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

Co-cyprindiol Tablets

General Notices

Action and use

Treatment of acne.

DEFINITION

Co-cyprindiol Tablets contain Cyproterone Acetate and Ethinylestradiol in the proportions, two thousand parts of Cyproterone Acetate and 35 parts of Ethinylestradiol.

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

Content of cyproterone acetate, $C_{24}H_{29}ClO_4$

95.0 to 105.0% of the stated amount.

Content of ethinylestradiol, $C_{20}H_{24}O_2$

92.5 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) To a quantity of powdered tablets containing 2 mg of Cyproterone Acetate add 1 mL of *methanol (80%)*, shake in a water bath at 40° and disperse with the aid of ultrasound. Allow to cool, centrifuge and use the supernatant liquid.
(2) 0.0035% w/v of *ethinylestradiol BPCRS* and 0.2% w/v of *cyproterone acetate BPCRS* in *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 HPTLC plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 15 µL of each solution.
(d) Develop the plate to 8 cm.
(e) After removal of the plate, dry in air, spray with *sulfuric acid (20%)* in *methanol*, heat at 105° for 10 minutes and examine under *ultraviolet light (365nm)*.

MOBILE PHASE

8 volumes of *diethylamine*, 32 volumes of *toluene* and 60 volumes of *dichloromethane*.

CONFIRMATION

The principal spots in the chromatogram obtained with solution (1) correspond in position and colour to those in the chromatogram obtained with solution (2).

B. In the test for Assay, the principal peaks in the chromatogram obtained with solution (1) correspond to the peaks in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.
(b) Use 900 mL of a 0.07% w/v solution of *sodium dodecyl sulfate* in 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute the filtrate, if necessary, with dissolution medium to produce a solution expected to contain 0.0002% w/v of Cyproterone Acetate.
(2) 0.0002% w/v of *cyproterone acetate BPCRS* and 0.0000035% w/v of *ethinylestradiol BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (ODS-Hypersil is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a UV detection wavelength of 282 nm and fluorimetric detection with an excitation wavelength of 280 nm and an emission wavelength of 310 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

4 volumes of *water* and 6 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatograms obtained with solution (1), the *retention time* of the peak due to cyproterone acetate is between 3.5 and 5.5 minutes and the *retention time* of the peak due to ethinylestradiol is between 1 and 2.5 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{29}ClO_4$ and $C_{20}H_{24}O_2$ in the medium from the chromatograms obtained and using the declared content of $C_{24}H_{29}ClO_4$ in *cyproterone acetate BPCRS* and $C_{20}H_{24}O_2$ in *ethinylestradiol BPCRS*, respectively.

LIMITS

The amount of Cyproterone Acetate and Ethinylestradiol released is not less than 75% (Q) of the stated amount for each component.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 9 volume of *acetonitrile*, 36 volumes of *methanol* and 55 volumes of *water*.

(1) To a quantity of powdered tablets containing the equivalent of 20 mg of Cyproterone Acetate and 350 µg of Ethinylestradiol, add 10 mL of a mixture of 3 volumes of *acetonitrile*, 4 volumes of *water* and 13 volumes of *methanol*. Heat this solution in a water bath at 40° for 15 minutes with shaking, mix with the aid of ultrasound for 30 minutes and shake for a further 20 minutes. Cool to room temperature and centrifuge. Dilute 1 volume of the supernatant liquid to 2 volumes with the same solvent mixture.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.001% w/v each of *cyproterone acetate BPCRS* and *medroxyprogesterone acetate BPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (2.7 µm) (Ascentis Express C18 is suitable).
(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 40°.
(e) Use UV detection wavelengths of 260 nm and 280 nm, and fluorimetric detection with an excitation wavelength of 280 nm and an emission wavelength of 310 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 19 volumes of *acetonitrile* and 81 volumes of *methanol*.

Mobile phase B *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	45	55	isocratic
30-57	45→80	55→20	linear gradient
57-67	80→90	20→10	linear gradient
67-82	90→45	10→55	linear gradient
82-90	45	55	re-equilibration

When the chromatograms are recorded using the prescribed conditions the retention time of ethinylestradiol is about 25 minutes and the retention time of cyproterone acetate is about 46 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cyproterone acetate and medroxyprogesterone acetate is at least 1.3.

LIMITS

For Cyproterone Acetate at 280 nm:

In the chromatogram obtained with solution (1):

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

the sum of the areas of all *secondary peaks* is not greater than twice 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 (4) (0.1%).

For Cyproterone Acetate at 260 nm:

In the chromatogram obtained with solution (1):

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

the sum of the areas of all *secondary peaks* is not more than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

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

For Ethinylestradiol at excitation 280 nm and emission 310 nm:

In the chromatogram obtained with solution (1):

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

the sum of the areas of all *secondary peaks* is not more than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

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

Uniformity of content

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

(1) Shake one tablet with the aid of ultrasound with 20 mL of *methanol (80%)*, add sufficient *methanol (80%)* to produce a solution expected to contain 0.008% w/v of Cyproterone Acetate and filter.
(2) 0.008% w/v of *cyproterone acetate BPCRS* and 0.00014% w/v of *ethinylestradiol BPCRS* in *methanol (80%)*.
(3) 0.004% w/v each of *cyproterone acetate BPCRS* and *medroxyprogesterone acetate BPCRS* in *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 50 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cyproterone acetate and medroxyprogesterone acetate is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{29}ClO_4$ and $C_{20}H_{24}O_2$ in each tablet using the declared content of $C_{24}H_{29}ClO_4$ in *cyproterone acetate BPCRS* and $C_{20}H_{24}O_2$ in *ethinylestradiol BPCRS*, respectively.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of content.