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Miconazole and Hydrocortisone Ointment

General Notices

Action and use

Antifungal azole.

DEFINITION

Miconazole and Hydrocortisone Ointment contains Miconazole Nitrate and Hydrocortisone in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of miconazole nitrate, $C_{18}H_{14}Cl_4N_2O,HNO_3$

95.0 to 105.0% of the stated amount.

Content of hydrocortisone, $C_{21}H_{30}O_5$

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) Disperse a quantity of the ointment containing 0.15 g of Miconazole Nitrate by shaking with 25 mL of *tetrahydrofuran* for about 30 minutes, dilute to 50 mL with *methanol*, filter and use the filtrate.
(2) 0.3% w/v of *miconazole nitrate BPCRS* in equal volumes of *methanol* and *tetrahydrofuran*.
(3) 0.15% w/v of *hydrocortisone BPCRS* in equal volumes of *methanol* and *tetrahydrofuran*.
(4) 0.15% w/v of *hydrocortisone BPCRS* and 0.15% w/v of *hydrocortisone acetate BPCRS* in equal volumes of *methanol* and *tetrahydrofuran*.

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 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and expose to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

20 volumes of *ammonium acetate solution*, 40 volumes of *dioxan* and 40 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

CONFIRMATION

The principal spots in the chromatogram obtained with solution (1) are similar in position, colour and size to those in the chromatograms obtained with solutions (2) and (3).

B. In the Assay for miconazole nitrate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to miconazole nitrate in the chromatogram obtained with solution (2).
C. In the Assay for hydrocortisone, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to hydrocortisone in the chromatogram obtained with solution (2).

TESTS

Related substances

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

(1) Shake a quantity of the ointment containing 50 mg of Miconazole Nitrate with 50 mL of *tetrahydrofuran* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter (Whatman GF/F is suitable).
(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.
(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 235 nm.
(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the retention times are: hydrocortisone, about 8 minutes; miconazole, about 18 minutes.

MOBILE PHASE

Mobile phase A 0.01M *ammonium dihydrogen orthophosphate* adjusted to pH 6.0 with *dilute ammonia R1*.

Mobile phase B 10 volumes of *tetrahydrofuran* and 90 volumes of *acetonitrile*.

Time (minutes)	Mobile phase A % v/v	Mobile phase B % v/v	Comments
0→20	80→20	20→80	linear gradient
20→25	20	80	isocratic
25→27	20→80	80→20	linear gradient
27→32	80	20	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak other than those of hydrocortisone and miconazole is not greater than the area of the miconazole peak in the chromatogram obtained with solution (2) (0.5%);

the total area of any such peaks is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak due to nitrate ion and any peak with an area less than 0.2 times the area of the peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For miconazole nitrate

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

(1) Shake a quantity of the ointment containing 50 mg of Miconazole Nitrate with 50 mL of *tetrahydrofuran* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.
(2) 0.050% w/v of *miconazole nitrate BPCRS* in *methanol*.
(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{14}Cl_4N_2O$ in the preparation being examined using the declared contents of $C_{18}H_{14}Cl_4N_2O.HNO_3$ in *miconazole nitrate BPCRS*.

For hydrocortisone

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

(1) Shake a quantity of the ointment containing 25 mg of Hydrocortisone with 50 mL of *tetrahydrofuran* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.
(2) 0.025% w/v of *hydrocortisone BPCRS* in *methanol*.
(3) 0.02% w/v each of *miconazole impurity A BPCRS* and *2,4-dichlorobenzenemethanol* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is greater than 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{30}O_5$ in the preparation being examined using the declared content of $C_{21}H_{30}O_5$ in *hydrocortisone BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Miconazole Nitrate and the following:

2,4-dichlorobenzenemethanol,

2,4-dichloro-β-[2,4-dichlorophenyl)-methoxy]benzene ethanamine,

N-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)-methoxy]ethyl]formamide.