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Flumetasone and Clioquinol Ear Drops

General Notices

Action and use

Glucocorticoid and antibacterial.

DEFINITION

Flumetasone and Clioquinol Ear Drops contain Flumetasone Pivalate and Clioquinol.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of flumetasone pivalate, $C_{27}H_{36}F_2O_6$

95.0 to 105.0% w/v of the stated amount.

Content of clioquinol, C_9H_5ClINO

95.0 to 105.0% w/v 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 ear drops containing 1 mg of Flumetasone Pivalate in *acetone*, add sufficient *acetone* to produce 10 mL and filter.
(2) 0.01% w/v of *flumetasone pivalate BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.
(b) Use the mobile phase as described below.
(c) Apply 50 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air, heat at 105° for 5 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

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

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

TESTS

Related substances

For flumetasone pivalate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *methanol (80%)*.

(1) Shake a volume of the ear drops containing 1.2 mg of Flumetasone Pivalate with 50 mL of *methanol (80%)*, add 40 mg of *copper(II) acetate* and dilute to 100 mL. Place the solution in an ice bath for 1 hour, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.001% w/v of *flumetasone pivalate BPCRS* and 0.00001% w/v of *flumetasone acetate*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

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 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 235 nm.
(f) Inject 50 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of flumetasone pivalate.

MOBILE PHASE

0.2 volumes of *glacial acetic acid*, 20 volumes of *acetonitrile*, 40 volumes of *methanol* and 40 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to flumetasone acetate and flumetasone pivalate is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

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

Disregard any peak:

that elutes before 1.5 minutes;

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

For clioquinol

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

Solution A 0.1 volume of *orthophosphoric acid*, 10 volumes of *water*, 30 volumes of *acetonitrile* and 60 volumes of *methanol*.

(1) Dilute a volume of the ear drops containing 18 mg of Clioquinol with 1 mL of *tetrahydrofuran*, add sufficient solution A to produce 100 mL, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) Dilute 1 volumes of solution (2) to 5 volumes with solution A.
(4) 0.018% w/v of *clioquinol BPCRS* and 0.00018% w/v each of *5-chloroquinolin-8-ol, 5,7-dichloroquinolin-8-ol* and *5,7-diiodoquinolin-8-ol* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil 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 260 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of the peak due to clioquinol.

MOBILE PHASE

20 volumes of *water* and 80 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to clioquinol (retention time about 5 min) are: 5-chloroquinolin-8-ol, about 0.6; 5,7-diiodoquinolin-8-ol, about 0.8 and 5,7-dichloroquinolin-8-ol, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to clioquinol and 5,7-dichloroquinolin-8-ol is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 5-chloroquinolin-8-ol is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any peak corresponding to 5,7-diiodoquinolin-8-ol or 5,7-dichloroquinolin-8-ol 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 the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

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

ASSAY

For flumetasone pivalate

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

(1) Shake a weighed quantity of the ear drops containing 1.2 mg of Flumetasone Pivalate with 25 mL of the mobile phase, add 30 mg of *copper(II) acetate* and dilute to 50 mL with the mobile phase. Place the solution in an ice bath for 1 hour, centrifuge and use the supernatant liquid.
(2) 0.0024% w/v of *flumetasone pivalate BPCRS* in the mobile phase.
(3) 0.001% w/v of *flumetasone pivalate BPCRS* and 0.00001% w/v of *flumetasone acetate* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil 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 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *water* and 80 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to flumetasone acetate and flumetasone pivalate is at least 1.5. If necessary adjust the concentration of *methanol* in the mobile phase.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the ear drops, Appendix V G, and calculate the content of $C_{27}H_{36}F_2O_6$, weight in volume, using the declared content of $C_{27}H_{36}F_2O_6$ in *flumetasone pivalate BPCRS*.

For clioquinol

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

(1) To a weighed quantity of the ear drops containing 18 mg of Clioquinol add 5 mL of a solution containing 1 volume of *triethylamine* and 1 volume of *tetrahydrofuran*, add sufficient of the mobile phase to produce 50 mL and centrifuge. Dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.
(2) 0.0036% w/v of *clioquinol BPCRS* in the mobile phase.
(3) 0.0002% w/v of *clioquinol BPCRS* and 0.0004% w/v of *5,7-dichloroquinolin-8-ol* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil 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 256 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

0.1 volume of *orthophosphoric acid*, 10 volumes of *water*, 30 volumes of *acetonitrile* and 60 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between clioquinol and 5,7-dichloroquinolin-8-ol is at least 1.5. If necessary adjust the concentration of *methanol* in the mobile phase.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the ear drops, Appendix V G, and calculate the content of C_9H_5ClINO, weight in volume, using the declared content of C_9H_5ClINO in *clioquinol BPCRS*.