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Ergometrine and Oxytocin Injection

General Notices

Action and use

Oxytocic.

DEFINITION

Ergometrine and Oxytocin Injection is a sterile solution containing Ergometrine Maleate and either Oxytocin or Oxytocin Concentrated Solution in Water for Injections containing maleic acid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ergometrine maleate, $C_{19}H_{23}N_3O_2,C_4H_4O_4$

90.0 to 110.0% of the stated amount.

Content of oxytocin, $C_{43}H_{66}N_{12}O_{12}S_2$

90.0 to 105.0% of the stated amount.

By convention, for the purpose of labelling oxytocin preparations, 1 mg of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600 IU of biological activity.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. In the Related substances test for ergometrine maleate, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).
B. To a volume containing 0.1 mg of Ergometrine Maleate, add 0.5 mL of *water* and 2 mL of *dimethylaminobenzaldehyde solution R6*. After about 5 minutes a deep blue colour is produced.
C. In the Assay for oxytocin the peak in the chromatogram obtained with solution (2) corresponds to the peak due to oxytocin in the chromatogram obtained with solution (1).

TESTS

Acidity

pH, 2.9 to 3.5, Appendix V L.

Related substances

For ergometrine maleate

Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions prepared immediately before use, *protected from light*.

(1) Add 10 mL of absolute ethanol to a volume of the injection containing 0.5 mg of Ergometrine Maleate and evaporate to dryness at a temperature not exceeding 30° at a pressure of 2 kPa; to the residue add 0.2 mL of a mixture of 1 volume of 13.5M ammonia and 9 volumes of ethanol (80%), mix, centrifuge and use the supernatant liquid.
(2) 0.250% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(3) 0.0250% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(4) 0.0125% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(5) 0.0050% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(6) 0.00250% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 14 cm.
(e) After removal of the plate, dry it in a current of cold air, spray with *dimethylaminobenzaldehyde solution R7* and dry the plate at 105° for 2 minutes.

MOBILE PHASE

75 volumes of *chloroform*, 25 volumes of *methanol* and 3 volumes of *water*.

CONFIRMATION

Assess the intensities of any secondary spots in the chromatogram obtained with solution (1) by reference to the spots in the chromatograms obtained with solutions (3) to (6), making allowance for area in assessing the intensities of spots of different Rf values. The sum of the intensities so assessed does not exceed 10% of the intensity of the principal spot.

For oxytocin

Carry out the method for liquid chromatography, Appendix III D using the following solutions prepared immediately before use, *protected from light*.

(1) Dilute the injection, if necessary, with *water* to give a solution containing the equivalent of 0.00083% w/v oxytocin.
(2) Prepare a 0.00083% w/v *oxytocin EPCRS* in a 0.1M *sodium dihydrogen orthophosphate* solution.
(3) Dilute 2.5 volumes of solution (2) to 100 volumes with *water*.
(4) To 900 µL of solution (2) add 100 µL of 1M *hydrochloric acid* and heat at approximately 100° for 10 minutes for in situ generation of oxytocin impurity 1.
(5) Dilute 2 volumes of solution (3) to 25 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography R1* (3 µm) (Nucleosil is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 40°.
(e) Use detection wavelengths of 220 nm and 320 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1M *sodium dihydrogen orthophosphate*.

Mobile phase B 1 volume of *acetonitrile* and 1 volume of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	69	31	isocratic
3-20	69→57	31→43	linear gradient
20-22	57	43	isocratic
22-22.1	57→69	43→31	linear gradient
22.1-28	69	31	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to oxytocin (retention time about 10 minutes) is: impurity 1, about 0.9.

SYSTEM SUITABILITY

At 220 nm

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to oxytocin and impurity 1 is at least 1.5.

LIMITS

At 220 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than three times the area of the principal peak in the chromatogram obtained with solution (3) (7.5%);

the area of any *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the sum of the areas of all the secondary peaks is not greater than 3.8 times the area of the principal peak in the chromatogram obtained with solution (3) (9.5%);

disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%) and any peak that is visible at 320 nm.

ASSAY

For ergometrine maleate

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared immediately before use, *protected from light*.

(1) Dilute the injection, if necessary, with water to give a solution containing the equivalent of 0.05% w/v ergometrine maleate.
(2) 0.05% w/v of *ergometrine maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 320 nm.

MOBILE PHASE

92 volumes of a 0.2% v/v solution of *orthophosphoric acid* and 8 volumes of *acetonitrile*.

Calculate the content of $C_{19}H_{23}N_3O_2,C_4H_4O_4$ from the declared content of $C_{19}H_{23}N_3O_2,C_4H_4O_4$ in *ergometrine maleate BPCRS*.

For oxytocin

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared immediately before use, *protected from light*.

(1) Dilute the injection, if necessary, with *water* to give a solution containing the equivalent of 0.00083% w/v of oxytocin.
(2) 0.00083% w/v *oxytocin EPCRS* in 0.1M *sodium dihydrogen orthophosphate* solution.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography R1* (3 µm) (Nucleosil 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 a column temperature of 40°.
(e) Use detection wavelength of 220 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1M *sodium dihydrogen orthophosphate*.

Mobile phase B 1 volume of *acetonitrile* and 1 volume of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-35	76	24	isocratic
35-40	76→20	24→80	linear gradient
40-45	20	80	isocratic
45-45.1	20→76	80→24	linear gradient
45.1-50	76	24	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (1), the peak due oxytocin elutes between 23 and 35 minutes

DETERMINATION OF CONTENT

Calculate the content of $C_{43}H_{66}N_{12}O_{12}S_2$ from the declared content in *oxytocin EPCRS*.

STORAGE

Ergometrine and Oxytocin Injection should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The strength with respect to oxytocin is stated as the number of IU (units) per mL. The label also states the equivalent number of µg of oxytocin per mL.

IMPURITIES

The impurities limited by the requirements of this monograph include:

1. Oxytocin impurity 1, unknown structure.