 mL volumetric flask, add 1.0 mL of solution (1) and make up to volume.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 261 nm.

Maintain the column at 40 °C.

Inject separately 20 µL each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid unless in the chromatogram obtained with solution (4), the resolution between the peaks due to impurity C and due to fluconazole is at least 3.0

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 peak corresponding to impurity B, when multiplied by a correction factor of 1.5, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);
- -the area of any peak corresponding to impurity C is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);
- -the area of any other impurity peak, other than the principal 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 all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Dissolution test

Carry out the test as described under *5.5 Dissolution test for solid oral dosage forms* using as the dissolution medium 500 mL of pH 6.8 dissolution buffer TS, rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of about 10 mL of the medium through a suitable 0.45 µm filter. Measure the absorbance (*1.6*) of a 1 cm layer of the filtered solution, suitably diluted if necessary, at the maximum at about 261 nm. At the same time measure the absorbance (*1.6*) of a solution containing 0.1 mg of fluconazole RS per mL in the dissolution medium at the same wavelength, using the same solvent as the blank.

For each of the capsules tested calculate the total amount of fluconazole ($C_{13}H_{12}F_2N_6O$) in the medium using the declared content of $C_{13}H_{12}F_2N_6O$ in fluconazole RS. Use the requirements as described under *5.5 Dissolution test for solid oral dosage forms, Acceptance criteria* to evaluate the results. The amount in solution is not less than 75% (Q) of the amount declared on the label.

*[**Note from the Secretariat.** It is intended to determine the absorptivity value of fluconazole during the establishment of fluconazole RS and to use this value for the calculation of the test result.]*

Assay

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm). As the mobile phase use a mixture of 86 volumes of a 0.63 g/L solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules, accurately weighed, to produce a solution containing 0.5 mg of Fluconazole per mL and filter the solution. For solution (2) use 0.5 mg of fluconazole RS per mL. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per mL and 1 mg of fluconazole RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 261 nm.

Maintain the column at 40 °C.

Inject separately 20 µL of each of solutions (1), (2) and (3). The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to impurity C and to fluconazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of fluconazole ($C_{13}H_{12}F_2N_6O$) in the capsules using the declared content of $C_{13}H_{12}F_2N_6O$ in fluconazole RS.