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Estradiol Tablets

General Notices

Action and use

Estrogen.

DEFINITION

Estradiol Tablets contain Estradiol Hemihydrate.

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

Content of estradiol, $C_{18}H_{24}O_2$

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) Add 0.2 mL of *water* to a quantity of powdered tablets containing the equivalent of 2 mg of estradiol and shake to disperse. Add sufficient *ethanol (96%)* to produce a solution containing the equivalent of 0.04% w/v of estradiol, centrifuge and filter the supernatant liquid.
(2) 0.04% w/v of *estradiol hemihydrate BPCRS* in *ethanol (96%)*.
(3) 0.04% w/v each of *estradiol hemihydrate BPCRS* and *norethisterone BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck HPTLC *silica gel 60* plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 2 µL of each solution.
(d) Develop the plate to 8 cm.
(e) After removal of the plate, dry in air and spray with *ethanolic sulfuric acid (5%)*. Heat the plate at 105° for 15 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

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

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B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak 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 2, rotating the paddle at 50 revolutions per minute.
(b) Use 500 mL of a 0.3% w/v solution of *sodium lauryl sulfate* in *water*, 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, discarding the first 5 mL of the filtrate. Dilute the filtrate, if necessary, with the dissolution medium to produce a solution expected to contain the equivalent of 0.0002% w/v of estradiol.
(2) Dissolve 20 mg of *estradiol hemihydrate BPCRS* in 100 mL of *methanol (80%)*, dilute 1 volume of this solution to 100 volumes with the dissolution medium.
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS* and 0.00066% w/v of *estrone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 235 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

450 volumes of *water* and 550 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions, the retention time of estradiol is about 3 minutes.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the total content of estradiol, $C_{18}H_{24}O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS*.

LIMITS

The amount of estradiol released is not less than 75% (Q) of the stated amount.

Related substances

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

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(1) Add 20 mL of the mobile phase to a quantity of powdered tablets containing the equivalent of 5 mg of estradiol, mix with the aid of ultrasound and add sufficient mobile phase to produce 25 mL. Centrifuge and use the clear supernatant liquid.
(2) 0.0001% w/v of *estrone BPCRS* in the mobile phase.
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS* and 0.0066% w/v of *estrone BPCRS* in the mobile phase.
(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but using an injection volume of 20 µL.

When the chromatograms are recorded under the prescribed conditions, the retention time of estrone relative to estradiol (retention time, about 3 minutes) is about 1.2.

SYSTEM SUITABILITY

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

CALCULATION OF IMPURITIES

For each impurity, use the concentration of estrone in solution (2).

For the reporting threshold, use the concentration of estrone in solution (4).

LIMITS

- unspecified impurities: not more than 0.5%;

- total impurities: not more than 1.5%;

- reporting threshold: 0.1%.

Uniformity of content

Tablets containing less than the equivalent of 2 mg and/or less than 2% w/w of estradiol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of the mobile phase to one tablet, mix with the aid of ultrasound, cool, add sufficient of the mobile phase to produce 50 mL and centrifuge. Dilute the supernatant liquid, if necessary, with the mobile phase to produce a solution containing the equivalent of 0.002% w/v of estradiol.
(2) 0.002% w/v of *estradiol hemihydrate BPCRS* in the mobile phase.
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS* and 0.0066% w/v of *estrone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but using an injection volume of 20 µL.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{24}O_2$ in each tablet using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of estradiol

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

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of estradiol

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 40 mL of the mobile phase to a quantity of powdered tablets containing the equivalent of 10 mg of estradiol, mix with the aid of ultrasound, dilute to 50 mL with the mobile phase and centrifuge. Dilute 1 volume of the clear supernatant liquid to 10 volumes with mobile phase.
(2) 0.002% w/v of *estradiol hemihydrate BPCRS* in the mobile phase.
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS* and 0.0066% w/v of *estrone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but using an injection volume of 20 µL.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the content of estradiol, $C_{18}H_{24}O_2$, in the tablets using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS*.

LABELLING

The quantity of Estradiol Hemihydrate is stated in terms of the equivalent amount of estradiol.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Estradiol Hemihydrate.

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